CASE REPORTS

PHOTODYNAMIC THERAPY FOR FACIAL SKIN CANCER DEVELOPED IN THE ZONE OF PREVIOUS RADIOTHERAPY (CLINICAL CASE)

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Abstract

The results of a 13-year clinical observation of a patient after treatment for basal cell carcinoma of the skin of the right cheek Ist cT1N0M0 are presented. The history of the course of the disease is associated with the fact that the patient underwent radiation therapy in early childhood for hemangioma of the lower eyelid of the right eye and right cheek. In 2008, against the background of post-radiation changes in the area of the right cheek, basal cell carcinoma was diagnosed at the Moscow Oncological Research Institute. P.A. Herzen. At the Center for Laser and Photodynamic Diagnostics and Tumor Therapy, the patient underwent organ-preserving PDT treatment. A course of photodynamic therapy (PDT) with 5-aminolevulic acid was carried out. Subsequently, the patient was followed up until 2021 without relapse in the PDT area. In 2016, the patient was diagnosed with a relapse of the disease in the form of a new focus of basal cell carcinoma of the upper eyelid skin on the right Iast cT1N0M0. The patient underwent a course of PDT with a chlorin e6-based photosensitizer. Complete regression of the tumor was achieved, the period of relapse-free follow-up was 5 years.

Keywords: basal cell skin cancer, photodynamic therapy, radiation therapy, photosensitizer, chlorin e6, 5-aminolevulinic acid, induced cancer.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРИ РАКЕ КОЖИ ЛИЦА, РАЗВИВШЕГОСЯ В ЗОНЕ ПРЕДШЕСТВУЮЩЕЙ ЛУЧЕВОЙ ТЕРАПИИ (КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ)

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Резюме

Приведены результаты 13-летнего клинического наблюдения пациентки после лечения базальноклеточного рака кожи правой щеки I ст cT2N0M0. Анамнез заболевания связан с тем, что пациентке в раннем детстве по поводу гемангиомы нижнего века правого глаза и правой щеки выполнена лучевая терапия. В 2008 г., на фоне постлучевых изменений в области правой щеки, диагностирован базальноклеточный рак в МНИОИ им. П.А. Герцена. В Центре лазерной и фотодинамической диагностики и терапии опухолей пациентке проведено органосохраняющее лечение методом ФДТ. Проведен курс фотодинамической терапии (ФДТ) с 5-аминолевульновой кислотой. В последующем больная наблюдалась 13 лет без рецидива в зоне ФДТ. В 2016 г у пациентки диагностирован рецидив заболевания в виде нового очага базальноклеточного рака кожи верхнего века справа IA ст cT1N0M0. Пациентке проведен курс ФДТ с фотосенсибилизатором на основе хлорина е6. Достигнута полная регрессия опухоли, срок безрецидивного наблюдения – 5 лет.

Ключевые слова: базальноклеточный рак кожи, фотодинамическая терапия, лучевая терапия, фотосенсибилизатор, хлорин е6, 5-аминолевулиновая кислота, индуцированный рак.

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Introduction

Photodynamic therapy (PDT) is a method of antitumor therapy successfully used in clinical practice. In several decades of its use in Russia, the method has proven to be effective and safe for the treatment of patients with cancer of various localizations. PDT is used for malignant neoplasms of the skin, genitourinary system organs, gastrointestinal tract, brain, bronchi, and other nosologies [1-3]. In recent years, the range of indications for the use of the method has been constantly expanding, and new effective photosensitizers and PDT methods have appeared [4-6].

Clinical example

We present a clinical observation of the treatment of a patient with a diagnosis of primary multiple metachronous cancer: 1) basal cell skin cancer (BCSC) of the right cheek, I degree, cT2N0M0, the condition after PDT in 2008; 2) BCSC of the upper eyelid of the right eye IA deg. cT1N0M0, the condition after PDT in 2016.

In 1991, patient Sh., DOB: 1986, aged 5, underwent radiation therapy in connection with a hemangioma of the right cheek spreading to the lower eyelid of the right eye, at Helmholtz Moscow Research Institute of Eye Diseases.

In 2008, the patient noted a lesion on the skin of the right cheek in the area of previous treatment, and applied independently to P. A. Hertsen Moscow Oncology Research Center. When examined, the patient was found to have, against the background of post-radiation skin changes, an area of superficial tumor infiltration of the skin with fuzzy borders, with a maximum size of 2.3 cm (Fig. 1a). A cytological study of the lesion was performed, and BCSC was diagnosed. The patient was discussed at an extended medical board, and PDT was recommended.

In May 2008, the patient underwent a course of PDT with a drug based on 5-aminolevulinic acid. The patient tolerated treatment satisfactorily, without complications. Complete regression of the tumor was achieved after one course of PDT (Fig. 1c). Subsequently, the patient was observed without tumor recurrence in the treatment area with periodic confirmation of the achieved effect by control cytological studies from the PDT zone (Fig. 1d; 2c, d).

In September 2015, the patient noted the appearance of a lesion on the skin of the upper eyelid of the right eye; a biopsy of the tumor mass was performed in the ophthalmological clinic; BCSC was diagnosed according to the histological test. In December 2015, the patient independently applied to P. A. Hertsen Moscow Oncology Research Center. During examination, a trace from the tumor biopsy and a tumor infiltration of the skin of the upper eyelid is visualized in the upper eyelid area. The data of the revision of histology slides No. 51232/15 showed the presence of BCSC (Fig. 2a). The patient was discussed at a medical board, and PDT of the skin tumor on the upper eyelid of the right eye was recommended.

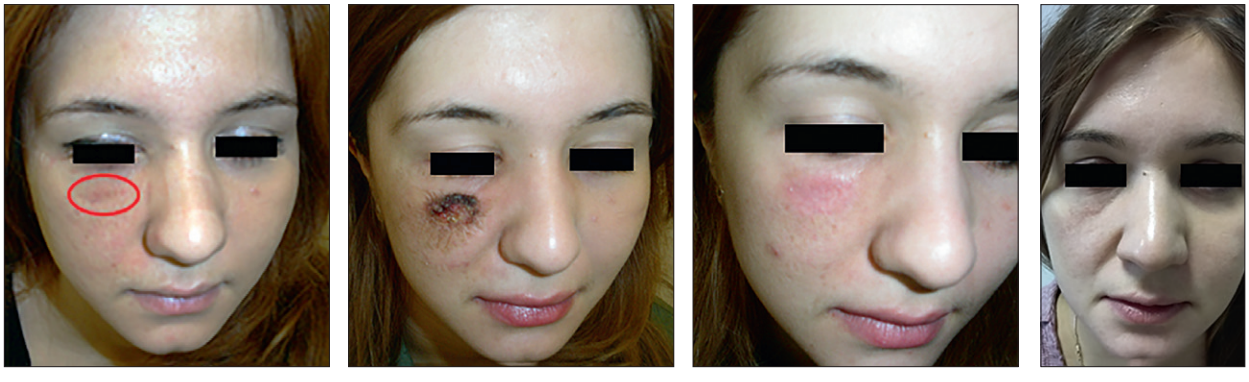

Рис. 1. Лечение БКРК правой щеки:
a – опухоль правой щеки до лечения;
b – некроз опухоли через неделю после ФДТ;
c – полная регрессия опухоли через месяц после ФДТ;
d – состояние без рецидива после лечения через 6 лет после ФДТ (2014 г.)

Fig. 1. Treatment of basal cell carcinoma of the skin of the right cheek:
a – tumor of the right cheek before treatment;
b – tumor necrosis a week after PDT;
c – complete tumor regression one month after PDT;
d – condition without relapse after treatment 6 years after PDT (2014)

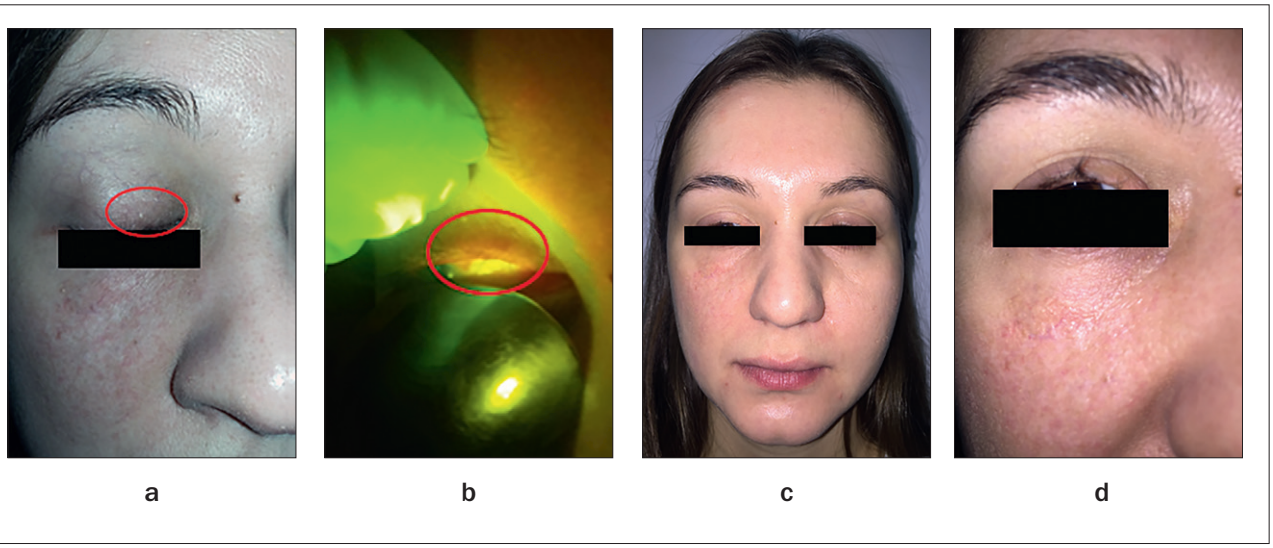

Рис. 2. Лечение БКРК верхнего века правого глаза:
а – опухоль до ФДТ (после биопсии);
б – флуоресценция опухоли при проведении ФД (определение границ опухоли);
в, г – полная регрессия опухоли верхнего века справа через 1 год после ФДТ, состояние без рецидива опухоли правой щеки через 9 лет после ФДТ (2017 г.)

Fig. 2. Treatment of basal cell skin cancer of the upper eyelid of the right eye:
a – tumor before PDT (after biopsy);
b – tumor fluorescence during PD (definition of tumor boundaries);
c, d – complete regression of the tumor of the upper eyelid on the right 1 year after PDT, condition without tumor recurrence in the right cheek 9 years after PDT (2017)

On 26.01.2016, a course of PDT with chlorin e6 as photosensitizer was performed on the skin tumor of the upper eyelid of the right eye. Before the laser irradiation session, a fluorescence diagnostics (FD) session was performed. The boundaries of the upper eyelid tumor were evaluated for planning radiation fields (Fig. 2b), and other skin areas were examined, including the area of scarring after PDT of the tumor on the right cheek. No additional areas of increased fluorescence were detected. A laser irradiation session was performed with due account for the boundaries of the tumor lesion determined by the results of FD. The patient tolerated treatment well, without complications. Complete regression of the tumor was achieved (Fig. 2c, d). The patient has had follow-up monitoring and has been found relapse-free after PDT in the area of tumor treatment on the upper eyelid on the right eye for 5 years, and on the right cheek, for 13 years.

Discussion

The patient was diagnosed with two foci of skin cancer in areas that were located either directly in the radiation exposure zones or along the edge of the irradiation zone 22 years and 29 years after radiation therapy for a benign skin pathology. Is it possible to see the development of these foci of skin cancer as a consequence of previous radiation therapy?

One of the most significant effects of radiation therapy (RT) on normal tissues is mutagenesis, which is the basis for the development of radiation-induced malignant neoplasms. Radiation-induced malignant neoplasms are late complications that occur after RT, the frequency of which increases among survivors, including both children and adults [7].

There are three main criteria by which malignant neoplasms are classified as RT-induced: the occurrence at the site of previous irradiation, a latent period of at least 2 years after the start of RT, and a histology different from the primary tumor (if present) [8-10].

Friedman D. L. et al. (2010) conducted a retrospective study to evaluate the frequency of the development of second primary multiple neoplasms in survivors of childhood cancer [11]. Of the 14,359 patients with a 5-year overall survival, 1,402 subsequently developed 2703 neoplasms. Cumulative incidence at 30 years after the childhood cancer diagnosis was 20.5% for all subsequent neoplasms, including 7.9% for second malignant neoplasms (excluding nonmelanoma skin cancer), 9.1% for nonmelanoma skin cancer, and 3.1% for meningioma. The association of RT with an increased risk of developing second neoplasms was proved by the authors by use of multivariable Poisson regression. Cumulative incidence at 30 years after childhood cancer diagnosis was 20.5% for

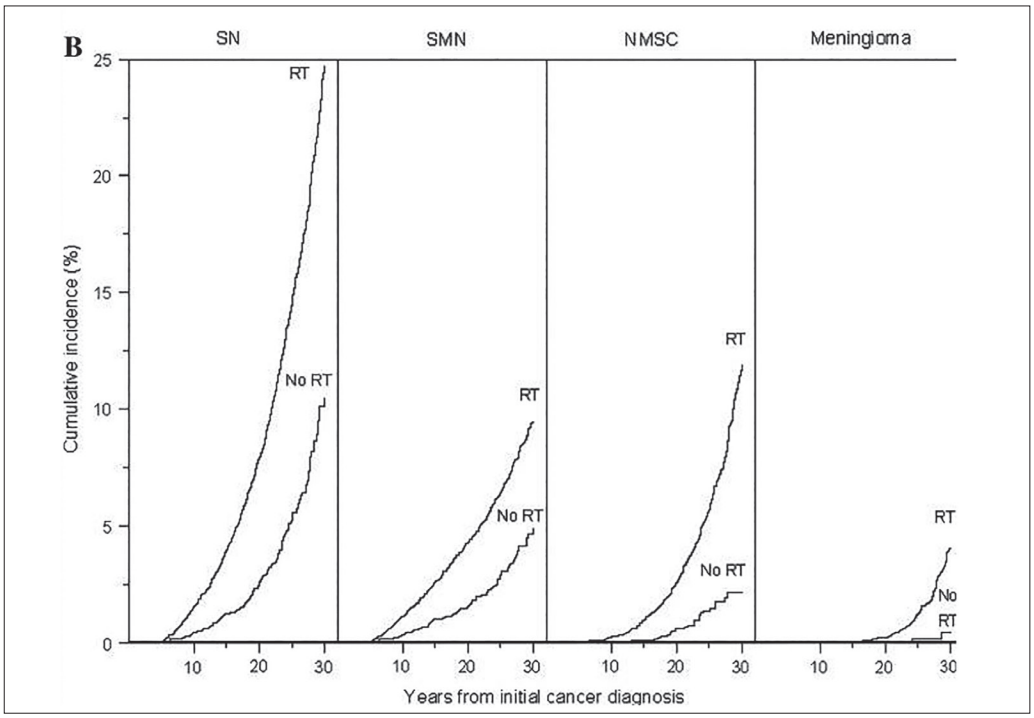

Рис. 3. Кумулятивная частота вторых новообразований через 30 лет после первого рака у пациентов с ЛТ и без ЛТ (Friedman D.L. и соавт., 2010 [11]); RT – ЛТ; No RT – без ЛТ; SN – второе новообразование (доброкачественное или злокачественное); SMN – второе злокачественное новообразование; NMSC – немеланомный рак кожи
Fig. 3. Cumulative incidence of second neoplasms (SNs) at 30 years after initial cancer diagnosis, stratified by radiation therapy (RT) treatment or no RT (Friedman D.L. et al., 2010 [11]); SN – second neoplasm; SNM – second malignant neoplasm; NMSC – nonmelanoma skin cancer

all first of the subsequent neoplasms and was higher for patients treated with radiation therapy for their primary cancer than for those not receiving radiation therapy (Fig. 3). The results of the study showed that RT increased the risk of any subsequent neoplasm by 2.7 times. The analysis confirmed that the effect of RT was associated with an increased risk of second tumors of the central nervous system, soft tissue and bone sarcomas, as well as thyroid cancer [11].

After the brain is included in the irradiation zone, the most common RT-induced second tumors are neoplasms of the central nervous system. For instance, in 1991 Neglia J. P. et al. [12] conducted a retrospective study including 9720 children who had previously been diagnosed with acute lymphoblastic leukemia and who were treated in accordance with the therapeutic protocols of the Children's Cancer Research Group using radiation of the cranial and craniospinal zones. The average follow-up time was 4.7 years (from 2 months to 16 years). The authors found that 43 second neoplasms occurred in the children included in the study, including 24 (55.8%) had neoplasms of the central nervous system (14 patients with high-grade astrocytoma and glioblastoma multiforme, 3 with primitive neuroectodermal tumor, 2 with meningioma, 2 with astrocytoma or low-grade glioma, 1 with medulloblastoma, 1 with brain stem glioma, 1 with ependymoma), 10 (23.3%) new leukemias and lymphomas (6 patients had non-Hodgkin's lymphoma, 2 – acute non-lymphoblastic leukemia, 1 – immunoblastic sarcoma, 1 – Hodgkin's disease) and 9 (20.9%) had other neoplasms (3 cases of thyroid cancer, 2 cases of mucoepidermoid carcinoma of the parotid gland, 1 of dysgerminoma, 1 of melanoma, 1 of ganglioneuroblastoma, 1 of leiomyosarcoma of the ileum). The authors point out that these figures represent a 7-fold excess of all cancers and a 22-fold excess of neoplasms of the central nervous system compared to the general population of this age. All neoplasms of the central nervous system occurred in children who had previously undergone radiation therapy. There was no association with the effects of cyclophosphamide or anthracyclines. This proves the inducing effect of RT on the development of tumors of the central nervous system [12].

In their study, Armstrong G. T. et al. (2011) analyzed the incidence of primary multiple metachronous malignancies in patients who had treatment for childhood cancer [13]. Of the 14,358 childhood cancer survivors, 1382 (9.6%) patients were diagnosed

with one metachronous multiple primary tumor. Of these, 386 (27.9%) patients, after treatment of their tumors, subsequently developed other metachronous primary multiple tumors. At the same time, among patients with a subsequent repeated metachronous tumor, 153 (39.6%) were diagnosed with more than two metachronous primary multiple tumors. The cumulative incidence of repeated primary multiple metachronous tumors 20 years after the diagnosis of the first primary multiple metachronous tumor was 38.8%. At the same time, the cumulative frequency of repeated primary multiple metachronous tumors in the group of patients who survived RT of the first cancer was 41.3% after 15 years, compared with 25.7% for patients who did not receive RT [13].

The study by Travis L. B. et al. (2003) presents the results on the association of RT with the development of second tumors in patients with Hodgkin's disease [14]. Hodgkin's disease usually affects cervical and mediastinal lymph nodes, and classical RT in Hodgkin's disease targets the areas of the lymph nodes, which leads to irradiation of the breast and lung tissues. The authors showed that the risk of breast cancer after RT+CT in Hodgkin's disease depends on the radiation dose, while a dose of 4 Gy or more is associated with a 3.2-fold increase in risk compared to patients receiving lower doses, and the risk increases up to eight times at doses of more than 40 Gy. The authors conclude that the risk of breast cancer after CT+RT seems to be primarily associated with RT, since treatment with alkylating agents alone led to a decrease in the risk of developing breast cancer. The probability of developing breast cancer decreased with an increase in the number of cycles of alkylating agents and a reduction in the use of RT in these patients [14].

A review by Braunstein S. et al. (2013) presents data on the frequency of second tumor development after RT of primary neoplasms of various localization. The authors point to an increased risk of developing RT-induced tumors after irradiation of the pelvic organs and abdominal cavity. Thus, patients after RT of testicular cancer are at an increased risk of developing RT-induced tumors of the intestinal and genitourinary tracts, and patients after RT of cervical and endometrial cancer are at an increased risk of a second cancer of the colon and rectum, bladder and genitals. People who have survived prostate cancer are also at risk of developing radiation-induced tumors, which is especially important, given that these patients usually receive treatment at a much older age than patients with testicular or cervical cancer. A study of men with prostate cancer treated in the period from 1988 to 2003 showed that the relative risk of developing a second bladder cancer is 1.88 for patients who received remote RT, compared with prostatectomy. Patients after RT of head and neck cancer are at an increased risk of developing RT-induced tumors in the head and neck, esophagus or lungs, with 15% probability of occurrence of an RT-induced tumor within 5 years [7].

The most common type of induced skin cancer in patients after RT is BCSC [15]. At the same time, RT-induced BCSC usually occurs with the use of low and moderate doses of radiation, e. g., when RT is used for the treatment of pathology other than malignant neoplasms: shingles, hypertrophic tonsillitis, common acne, atopic dermatitis, and hyperthyroidism. There is evidence indicating that squamous cell skin cancer (SCSC) develops more often after higher doses of radiation [10, 16-18].

There are both radiation-dependent and independent risk factors for developing RT-induced skin cancer. Radiation-dependent risk factors include a higher total radiation dose, the RT technique (two-dimensional conformal RT > RT with intensity modulation > 3-dimensional conformal RT > proton therapy), increased sensibility to ultraviolet light / lighter skin type and a younger age during radiation exposure. Risk factors that do not depend on radiation include genetic predisposition to malignant neoplasms, lifestyle aspects (alcohol, tobacco, and medications) and exposure to other carcinogens [8].

The development of RT-induced malignant neoplasms is characterized by a number of features. Thus, carcinogenesis in this case is induced by fairly low levels of radiation doses, and the risk increases with the dose. At higher radiation doses (as well as when exposed to sunlight on previously irradiated areas), the duration of the latency period is significantly lower [7, 10]. The second feature is the fact that young age during exposure to RT is a risk factor for carcinogenesis [7, 19, 20]. There are also indications that the incubation period between exposure to ionizing radiation and the appearance of BCSC symptoms is shorter in young patients [10]. Another feature is that the development of RT-induced tumors is characterized by a long latency period, which is usually several years, but can be decades [7]. The literature describes cases of induced skin cancer 2 to 65 years after radiation therapy. Most often, according to literary data, this period is 20-45 years [10]. Finally, although BCSC is usually characterized by slow growth, minimal invasiveness into the underlying tissues and high cure rates, RT-induced BCSC tends to be more aggressive and more prone to relapses [19, 21, 22].

There are few studies describing the molecular mechanism underlying the pathogenesis of aggressive radiation-induced BCSC [19]. A few years ago, Boaventura P. et al. found that the frequency of the D-Loop D310 mitochondrial mutation was associated with a higher radiation dose, although the role of this

mutation in the development of BCSC in children has yet to be shown [23].

Previously, indications for the clinical use of radiation therapy included various benign conditions, for example, rheumatological, dermatological, and infectious diseases. This is an important context in which late radiation effects can be identified, because, unlike malignant diseases, the long survival of these patients allows us to track radiation-induced malignant neoplasms with a long latent period [7].

Before the advent of antifungal drugs in the 1950s, X-ray irradiation was widely used for the treatment of shingles. It is estimated that about 200,000 children worldwide have received X-ray treatment for this disease [19]. The first study of the long-term effects of RT in dermatomycosis on the head was reported by Albert R. E. et al. in 1968. Among 2,043 children treated at the New York University Hospital, 14 cases of malignant tumors were detected, 7 of which were cases of BCSC [19, 24]. A subsequent study involving 2,215 patients, the results of which were published in 1976, confirmed that RT in children with shingles infection on the head was associated with an increased risk of skin cancer (including BCSC), as well as malignant neoplasms of the brain, parotid gland, bones, and thyroid gland. In all subsequent studies, BCSC was the main type of skin cancer affected by therapeutic radiation, while the frequency of SCSC and melanoma did not change significantly. The treated patients had a high prevalence of multiple forms of BCSC, most of which were of the nodular type [19, 25].

In the study of Shore R. E. et al., 2224 children who received RT for dermatomycosis on the head (ringworm of the scalp) were observed for 50 years to determine the incidence of cancer. The control group consisted of 1380 patients with shingles of the scalp who received only topical medications. The study assessed the relative risk of developing BCSC during irradiation of the scalp as the ratio of the probability of developing BCSC in the group exposed to RT to the probability of its development in the unexposed group. BCSC developed in 124 patients in the group that had RT, and in 21 patients in the group without RT. Thus, with scalp irradiation at a total dose of 4.8 Gy, the relative risk of developing BCSC was 3.6. Cases of the development of melanoma of scalp and neck were not observed, isolated cases of SCSC were registered. Among patients with BCSC, about 40% had multiple forms. The study also showed that the level of risk for developing BCSC is approximately constant over time from the moment of exposure, which suggests that the risk is likely to persist throughout life [20].

In a multicenter retrospective study by Ron E. et al., it was shown that CT of the scalp in children with dermatomycosis led to a four-fold increase in the incidence of skin cancer, primarily BCSC, and to a threefold increase in the incidence of benign skin tumors. However, as in previous studies, the risk of developing malignant melanoma in such patients was not increased [26].

Maalej M. et al. reported on 98 patients who developed RT-induced cancer of the scalp after irradiation in childhood for shingles, including 81 (82%) patients who had only one RT session. In 98 patients, 150 foci of malignant neoplasms were registered, 125 of which were BCSC, 16 SCSC, 2 malignant non-Hodgkin's lymphomas, 4 foci of melanoma, and 3 other tumors. The period from RT to the development of skin cancer averaged 36±14 years [15].

The study by Mseddi M. et al. describes 33 patients with BCSC induced by previous RT of shingles foci. The latency period was 21-51 years [27].

Currently, a significant group of patients with RT-induced skin malignancies are patients who have undergone radiation for oncological diseases in childhood. Thus, the study of Watt T. C. et al. showed the connection between eadiation therapy and an increased risk of developing BCSC. The study included 199 childhood cancer survivors, who subsequently developed BCSC. The comparison group consisted of 597 childhood cancer survivors without BCSC. This study revealed a dose-response relationship showing an increase in the incidence risk ratio with a coefficient of 1.09 per 1 Gy. Thus, in patients who received a dose of 35 Gy, the risk of developing BCSC was 39.8 times higher than in survivors who did not receive radiation therapy [28].

Over 40 years of the use of hematopoietic cell transplantation, another large cohort of patients who have undergone RT and have high risks of developing induced malignant neoplasms has appeared. In these patients, an increased frequency of malignant neoplasms was detected, the most frequent being BCSC [19]. Many of the patients undergo preliminary total irradiation of the entire body as a preparation for hematopoietic cell transplantation. Leisenring W. et al. reported that the use of a regime with total body irradiation was a significant risk factor for the development of BCSC, but not for SCSC, in a study involving 4,810 survivors with allogeneic hematopoietic cell transplantation who received treatment between 1969 and 2003. A single or fractional dose of 14 Gy significantly increased the frequency of BCSC: more than 1.8 times compared to regimens without total irradiation [29]. Schwartz J. L. et al. present the results of a study in which the risks of developing BCSC were assessed in 6306 patients treated with hematopoietic cell transplantation with or without total body irradiation, and reported that the overall relative risk of developing BCSC was 1.76 in patients with total irra-

diation who were exposed to prescribed radiation doses from 7.5 to 18.4 Gy. The risk of developing BCSC was highest in patients exposed at the age of under 10 years, and decreased by 10.9% per year for patients older than 10 years. There was no increased risk of developing BCSC associated with total whole-body irradiation for patients over the age of 40 years during hematopoietic cell transplantation [30].

The authors of all the described studies indicate the need for careful monitoring of patients with a history of RT. Unfortunately, as already noted, RT-induced BCSC tends to be more aggressive, more difficult to treat, and more prone to relapses than sporadic lesions. Patients with a history of RT are recommended to undergo regular lifelong examination of the irradiated areas. Moreover, it is very important to inform patients that they should contact their doctor in case of any suspicious lesions.

Conclusion

This clinical observation demonstrates the importance of follow-up monitoring of cured cancer patients even after the completion of a 5-year relapse-free period. The patient developed a skin tumor 8 years after radical PDT of another skin tumor. It is only regular observation by an oncologist that makes it possible to diagnose the second tumor at an early stage, when photodynamic therapy, an organ-preserving method with a high cosmetic effect, can be applied.

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