TRANSPUPILLARY THERMOTHERAPY OF CHOROIDAL MELANOMA

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Abstract

A retrospective analysis of the immediate and long-term effectiveness of the treatment of the choroidal melanoma using transpupillary thermotherapy (TTT) was carried out. The study included 84 patients with choroidal melanoma (C69.3) who received treatment between 2007 and 2018. Patients were sampled from the Belarusian Cancer Register. The average values of the thickness of the tumor were 2.6±1.3 mm, the diameter of the base - 7.2±3.3 mm. TTT was carried out using a diode laser with a wavelength of 860 nm and radiation power of 200 - 800 mW, the exposure time was 60 s, and the diameter of the laser spot was varied between 1 and 3 mm. The entire surface of the tumor was thermally treated with overlapping fields from the periphery to the top. 75 patients underwent a single session of TTT, while 9 - two sessions with an interval of 3–4 weeks. As a result of the treatment, 51 (60.7%) patients showed complete tumor resorption, 28 (33.3%) patients had stabilization of the tumor process, and 5 (6.0%) patients had no effect. In the group of patients with stabilization of the tumor process, continued growth was recorded in 16 (19.1%) patients with follow-up periods of 3 months to 4 years. In 19 (37.3%) patients from the group with complete tumor regression, relapse was observed 1 to 8 years after TTT. Metastatic disease (disease progression) developed in 5 (5.9%) patients, of which in 1 patient during the first 12 months, in 1 patient - after 4 years, and in 3 patients more than after 5 years of the follow-up observation. Analysis of the effectiveness of TTT of choroidal melanoma showed that an increase in the thickness and diameter of the base of the tumor focus results in the decrease of immediate effectiveness, and the rise of the likelihood of continued tumor growth.

Keywords: choroidal melanoma, transpupillary thermotherapy, photodynamic therapy, brachytherapy.

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ТРАНСПУПИЛЛЯРНАЯ ТЕРМОТЕРАПИЯ МЕЛАНОМЫ СОСУДИСТОЙ ОБОЛОЧКИ ГЛАЗА

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Резюме

Проведен ретроспективный анализ непосредственной и отдаленной эффективности лечения меланомы сосудистой оболочки глаза методом транспупиллярной термотерапии (ТТТ). Исследование включало 84 пациента с меланомой сосудистой оболочки глаза (С69.3), получивших лечение в период 2007–2018 гг. Выборка больных проведена из базы Белорусского канцер-регистра. Средние значения толщины опухоли составили 2,6±1,3 мм, диаметра основания – 7,2±3,3 мм. ТТТ проводили с использованием диодного лазера, длина волны 860 нм, мощность излучения 200 – 800 мВт, экспозиция 60 с, диаметр лазерного пятна от 1 до 3 мм. Термическому воздействию подвергали всю поверхность опухоли, поля располагали с перекрытием, от периферии к вершине опухоли. У 75 пациентов проведен один, у 9 – два сеанса ТТТ с интервалом 3 – 4 нед. В результате проведенного лечения у 51 (60,7%) пациента зарегистрирована полная резорбция опухоли, у 28 (33,3%) – стабилизация опухолевого процесса, у 5 (6,0%) – отсутствие эффекта от лечения. В группе пациентов со стабилизацией опухолевого процесса продолженный рост зафиксирован у 16 (19,1%) при сроках наблюдения от 3 мес до 4 лет. У 19 (37,3%) больных из группы с полной регрессией опухоли зарегистрирован рецидив заболевания на сроках от 1 до 8 лет наблюдения после проведения ТТТ. Метастатическая болезнь (прогрессирование заболевания) развилась у 5 (5,9%) пациентов, из них в течение первых 12 мес – у 1 больного, через 4 года – у 1, в сроки наблюдения более 5 лет – у 3. Анализ эффективности ТТТ в зависимости от размеров меланомы хориоидеи показал, что с увеличением толщины и диаметра основания опухолевого очага непосредственная эффективность снижается, а вероятность продолженного роста опухоли возрастает.

Ключевые слова: меланома хориоидеи, транспупиллярная термотерапия, фотодинамическая терапия, брахитерапия.

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Introduction

Melanoma of the choroid of the eye is the most common tumor in the membranes of the eye among adult population. According to the Belarusian Cancer Registry, the gross intensive incidence rate per 100,000 population was 1.1 in 2011, and 1.2 in 2016 [1]. Over a 5–year period, the detection rate of stage I of the disease increased from 5.4% in 2011 to 16.4% in 2016 [2].

Despite a large range of treatment possibilities, choroidal melanoma is prone to hematogenous metastasis, which leads to a fatal outcome. Improving patient survival is possible only when the tumor is diagnosed at the early stages of the disease. Small tumors are now treated with laser technologies, one of which is transpupillary thermotherapy (TTT). The method is non-invasive. The infrared spectrum of a diode laser is delivered with a wavelength of 810 nm to the surface of choroidal melanoma (CM) through transparent optical media of the eye at the height of the cycloplegia [3, 4]. When exposed to the laser, the temperature of the tumor increases to 45-60° C, which leads to obliteration of the tumor vessels with the development of necrosis. According to various authors, lasers can achieve therapeutic effect if the tumor is no more than 2 mm thick [5].

C.L. Shields, J.A. Shields et al. believe that the maximum depth of penetration of TTT is 4 mm, which allows treatment of small CM tumors [3]. Absorption of diode laser radiation is higher in more pigmented tumors. The advantages of TTT in comparison with radiation therapy include precise localization of the laser beam, rapid tumor necrosis, and the ability to treat patients on an outpatient basis with minimal damage to the surrounding intact vascular membrane. According to various authors, tumor relapses after TTT in CM range from 9 to 28% [3]. Due to the energy of the laser beam, complications may include tractional retinal detachment (44%), retinal vein occlusion (26–41%), retinal artery occlusion (12%), cystic macular edema (9–23%), epiretinal membrane development (23%), vitreous hemorrhage (10%), retinal neovascularization (6%), foveal traction (4%), chorioretinal scarring (4%), optic disc atrophy (2%), regmatogenic (1%) and serous retinal detachment (1%), optic disc edema (<1%), and cataract (<1%) [3, 5].

A direct correlation was found between the development of disease recurrence and the number of prognostic risk factors (RF) for tumor growth. The latter include tumor thickness of > 2 mm (according to ultrasonography), the presence of subretinal fluid found at optical coherence tomography, clumped orange pigment, the localization of tumor edge near the optic nerve disc, hypoechoic character of the tumor with hyperreflexive contour, absence of drusen, the base diameter being > 5 mm [5]. According to A. Mashayekhi et al., the relapse rate after 10 years of follow-up was 18% in patients with one to two RFs, 35% in those with three to five RFs, and 55% in people with more than six RFs [6]. TTT is less preferable in cases where the number of RFs exceeds three. S. Turcotte et al. presented the results of treatment of 8 patients with CM who received an average of three sessions of TTT. The average thickness of the tumor before treatment was 2±0.8 mm. In 3 (38%) patients, continued growth of the tumor was registered. No deaths due to metastases were registered. The authors conclude that patients with continued tumor growth have a high risk of relapse when the number of RFs is more than one. Loss of visual acuity directly related to TTT treatment was observed in 25% of the patients [7].

In a prospective non-randomized study, M. M. Chojniak et al. [8] evaluated the results of treatment of 27 patients with an average tumor thickness of 2.7 mm and a base diameter of 8.52 mm. After 3 sessions of treatment with a follow-up period of 45 months, the average thickness of the tumor decreased to 1.34 mm ($p<0.001$), and the diameter of the base of the tumor, to 5.48 mm ($p<0.001$). Complications were observed in 12 (44%) patients and included retinal vascular occlusion, optic disc atrophy, vitreous hemorrhage, regmatogenic retinal detachment, and maculopathy. The rate of optic disc atrophy after treatment was high, being observed in 60% of patients. Visual acuity remained unchanged in 9 (33%) patients, improved in 5 (19%) and decreased during the first 6 months after treatment in 13 (48%). Marginal recurrence of the tumor was detected in 2 (7%) patients. The eyes were preserved in all patients. In 1 case, the development of metastases was observed. The authors conclude that TTT is an effective treatment for small-sized CM. Reduced visual acuity occurred in the early stages after treatment and was mainly associated with the treatment of subfoveal and perifoveal tumors. According to the authors, it is necessary to conduct long-term randomized studies in order to achieve a better insight into the effectiveness of the treatment method.

B. M. Stoffelns et al. evaluated 10-year TTT results in 26 patients with small-sized CMs. The tumors were located behind the equator and had a base diameter of ≤12 mm and a thickness of ≤4.5 mm. The patients had an average of 1.4 treatment sessions. Ten years after treatment, tumor regression was achieved in 16 patients, initial regression with subsequent tumor recurrence in 6, and insufficient tumor regression in 4. Two patients died due to metastatic liver damage. The authors conclude that MCs treated with TTT require careful monitoring, as local relapses and complications later develop in the treatment area. Complications were observed in 14 patients, including maculopathy in 8 cases, macular edema in 6, choroidal neovascularization in 4, and posterior synechiae with iris atrophy in 1 case [9].

In the study of A. A. Yarovoy et al. ("MNTK "Eye Microsurgery"", Russia), 78 CM patients with a tumor thickness of up to 3.6 mm were treated; the follow-up period

ranged from 2.5 to 108 months. The criteria for evaluating the treatment were the status localis, the number of enucleations, tumor relapses, complications, and visual acuity. In 51 patients, the tumor regressed completely, and in 20 patients, partially. The absence of results from treatment was registered in 7 cases: 2 of them were followed with ophthalmectomy, and 5 with brachytherapy with ^{106}Ru. Tumor recurrence was detected in 10 patients within 7 to 54 months after the end of the treatment. It should be noted that in 8 patients the tumor regression was partial. Additional TTT was used to successfully treat 6 patients with relapsed disease, and 4 were administered brachytherapy. No metastases were registered. The authors concluded that the main prognostic adverse factors of TTT are the thickness of the tumor of more than 3 mm, basal diameter of more than 10.2 mm, non-pigmented tumor, maximum systolic blood flow rate of more than 11.7 cm/s, the presence of subretinal fluid and incomplete regression after treatment. The TTT method is an experimental method for treating CM. Patient preparation for TTT has to be based on careful selection of patients with due consideration of prognostic factors and functional perspectives [10].

Data from a retrospective review by K. Gündüz et al. [11] on the use of TTT in 20 patients with CM and 4 with choroidal nevi, showed that patients with vascular nevi were found to have risk factors for the development of melanoma, or secondary neovascularization of the vascular membrane was observed. The average initial initial diameter of the tumor was 6.6 mm, and its thickness was 3 mm. The average number of TTT sessions was 2.5 (from 1 to 6), and the average resorption of the tumor thickness was 1.2 mm. In 9% of patients, a relapse developed after 12 months, in 27%, 5 years after the treatment. Due to neovascular glaucoma, the eye was enucleated in 2 (8.3%) patients, and one (4.1%) patient underwent exenteration due to extraocular spread of the tumor. A positive result was achieved in 21 (87.5%) patients. In one (4.1%) patient with relapse and extracranial spread of the tumor, liver metastasis was detected. The authors believe that TTT can be used in the treatment of small-sized CMs, but the high incidence of complications and relapses requires careful monitoring of patients even upon the achievement of a flat chorioretinal scar.

J.M. Caminal et al. [12] presented the treatment results of 13 patients with CM (average height 2.02±0.54 mm, diameter 7.60±1.98 mm). In 11 (84.6%) patients with an average follow-up period of 42.46±26.29 months, the foveal subretinal fluid was completely absent. The average number of TTT sessions was 1.38±0.77. 69.3% of the patients had their visual acuity preserved or improved after treatment. Continued growth of the tumor was registered in 5 patients, regardless of the presence of subretinal fluid. In those cases, brachytherapy was performed. The authors concluded that TTT in most cases can be effective in achieving good visual acuity in the presence of foveal subretinal fluid with small CMs.

The data of academician A. F. Brovkina et al., obtained by analyzing the results of treatment of 30 patients with CM, show that the effectiveness of the technique is confirmed only in tumors with thickness less than 2 mm [13]. With a larger tumor thickness, TTT can only be used in combination with brachytherapy. The risk factors that impair the effectiveness of TTT were identified: tumors with a thickness of more than 2 mm, amelanotic or slightly pigmented, as well as having subretinal exudate. The development of complications and their nature depend on the basic size of the CM, the number of sessions, and previous treatment (local destruction of the tumor). A comparison of the data available in the scientific literature and the experience of the authors allows us to determine clear indications for TTT in the treatment of choroidal melanoma and identify factors that contribute to the prevention of possible complications.

In the study by V. M. Stoffelns et al. [14], TTT was administered to 26 patients with MH with a tumor prominence of up to 3 mm. During the follow-up period of 20 weeks, complete tumor resorption was achieved in 89% of patients. In CM, the probability of complete resorption of the tumor while preserving the eye declines with the increasing prominence of the tumor. In small CM tumors with a posterior location, tumor resorption was achieved much faster after TTT treatment compared to brachytherapy.

Although the penetration capacity of TTT according to literature data reaches 4 mm, the best effect from TTT is obtained in the treatment of tumors with prominence of up to 2-3 mm and a base diameter of less than 10 mm, well pigmented, with no subretinal fluid and low blood flow rate. The prognosis for maintaining residual visual acuity after TTT (especially when the number of sessions increases) is debatable and depends on the localization of the tumor process; it is often impossible to maintain visual acuity and visual field. Complications that develop after TTT are associated with the area of thermal exposure, the proximity to the macular zone and the optic disc.

Materials and methods

The study included 84 patients with choroidal melanoma (ICD-10: C69.3) who received treatment in the period from 2007 to 2018. A sample of patients was taken from the database of the Belarusian Cancer Registry.

In 75 (89.3%) of the patients, a melanoma of the vasculature of the eye was the only tumor. Synchronous colon cancer was registered in 1 (1.2%) patient. 8 (9.5%) patients were diagnosed with metachronous cancer, including one case of basal cell skin cancer, ductal breast carcinoma, pancreatic cancer, prostate cancer, lung cancer, skin melanoma, and 2 cases of kidney cancer. The

sample included 29 (34.5%) men, and 55 (65.5%) women, the minimum age being 20 years, and the maximum 84, with the average age of patients being 59±13 years. The average value of the tumor thickness was 2.6±1.3 mm, and that of the base diameter was 7.2±3.3 mm. The average systolic blood flow rate was 7.7±3.4 cm/s. The level of blood flow in the tumor was assessed by a Doppler ultrasound scan.

TTT was performed with a diode laser with the wavelength of 860 nm, the radiation power from 200 to 800 mW, the exposure of 60 seconds, and the diameter of the laser spot from 1 to 3 mm. The entire surface of the tumor was subjected to thermal exposure, the exposure fields were placed with overlapping, from the periphery to the top of the tumor. 75 patients had one, and 9 had two sessions of TTT with an interval of 3 or 4 weeks.

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 location of the tumor, but a possible dispersion or a slight accumulation of pigment were allowed. The criteria for the stabilization of the neoplastic process were a decreased size of the tumor or, in severe pigmentation, no size changes and the absence of blood circulation. The absence of effect from the treatment was understood as no changes on the part of the tumor or an increase in its size with the preservation or reinforcement of the blood flow in it. The positive result of treatment was understood as complete resorption or stabilization of the tumor process.

In the dynamic monitoring of patients with tumor process stabilization, a continued growth of the tumor in the eye membranes was understood as a condition when, against the background of stabilization, an increase in the size and appearance of the vascular network in the tumor were registered. A relapse was understood as a condition when the growth of the tumor was registered against the background of an atrophic chorioretinal focus (complete regression). The progression of the disease was understood as the emergence of distant metastases in other organs.

To calculate the survival rate, we used the adjusted cumulative 5-year survival rate with the actuarial method.

Results and discussion

In 79 of 84 patients (94.0%), the immediate effect of treatment was assessed as stabilization or complete resorption of the tumor. Complete resorption of the tumor was registered in 51 (60.7%) patients, and stabilization of the tumor process in 28 (33.3%) patients. 5 (6.0%) patients were observed to have no effect from the treatment. Of 28 patients with tumor process stabilization achieved, continued growth was recorded in 16 (19.1%), with follow-up periods of 3 months to 4 years.

Of the 51 patients with complete tumor regression, 19 (37.3%) had a relapse in the observation period, one to eight years of follow-up after TTT. In all cases, TTT or brachytherapy was performed to preserve the eye. In 3 patients, after the relapse treatment with brachytherapy, the tumor process progressed. Enucleation due to continued growth, relapse, and complications of TTT was performed in 12 (14.3%) patients. 5 (5.9%) patients developed distant metastases, including one case during the first 12 months and one in 4 years, and 3 cases during the follow-up period of more than 5 years. Complications registered in connection with TTT included post-radiation opticoretinopathy in 6 (7.1%) patients, local retinal hemorrhage in 3 (3.6%) patients, and partial hemophthalmia in 1 (1.2%) patient with diabetic retinopathy.

For a more accurate assessment of the treatment outcomes with due consideration for the size of the tumor, patients were divided into five subgroups.

Table 1 shows the height and diameter of the tumor base before treatment.

Tables 2 and 3 provide summary data on immediate and long-term TTT results in patients with CM, depending on the size of the tumor.

In the first subgroup, 8 (57.2%) patients had complete tumor resorption, 6 (42.8%) had stabilization, and 2 (14.3%) had relapse. In a patient with juxtapapillary localization of the tumor, relapse was detected in the fourth year of follow-up after registering the effect of TTT. In connection with a relapse, 2 additional courses of TTT were conducted. The eyeball was removed after 9 months due to the development of secondary painful glaucoma against the background of a complete resorption of the tumor. In the second patient, a local relapse was detected in the fifth year of the follow-up after the registration of atrophy; the eye was removed, and a year later liver metastasis was registered. A continued growth against the background of stabilization of the tumor process was recorded in a female patient four years after the registration of the effect of treatment. Brachytherapy was performed, the process was stabilized, but a year later, a distant metastasis process was diagnosed.

In the second subgroup of patients, 9 (52.9%) cases showed complete tumor resorption, and stabilization in 8 (47.1%) patients. A relapse was diagnosed in 2 (17.7%) patients, one of them had two relapses registered one after another: 3 years and then 4 years after the treatment. In the second case, the relapse developed a year later. Both patients were administered brachytherapy as additional organ-preserving treatment. Continued growth against the background of stabilization was observed in 1 (5.9%) patient, ophthalmectomy was performed, but a year later metastatic disease was detected.

Таблица 1
Характеристика высоты и диаметра основания меланомы хориоидеи (M ± m)
Table 1
Characterization of the height and diameter of the base of the choroidal melanoma (M ± m)

Показатели Parameters	Подгруппы Subgroups				
	1 (n=14)	2 (n=17)	3 (n=21)	4 (n=13)	5 (n=19)
Диаметр основания, мм Base diameter, mm	2,4±1,2	5,0±0,5	7,0±0,6	8,8±0,5	11,5±1,5
Высота, мм Height, mm	1,5±1,0	2,1±0,9	2,7±1,2	2,5±1,3	3,8±1,1

Таблица 2
Непосредственные результаты транспупиллярной термотерапии в зависимости от размеров меланомы хориоидеи (абс. ч./%)
Table 2
Immediate results of transpupillary thermotherapy depending on the size of the choroidal melanoma (No. patients / %)

Эффект лечения Treatment effect	Подгруппы Subgroups				
	1 (n=14)	2 (n=17)	3 (n=21)	4 (n=13)	5 (n=19)
Полная резорбция Complete resorption	8/57,2	9/52,9	15/71,4	9/69,2	10/52,6
Стабилизация Stabilization	6/42,8	8/47,1	6/28,6	3/23,1	5/26,3
Отсутствие эффекта No effect	–	–	–	1/7,7	4/21,1

Таблица 3
Отдаленные результаты транспупиллярной термотерапии в зависимости от размеров меланомы хориоидеи (абс. ч./%)
Table 3
Long-term results of transpupillary thermotherapy depending on the size of the choroidal melanoma (No. patients / %)

Отдаленные результаты ТТТ Long-term results of TTT	Подгруппы Subgroups				
	1 (n=14)	2 (n=17)	3 (n=21)	4 (n=13)	5 (n=19)
Рецидив Reccurence	2/14,3	2/17,7	7/33,3	3/23,1	5/26,3
Продолженный рост Continued growth	1/7,1	1/5,9	2/9,5	2/15,4	4/21,1
Энуклеация Enucleation	2/14,3	1/5,9	3/14,3	1/7,7	5/26,3
Прогрессирование Progression	2/14,3	1/5,9	2/9,5	1/7,7	–

In the third subgroup, complete resorption of the tumor was observed in 15 (71.4%), and stabilization in 6 (28.6%) patients. Relapse occurred in 7 (33.3%) patients in follow-up periods of one year (2 cases), 2 years (3 cases), 3 years (1 case), and 4 years (1 case). Enucleation was performed on 3 patients, including, in one case, due to the relapse and painful glaucoma in the fourth year of the follow-up, and on 2 patients due to the relapse in the follow-up periods of 4 and 5 years. Brachytherapy was performed in 4 patients in connection with local relapse. Metastases in the liver and bones were detected in 2 patients with recurrent CM in a year and in 5 years. In 2 observations, during the year, continued growth was recorded against the background of stabilization. Pa-

tients were successfully treated with brachytherapy and 2 courses of TTT.

Complete resorption of the tumor in the fourth subgroup was registered in 9 (69.2%) patients, stabilization in 3 (23.1%); in one case (7.7%), the effect of treatment was absent. Relapse occurred in 3 patients in the second, fourth and seventh years of follow-up. Continued growth was recorded in 2 cases. All patients were administered TTT and brachytherapy. Enucleation was performed in one case under the observation due to the lack of effect from treatment. A patient with continued growth was diagnosed with metastatic liver damage 4 years after the treatment.

In the fifth subgroup, tumor resorption was recorded in 10 (52.6%), stabilization in 5 (26.3%), and no effect from treatment in 4 (21.1%) patients. Relapse was registered in 5 patients: in one, it occurred in 2 years after the registration of complete resorption of the tumor, in 3, in 5 years, and in one case, 8 years after the registration of complete resorption of the tumor. Five enucleations were performed in the periods from 2 months to 2 years, two of them due to the continued tumor growth, and three due to the lack of effect from treatment. No cases of metastatic disease were registered in this subgroup.

The survival rate of patients with a single eye tumor (n=75) was analyzed, without including patients with multiple primary diseases. One-year overall survival was 100%, 5-year and 10-year survival was 95.4±2.1% and 79.8±6.9%, respectively.

Conclusion

As a result of TTT, 51 (60.7%) patients were registered to have complete resorption of the tumor, 28 (33.3%) had the tumor process stabilized, and 5 (6.0%) had no effect from the treatment. Of 28 patients with tumor process stabilization, continued growth was recorded in 16 (19.1%) cases with follow-up periods of 3 months to 4 years. Of the 51 patients with complete tumor regression, 19 (37.3%) had a relapse in the observation period, one to eight years of follow-up after TTT. 5 (5.9%) patients developed distant metastases, including one case during the first 12 months and one in 4 years after the completion of TTT, and 3 cases during the follow-up period of more than 5 years. The analysis of the TTT effectiveness in relation to the size of the focus of choroid melanoma showed that the method's direct efficiency is reduced in proportion to the increase in the thickness and diameter of the base of the tumor, and the probability of tumor growth after TTT administration increases. One-year overall survival in patients who had only one tumor, that of the eye, was 100%, 5-year and 10-year survival was 95.4±2.1% and 79.8±6.9%, respectively.

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