ORIGINAL ARTICLES

# PHOTODYNAMIC THERAPY IN PATIENTS WITH SKIN METASTASES OF DESSIMINATED MELANOMA

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## Abstract

The aim of the study was to evaluate the immediate results of photodynamic therapy (PDT) in patients with intradermal metastases of skin melanoma. The study included 50 patients who received treatment at the department of hyperthermia and photodynamic therapy. The study included 23 (46%) men and 27 (54%) women with an average age of 60.7±10.4 years. PDT of tumors was carried out 3–4 hours after intravenous administration of a chlorine-based photosensitizer (Photolon) in doses of 1.5–3 mg/kg using a semiconductor laser «UPL-PDT» (Lemt, Belarus, λ=660±5 nm). The exposure doses varied from 100 to 400 J/cm$^2$; power density – from 0.2 to 0.9 W/cm$^2$; power – from 0.25 to 1 W and time of PDT of one focus was dependent on the size and location of the tumor and was 5 to 20 minutes. Evaluation of antitumor efficacy of PDT was carried out according to WHO criteria. The terms of follow-up of patients were between 3 and 23 months. At follow-up observation, 1–3 months after the treatment, complete regression of intradermal metastases of skin melanoma was achieved in 9 (18%) patients, partial – in 28 (56%), process stabilization in 8 (16%) and progression in 5 (10%)) patients. The objective effect was achieved in 74% of patients, the therapeutic – in 90%. PDT can be used in the treatment of intradermal metastases of disseminated skin melanoma with palliative purposes and allows reducing the tumor volume, which significantly improves the quality of life of patients.

**Keywords:** skin melanoma, intradermal metastases, photodynamic therapy.

**For citations:** Tzerkovsky D.A., Petrovskaya N.A., Mazurenko A.N. Photodynamic therapy in patients with skin metastases of disseminated melanoma, *Biomedical Photonics*, 2019, vol. 8, no. 1, pp. 14–28 (in Russian) 10.24931/2413–9432–2019–8–1-24–28.

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# ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПАЦИЕНТОВ С ВНУТРИКОЖНЫМИ МЕТАСТАЗАМИ ДИССЕМИНИРОВАННОЙ МЕЛАНОМЫ КОЖИ

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## Резюме

Целью работы была оценка непосредственных результатов применения фотодинамической терапии (ФДТ) у пациентов с внутрикожными метастазами меланомы кожи. В исследование было включено 50 пациентов с внутрикожными метастазами диссеминированной меланомы кожи, получавших лечение на базе отделения гипертермии и фотодинамической терапии. Среди них было 23 (46%) мужчины и 27 (54%) женщин; средний возраст пациентов составил 60,7±10,4 лет. Облучение опухолей проводили через 3–4 ч после внутривенного введения фотосенсибилизатора хлоринового ряда (фотолон) в дозах 1,5–3 мг/кг с использованием полупроводникового лазера «УПЛ-ФДТ» (НТЦ «ЛЭМТ» БелОМО, Республика Беларусь, λ=660±5 нм). Суммарная доза света варьировалась от 100 до 400 Дж/см$^2$; плотность мощности – от 0,2 до 0,9 Вт/см$^2$; мощность – от 0,25 до 1 Вт; длительность облучения одного очага зависела от размеров и локализации опухоли и составляла от 5 до 20 мин. Оценку противоопухолевой эффективности ФДТ осуществляли по критериям ВОЗ. Сроки наблюдения за пациентами составили от 3 до 23 мес. При контрольном наблюдении через 1–3 мес после проведенного лечения полная регрессия внутрикожных метастазов меланомы кожи достигнута у 9 (18%), частичная – у 28 (56%), стабилизация процесса – у 8 (16%) и прогрессирование – у 5 (10%) пациентов. Объективный эффект достигнут у 74% пациентов, лечебный – у 90%. Метод ФДТ может быть применен в лечении внутрикожных метастазов диссеминированной меланомы кожи в паллиативных целях и позволяет уменьшать объем опухоли, что существенно повышает качество жизни пациентов.

**Ключевые слова**: меланома кожи, внутрикожные метастазы, фотодинамическая терапия.

**Для цитирования:** Церковский Д.А., Петровская Н.А., Мазуренко А.Н. Фотодинамическая терапия пациентов с внутрикожными метастазами диссеминированной меланомы кожи // Biomedical photonics. – 2019 – Т. 8, № 1 – С. 24–28. doi: 10.24931/2413–9432–2019–8–1-24–28.

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## Introduction

Skin melanoma is one of the aggressive forms of malignant tumors with high growth and regional metastasis potential, with the ability to disseminate over the skin and produce multiple hematogenous metastases. The number of patients with this pathology has increased significantly in the recent years: the average annual growth rate of the incidence of melanoma in the world is about 5%, which can be considered one of the highest among all malignant neoplasms. Despite the fact that the proportion of melanoma in the structure of all tumor skin diseases is on average 4%, this disease is the main cause of death for patients with skin cancer. The average life expectancy of patients with melanoma varies from 6 to 9 months with a 5-year survival rate of less than 18% [1].

Today, one of the most challenging problems of clinical oncology is the treatment of disseminated melanoma, which is associated with the low sensitivity of this tumor to the traditionally used chemo-, hormone-, and immunotherapy. Despite certain advances in drug therapy for the metastatic form of skin melanoma and the variety of antitumor drugs, only a small fraction of them are found to achieve with relative success in the treatment of this disease.

All of the above shows that the problem of the combined treatment of disseminated skin melanoma is still far from being resolved and remains very relevant for clinical oncology. Insufficient efficiency of the existing therapies for disseminated skin melanoma is the main prerequisite for the search and testing of new methods in this area.

One of the methods which have proven their effectiveness and safety in clinical settings, is photodynamic therapy (PDT).

PDT is a method of local activation of the photosensitizer (PS) selectively accumulated in the tumor tissue with visible red color, which in the presence of tissue oxygen leads to the development of photochemical reactions of types I and II, which lead to the destruction of tumor cells [2].

PDT is the result of the combined interaction of three components: PS, light and oxygen. The implementation of the antitumor effect is based on selective laser photodestruction of pre-sensitized tumor tissue. One of the main targets for photodynamic effects is blood vessel endotheliocytes and a system of macrophage cells, irradiation of which leads to the development of inflammatory mediators and cytokines (lymphokines, thromboxanes, prostoglandins) playing a significant role in the vascular component of tumor stroma destruction [3]. The PDT mechanism includes a direct cytotoxic effect on the tumor, leading to the necrosis and apoptosis of the tumor cell, damage to the microvascular bed of the tumor due to developing vascular stasis, thrombosis and hemorrhage. The result of these processes is tumor hypoxia and its subsequent death [4].

There have been a number of publications on the results of experimental and clinical studies that confirm the sensitivity of skin melanoma to PDT with the use of photosensitizing agents of various classes [1, 5–7].

The purpose of this work was to study the effectiveness of PDT with chlorine-type PS in patients with intradermal metastases of skin melanoma.

## Materials and methods

*Patients*

The study included 50 patients with intradermal metastases of disseminated skin melanoma. The sample was 23 (46%) men and 27 (54%) women aged 27 to 82, the average age of patients being 60.7 ±10.4 years. In 32 (64%) patients, the primary focus was localized on the lower extremities, in 14 (28%), on the upper limbs, and in 4 (8%), on the trunk. In all patients, the diagnosis was morphologically verified and at the time of the clinical examination corresponded to stage IV cancer (T1-4N0-2M1 (a, b, c)) (according to AJCC classification, Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2002). All patients included in the study previously underwent combination treatment consisting of surgical excision of the primary tumor, radiation therapy, polychemotherapy and hormone therapy. At the beginning of treatment, all patients showed progression of the disease (numerous metastatic lesions on the skin). PDT method was used against the background of mono- or polychemotherapy. The exposure parameters were selected individually for each patient, depending on the general status, location of the lesion, the number and size of tumor foci. All patients included in the study were informed about the method of PDT, its possible adverse reactions and complications, the timing of follow-up and recommendations after treatment. Every patient signed an informed consent.

*Photosensitizer*

The PS was Photolon (RUE Belmedpreparaty, Republic of Belarus, registration certificate П N015948/01

of November 30, 2012), which is a complex of trisodium salt of chlorin $e_6$ with polyvinylpyrrolidone (RUE Belmedpreparaty, Republic of Belarus). Photolon was dissolved in 200 ml of physiological saline and was administered intravenously, by drop infusion, for 30 minutes at doses of 1.5–3 mg/kg.

*A PDT session*

One PDT session per patient was performed, in a darkened room 3-4 hours after intravenous administration of photolon ith the use of UPL-PDT semiconductor laser apparatus (STC LEMT BelOMO, Republic of Belarus, λ = 660 nm). Immediately before tumor irradiation, laser devices were calibrated with the help of power meters. Eye-protection glasses were used to protect the eyes of patients and medical personnel. Immediately before the session, patients were premedicated with intramuscular administration of Ketorolac 4.0. Tumors were irradiated remotely, perpendicularly to the surface of the pathological focus, with a fiber equipped with a microlens (Polironik, Russia) using one, two or three fields. The light dose of radiation ranged from 100 to 400 J/cm$^2$. The power density ranged from 0.2 to 0.9 W/cm$^2$, the laser radiation power was from 0.25 to 1 W. The size of the irradiation fields varied from 0.5 to 2.0 cm, and the number of fields ranged from 3 to 17. The total number of irradiation sessions was 125. The duration of irradiation of one lesion depended on the size and location of the tumor and ranged from 5 to 20 minutes. In order to prevent local marginal recurrence, normal unchanged tissues were exposed to radiation along the periphery of the tumor focus at a distance of 5–7 mm from its edges.

*Efficiency evaluation criteria*

For all patients, the antitumor efficacy of PDT for intradermal metastases of melanoma was assessed according to WHO criteria, based on clinical trial data in 1-3 months after treatment.

The criteria were as follows:

- complete regression (CR): 100% resorption of tumor foci 1 month after PDT, confirmed 3 months after treatment;
- partial regression (PR): a decrease in the total size of the tumor lesion by 50% or more with subsequent stabilization established after 1 month and confirmed 3 months after the PDT session;
- stabilization of the process: no increase in the tumor nodes size, no new nodes or other signs of disease progression within 3 months;
- progression of the process: an increase in the total size of the tumor node by 25% or more, or the development of new tumor foci.

Objective (the sum of CR and PR) and therapeutic (the sum of PR, CR and stabilization) effects were also evaluated.

## Results and discussion

The tolerance of the method was estimated based on the general condition of the patients before the PDT session, after the administration of the PS, after light exposure, and daily until the patient was discharged from the hospital, for 3 to 5 days. There were no adverse reactions during photolon infusion and PDT sessions.

During the PDT session, most patients experienced phenomena characteristic of the photodynamic reaction as a whole, such as itching, burning sensation, and soreness in the irradiated area. In the case of severe pain, non-narcotic analgesics were used and/or the laser radiation power was reduced while maintaining the light dose due to a proportional increase in the exposure time. In some cases, patients experienced symptoms of skin phototoxicity, which were due to non-observance of the light regime.

After a PDT session, hemorrhagic necrosis developed in tumor foci, followed by the formation of a scab within 4–12 days. In all cases, it was a dense crust of a dark brown color fused to the underlying tissues, which was independently rejected 3–6 weeks after treatment (Fig. 1).

At the site of the tumor focus, a connective tissue scar was formed, which was a smooth pinkish surface, sometimes with a small depression in the center.

To prevent skin phototoxicity, patients were prescribed antioxidants and light-protective ointments, which contributed to the early epithelization of the wound and increased connective tissue growth.

No adverse reactions and phenomena associated with the introduction of PS were observed.

When evaluating skin phototoxicity, it should be noted that in all patients who observed the photo regime for 2–3 days after a PDT session, i. e., avoided direct sunlight, there were no adverse reactions in the form of skin burns of various degrees and the development of hyperpigmentation. In the rare cases of intentional or unintentional non-compliance with the recommendations, mild hyperemia of the exposed skin areas of the skin was observed, which lasted for several hours.

The follow-up observation of the patients ranged from 3 to 23 months. During clinical follow-up, 1-3 months after the treatment, CR of intradermal metastases of cutaneous melanoma was achieved in 9 (18%), PR in 28 (56%), stabilization of the process in 8 (16%), and progression was observed in 5 (10%) patients. Objective therapeutic effect was achieved in 74% of patients, and therapeutic effect in 90%.

The results of PDT use in the treatment of patients with intradermal metastases of disseminated melanoma are consistent with the available literature. Thus, in the study of Professor M. A. Kaplan et al., 1–2 months after focal PDT, CR was achieved in 7 (11.5%) patients with skin

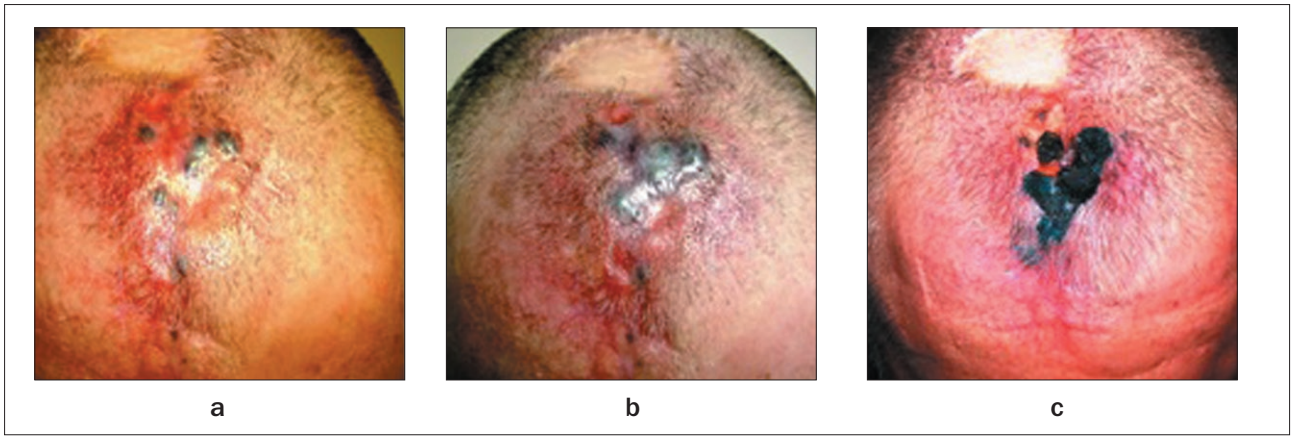


**Рис. 1.** Меланома кожи теменной области (T3N0M0). Состояние после хирургического лечения (2014 г.). Прогрессирование: внутрикожные метастазы лобно-теменной области:
*а* – состояние до ФДТ;
*б* – состояние непосредственно после сеанса ФДТ с фотолоном;
*с* – состояние через 1 мес после ФДТ

**Fig. 1.** Melanoma of the skin of the parietal region (T3N0M0). Condition after surgical treatment (2014). Progression: intradermal metastasis of the fronto-parietal region:
*a* – before PDT;
*b* – immediately after the PDT session with photolon;
*c* – 1 month after PDT

lesions, PR in 33 (54.1%) patients with skin and soft tissue lesions. The frequency of objective responses was 65.6%. Stabilization lasting more than 6–8 weeks was recorded in 13 (21.3%) foci. The therapeutic effect was achieved in 86.9% of the cases. At the same time, it should be noted that our colleagues used significantly higher light doses (600–900 J/cm$^2$) for irradiating tumor foci compared with our study [1].

## Conclusion

Thus, the advantage of PDT is the selectivity of tumor tissue targeting, the absence of severe local and systemic adverse reactions, and the possibility of repeating sessions. However, it should be noted that the treatment of patients with this pathology can be carried out on an outpatient basis, which provides economic advantages. The PDT method in the treatment of intradermal metastases of disseminated skin melanoma can be used for palliative purposes, its use can reduce the tumor volume and significantly improve the quality of life of patients.

## REFERENCES

1. Kaplan M.A., Kudryavtseva G.T., Kapinus V.N., Zakurdyaeva I.G., Borgul O.V. Photodynamic therapy of disseminated skin melanoma using Fotolon photosensitizer, *Sib. onkol. zhurn.*, 2011, no. 1. pp. 56–60.
2. Stranadko E.F. Historical essay on the development of photodynamic therapy, *Lazernaya medicina*, 2002, vol. 6, is. 1, pp. 4–8.
3. Mroz P., Yaroslavsky A., Kharkwal G.B. Cell death pathways in photodynamic therapy of tumors, *Cancers*, 2011, vol. 3, pp. 2516–2539.
4. Weiss A., den Bergh H.V., Griffioen A.W. Angiogenesis inhibition for the improvement of photodynamic therapy: The revival of a promising idea, *Biochim. Biophys. Acta*, 2012, vol. 1826, pp. 53–70.
5. Sharma K.V., Bowers N., Davids L.M. Photodynamic therapy-induced killing is enhanced in depigmented metastatic melanoma cells, *Cell Biol. Int.*, 2011, vol. 35, pp. 939–949.
6. Sparsa A., Bellaton S., Naves T., Jauberteau M.O., Bonnetblanc J.M. Photodynamic treatment induces cell death by apoptosis or autophagy depending on the melanin content in two B16 melanoma cell lines, *Oncol. Rep.*, 2013, vol. 29, pp. 1196 –1200.

## ЛИТЕРАТУРА

1. Каплан М.А., Кудрявцева Г.Т., Капинус В.Н. и др. Фотодинамическая терапия диссеминированной меланомы кожи с фотосенсибилизатором «Фотолон» // Сиб. онкол. журн. – 2011. – № 1. – С. 56–60.
2. Странадко Е.Ф. Исторический очерк развития фотодинамической терапии // Лазерная медицина. – 2002. – Т.6, вып. 1. – С. 4–8.
3. Mroz P., Yaroslavsky A., Kharkwal G.B. Cell death pathways in photodynamic therapy of tumors // Cancers. – 2011. – Vol. 3. – P. 2516–2539.
4. Weiss A., den Bergh H.V., Griffioen A.W. Angiogenesis inhibition for the improvement of photodynamic therapy: The revival of a promising idea // Biochim. Biophys. Acta. – 2012. – Vol. 1826. – P. 53–70.
5. Sharma K.V., Bowers N., Davids L.M. Photodynamic therapy-induced killing is enhanced in depigmented metastatic melanoma cells // Cell Biol. Int. – 2011. – Vol. 35. – P. 939–949.
6. Sparsa A., Bellaton S., Naves T., et al. Photodynamic treatment induces cell death by apoptosis or autophagy depending on the

7. Chang C.J., Yu J.S., Wei F.C. In vitro and In vivo photosensitizing applications of photofrin in malignant melanoma cells, *Chang Gung Med. J.*, 2008, vol. 31, pp. 260–267.

melanin content in two B16 melanoma cell lines // Oncol. Rep. – 2013. – Vol. 29. – P. 1196–1200.
7. Chang C.J., Yu J.S., Wei F.C. In vitro and In vivo photosensitizing applications of photofrin in malignant melanoma cells // Chang Gung Med. J. – 2008. – Vol. 31. – P. 260–267.