ORIGINAL ARTICLES

INFLUENCE OF PHOTODYNAMIC THERAPY ON THE LEVEL OF MATRIX METALLOPROTEINASES IN SQUAMOUS CELL SKIN CANCER

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Abstract

The effect of photodynamic therapy (PDT) on the level of matrix metalloproteinases in squamous cell skin cancer (SCSC) was studied. The study involved 202 people, including 185 patients with SCSC, who were on outpatient and inpatient treatment in medical institutions of Engels and Saratov during the period from 2015 to 2019, and 17 donors. The study design included studies in three main groups. The first (intervention) group included 74 (36.6%) patients with SCSC who underwent combined treatment, including PDT at the first stage and surgical treatment at the second stage. The second group consisted of 111 (55.0%) patients with SCSC who underwent only surgical treatment. The third group consisted of 17 (8.4%) relatively healthy volunteer donors, comparable in age and sex with the patients of the main group. As a result of the study, it was found that the level of metalloproteinase-1 inhibitor (TIMP-1) in the blood serum of patients with SCSC was reduced compared with physiologically normal indicators, which led to a statistically significant increase in matrix metalloproteinases (MMPs) MMPs-2, MMPs-7 and MMPs-9. Performing only surgical treatment for this pathology does not lead to a complete recovery of these indicators. However, the use of combined treatment including PDT showed a statistically significant increase in the amount of TIMP-1 before the start of surgical treatment, which naturally led to a decrease in MMPs-2, MMPs-7 and MMPs-9. Later, after excision of the tumor, the patients of this group had a complete normalization of TIMP-1, which, in turn, contributed to a decrease and then restoration of the number of MMPs-2, MMPs-7 and MMPs-9 to physiologically normal values.

Keywords: Squamous cell skin cancer, photodynamic therapy, metalloproteinases.

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ВЛИЯНИЕ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ НА УРОВЕНЬ МАТРИКСНЫХ МЕТАЛЛОПРОТЕИНАЗ ПРИ ПЛОСКОКЛЕТОЧНОМ РАКЕ КОЖИ

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Резюме

Изучено влияние фотодинамической терапии (ФДТ) на уровень матриксных металлопротеиназ при плоскоклеточном раке кожи (ПКРК). В исследовании участвовали 202 человека, из них 185 пациентов с ПКРК, находившихся на амбулаторном и стационарном лечении в лечебных учреждениях г. Энгельса и г. Саратова в период с 2015 по 2019 гг., и 17 доноров. Дизайн исследования включал в себя исследования в трех группах. В первую (основную) группу пациентов вошли 74 (36,6%) больных ПКРК, которым было проведено комбинированное лечение, включающее на первом этапе ФДТ, на втором – хирургическое лечение. Вторую группу составили

111 (55,0%) больных ПКРК, которым было выполнено только хирургическое лечение. Третья группа состояла из 17 (8,4%) относительно здоровых доноров-добровольцев, сопоставимых по возрасту и полу с пациентами основной группы. В результате проведенного исследования было установлено, что уровень ингибитора металлопротеиназы-1 (TIMP-1) в сыворотке крове у пациентов с ПКРК понижен по сравнению с физиологически нормальными показателями, что приводило к статистически достоверному повышению показателей матричных металлопротеиназ (MMPs): MMPs-2, MMPs-7 и MMPs-9. Выполнение только хирургического лечения при ПКРК не приводит к полному восстановлению данных показателей. Однако применение комбинированного лечения, включающего ФДТ, позволило уже до начала хирургического этапа статистически достоверно увеличить количество TIMP-1, что закономерно приводило к снижению уровня MMPs-2, MMPs-7 и MMPs-9. После иссечения опухоли у пациентов этой группы установлена полная нормализация TIMP-1, что, в свою очередь, способствовало снижению, а затем восстановлению количества MMPs-2, MMPs-7 и MMPs-9 до физиологически нормальных значений.

Ключевые слова: плоскоклеточный рак кожи, фотодинамическая терапия, металлопротеиназы.

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Introduction

Squamous cell skin cancer (SCSC) accounts for about 20% of all malignant skin diseases [1, 2, 3]. SCSC is the most malignant epithelial tumor of the skin and mucous membranes with squamous differentiation that develops from keratinocytes [4]. SCSC is characterized by a destructive growth pattern with a gradual progression of the tumor process, infiltration of underlying tissues, metastasis to regional and distant lymph nodes (85%), hematogenous metastasis to internal organs (15%), such as lungs and bones, which can lead to the death of the patient [5]. Currently, various methods of treating this pathology have been proposed, including surgical resection of the tumor, radiation therapy, cryosurgery, laser excision, and the use of photodynamic therapy (PDT).

The PDT method is one of the modern methods of treatment in oncology. PDT is a minimally invasive and effective treatment for SCSC based on the use of photodynamic damage to tumor cells during photochemical reactions [6, 7]. After the introduction of a special substance, a photosensitizer, into the body, the photosensitized tissue is irradiated with a laser with a certain wavelength [8-10]. The results presented in the literature indicate that PDT is an effective organ-preserving method for the treatment of malignant neoplasms of the skin and mucous membranes, especially with unfavorable localization of neoplasms and in cases where the possibilities of traditional methods are limited. It has been established that complete resorption of the tumor can be achieved with a single or staged exposure without the development of side effects with maximum preservation of the viability of surrounding healthy tissues [1]. According to the literature, metalloproteinases (MMPs) are of great importance in the prognosis and mechanism of skin cancer development [11]. An analysis of the literature has shown that the effect of PDT on the change in the level of MMPs in SCSC is currently insufficiently studied. In the present study, the effect of PDT on changes in the level of MMPs in SCSC was studied.

Materials and methods

The study involved 202 people, of which 185 patients with SCSC were on outpatient and inpatient treatment in medical institutions in Engels and Saratov cities in the period from 2015 to 2019, and 17 healthy volunteers. Of the total number of patients, there were 129 (69.7%) men and 56 (30.3%) women. Based on the analysis of the localization of SCSC by anatomical regions, it was found that in 25% of cases the tumor was localized in the lower extremities, in the face – in 15%, in the region of various parts of the upper extremities – in 20%, in the neck – in 18% , in different parts of the chest – in 12% of cases, in 10% of cases, the tumor occupied various anatomical regions of the back. The diagnosis of SCSC was based on the collection of anamnestic data, complaints made by patients, and morphological examination. For morphological examination, a biopsy of the tumor tissue was performed, after receiving the result, the final diagnosis was established.

The research program included studies in three main groups. The first included 74 (36.6%) patients who underwent combined treatment: PDT and surgery, including wide excision of the tumor under intravenous anesthesia. The second group consisted of 111 (55.0%) patients with SCSC who underwent only surgical treatment. To control and compare the obtained laboratory parameters, a third group was created, which included 17 (8.4%) donors without established oncological pathology, who voluntarily agreed to participate in the study.

Patients included in group 1 had disease stage T1N0M0 in 25 (33.8%) cases, stage T2N0M0 – in 49 (66.2%) cases. In group 2, patients had disease stages T1N0M0 and T2N0M0 in 26 (23.4%) and 85 (76.6%) cases, respectively. Based on the analysis of the morphological findings, it was found that in 16% of cases, the spindle cell form of SCSC was noted, in the remaining 84%, the acantholytic form.

In all patients of groups 1 and 2, risk factors for de-

veloping cancer were identified in the analysis of anamnesis data (Table 1).

Comorbidity was detected in 98 (52.7%) patients with SCSC, including 43 (23.4%) patients in group 2, 55 (29.7%) patients in group 1, whose patients underwent preoperative PDT. The number of patients and the nature of comorbidities are presented in Table 2.

The study included patients with stage T1-2N0M0 SCSC. Patients with disseminated oncological process and patients who underwent radiation and/or chemotherapy were not included.

The studies were carried out after clarifying its purpose and objectives and obtaining permission from patients to participate in the study, which was confirmed by written consent. The study plan was heard at the local ethics committee of the Reaviz Medical University, where it received permission and approval (protocol No. 12 of November 16, 2020).

Treatment of patients in group 1 was carried out in several stages. At the first stage, PDT was performed. Photolon, manufactured by Belmedpreparaty (Republic of Belarus), was used as a photosensitizer. Photolon was

Таблица 1
Факторы риска развития рака у больных плоскоклеточным раком кожи
Table 1
Risk factors for cancer development in patients with squamous cell skin cancer

Факторы риска Risk factors	Число пациентов в группах Number of patients in groups			
	Группа 1 Group 1 (n = 74)		Группа 2 Group 2 (n = 111)	
	абс. число absolute number	%	абс. число absolute number	%
Воздействие вредных производственных факторов Exposure to occupational hazards	47	63,5	22	19,8
Генетическая предрасположенность Genetic predisposition	25	33,8	88	79,3
Курение табака Tobacco smoking	50	67,6	52	46,8

Таблица 2
Структура сопутствующей патологии у пациентов с плоскоклеточным раком кожи
Table 2
Structure of comorbidity in patients with squamous cell skin cancer

Нозологическая форма сопутствующей патологии Nosological form of concomitant pathology	Количество пациентов в группах Number of patients in groups	
	Группа 1 Group 1 (n = 74)	Группа 2 Group 2 (n = 111)
Артериальная гипертензия Arterial hypertension	12 (16,2%)	14 (12,6%)
Ишемическая болезнь сердца Coronary heart disease	11 (14,9%)	12 (10,8%)
Ожирение различной степени Various degrees of obesity	9 (12,2%)	11 (9,9%)
Эрозивный гастрит Erosive gastritis	16 (21,6%)	5 (4,5%)
Хронический холецистит Chronic cholecystitis	7 (9,4%)	1 (0,9%)
Всего Total	55 (74,3%)	43 (38,7%)

injected intravenously at a dose of 2.0 mg/kg of body weight in 200 ml of natural saline solution, the administration time took about 30 minutes. At the same time, laser irradiation of blood was performed using a krypton laser having a wavelength of 647-675 nm, with a power density of 120-300 mW. 3-4 hours after the end of intravenous injection, a session of local irradiation of the tumor was performed, for this, a Latus laser device (λ–662 nm, E = 300 J/cm2) was used. Performed 3 courses of PDT (introduction of a photosensitizer and irradiation) for 3 days. 5 days after the end of the third course of PDT, patients in this group underwent surgery.

In the course of the study, the levels of the inhibitor of metalloproteinase-1 (TIMP-1), matrix metalloproteinases (MMPs): MMPs-2, MMPs-7, MMPs-9 in the blood serum were determined before the start of PDT in group 1, in group 2 – before surgical removal of the tumor. Then these indicators were determined in group 1 on the fifth day after the end of PDT and before the surgical stage. In the postoperative period, in both groups, the sampling of biological material (blood plasma) was carried out on the first, third, fifth, seventh, tenth days and after 18 months. Blood sampling and analysis of indicators in the comparison group (group 3) was carried out once.

The level of TIMP-1 was determined by enzyme immunoassay using R&D Diagnostics Inc. (USA) reagents. This method determines the quantitative content of the test substance in a biological substrate by combining the substance with antibodies. Quantitative determination of MMPs in blood serum was performed using Human/Mouse/Rat (total) sera from Quantikine®, R&D Systems, which are standard and designed for direct enzyme immunoassay. For measurements, an automatic universal reader ELX800 from Bio-TekInstruments, Inc. (USA) was used, designed for microplates.

The results obtained during the study were subjected to mathematical processing on a personal computer with the Statistica 6.0 application package, as well as Excel. Hypotheses about the type of distributions were tested (Shapiro-Wilks test). Most of our data do not follow the normal distribution law, therefore, to compare the values, the Mann-Whitney U-test was used, on the basis of which the Z-test and the significance indicator p were calculated. The differences were considered statistically significant at $p < 0.05$. In addition, the Spearman rank correlation coefficient (R) and its reliability index p were calculated.

Results

It has been proven that in the process of carcinogenesis, including skin lesions, changes in the levels of TIMP-1 and MMPs occur [11]. In order to clarify the nature of the change in these indicators, the parameters were studied in all 185 patients who participated in the study, before the start of treatment (initial background) and during subsequent follow-up (see Table 3).

Before the start of treatment in both groups, there was a statistically significant decrease in the amount of TIMP-1 and an increase in the level of MMPs in the blood serum.

The use of PDT before performing surgical treatment for SCSC (group 1) leads to a statistically significant increase in the amount of TIMP-1 and a regular decrease in the concentration of MMPs-2, MMPs-7 and MMPs-9. This is confirmed by the fact that in the group of patients subjected to only surgical treatment, a statistically significant decrease in the TIMP-1 index was revealed, and, as a result, an increase in all MMPs indices in comparison with the results obtained in donors and patients who received combined treatment. Clearly, SCSC leads to changes in levels of TIMP-1 and MMPs-2, MMPs-7 and MMPs-9. There were no significant statistically significant differences in the studied parameters in patients with stage T1-2N0M0 SCSC.

On the first postoperative day in patients of group II, a statistically significant decrease in TIMP-1 to 436.4 ng/ml and an increase in all studied MMPs parameters were registered compared to the data obtained from donors.

Таблица 3
Динамика изменения уровня TIMP-1 и MMPs в сыворотке крови у пациентов с плоскоклеточным раком кожи после лечения
Table 3
Dynamics of changes in the level of TIMP-1 and MMPs in blood serum in patients with squamous cell skin cancer after treatment

Исследуемые показатели Researched indicators	Уровень TIMP-1 и MMPs, нг/мл Level of TIMP-1 and MMPs, ng/ml		
	группа 1 ФДТ + операция group 1 PDT + surgery (n=74)	группа 2 операция group 2 surgery (n=111)	группа 3 доноры group 3 donors (n=17)
до начала лечения (исходный фон) before treatment (initial background)			
TIMP-1	573 (526;742) $p_2 = 0,038$ $p_3 = 0,045$	567,3 (557;684) $p_1 = 0,032$ $p_3 = 0,025$	789 (771;793)

Исследуемые показатели Researched indicators	Уровень TIMP-1 и MMPs, нг/мл Level of TIMP-1 and MMPs, ng/ml		
	группа 1 ФДТ + операция group 1 PDT + surgery (n=74)	группа 2 операция group 2 surgery (n=111)	группа 3 доноры group 3 donors (n=17)
MMPs-2	612 (510;627) $p_2 = 0,032$ $p_3 = 0,045$	616 (598;627) $p_1 = 0,012$ $p_3 = 0,045$	254 (252;257)
MMPs-7	12,1 (9,3;14,7) $p_2 = 0,042$ $p_3 = 0,045$	10,4 (11,9;12,5) $p_1 = 0,018$ $p_3 = 0,045$	3,8 (3,6;4,0)
MMPs-9	852 (708;918) $p_2 = 0,013$ $p_3 = 0,056$	864 (840;910) $p_1 = 0,036$ $p_3 = 0,046$	396 (394;398)
после завершения ФДТ (группа 1) after completion of PDT (group 1)			
TIMP-1	679 (626;742) $p_2 = 0,038$ $p_3 = 0,045$	567,3 (557;684) $p_1 = 0,032$ $p_3 = 0,025$	789 (771;793)
MMPs-2	312 (310;317) $p_2 = 0,032$ $p_3 = 0,045$	616 (598;627) $p_1 = 0,012$ $p_3 = 0,046$	254 (252;257)
MMPs-7	4,1 (3,8;4,7) $p_2 = 0,042$ $p_3 = 0,045$	10,4 (11,9;12,5) $p_1 = 0,018$ $p_3 = 0,045$	3,8 (3,6;4,0)
MMPs-9	412 (408;418) $p_2 = 0,013$ $p_3 = 0,056$	864 (840;910) $p_1 = 0,036$ $p_3 = 0,046$	396 (394;398)
первые сутки после операции first day after surgery			
TIMP-1	680 (657;684) $p_2 = 0,038$ $p_3 = 0,045$	436,4 (426,1;442,1) $p_1 = 0,032$ $p_3 = 0,026$	789 (771;793)
MMPs-2	315 (312;317) $p_2 = 0,032$ $p_3 = 0,045$	741 (738;743) $p_1 = 0,012$ $p_3 = 0,045$	254 (252;257)
MMPs-7	4,3 (4,1;4,5) $p_2 = 0,042$ $p_3 = 0,045$	12,3 (11,9;12,5) $p_1 = 0,018$ $p_3 = 0,045$	3,8 (3,6;4,0)
MMPs-9	414 (412;416) $p_2 = 0,013$ $p_3 = 0,056$	952 (950;952) $p_1 = 0,036$ $p_3 = 0,046$	396 (394;398)
третьи сутки после операции third day after surgery			
TIMP-1	787 (776;789) $p_2 = 0,038$ $p_3 = 0,655$	442,4 (440,1;443,6) $p_1 = 0,017$ $p_3 = 0,021$	789 (771;793)
MMPs-2	299 (296;301) $p_2 = 0,023$ $p_3 = 0,021$	741 (738;742) $p_1 = 0,041$ $p_3 = 0,012$	254 (252;257)
MMPs-7	4,2 (3,9;4,5) $p_2 = 0,015$ $p_3 = 0,022$	12,3 (11,2;13,4) $p_1 = 0,038$ $p_3 = 0,026$	3,8 (3,6;4,0)

Исследуемые показатели Researched indicators	Уровень TIMP-1 и MMPs, нг/мл Level of TIMP-1 and MMPs, ng/ml		
	группа 1 ФДТ + операция group 1 PDT + surgery (n=74)	группа 2 операция group 2 surgery (n=111)	группа 3 доноры group 3 donors (n=17)
MMPs-9	401 (398;403) $p_2 = 0,038$ $p_3 = 0,038$	952 (950;953) $p_1 = 0,013$ $p_3 = 0,057$	396 (394;398)
пятые сутки после операции fifth day after surgery			
TIMP-1	783 (782;7840) $p_2 = 0,023$ $p_3 = 0,017$	441,3 (440,2;442,3) $p_1 = 0,022$ $p_3 = 0,017$	789 (771;793)
MMPs-2	249 (247;251) $p_2 = 0,041$ $p_3 = 0,634$	741 (739;742) $p_1 = 0,042$ $p_3 = 0,023$	254 (252;257)
MMPs-7	3,6 (3,4;3,8) $p_2 = 0,021$ $p_3 = 0,634$	12,3 (11,2;13,5) $p_1 = 0,022$ $p_3 = 0,011$	3,8 (3,6;4,0)
MMPs-9	391 (389;393) $p_2 = 0,023$ $p_3 = 0,765$	952 (950;954) $p_1 = 0,017$ $p_3 = 0,028$	396 (394;398)
десятые сутки после операции tenth day after surgery			
TIMP-1	785 (784;787) $p_2 = 0,038$ $p_3 = 0,634$	345,1 (344,7;446,3) $p_1 = 0,048$ $p_3 = 0,012$	789 (771;793)
MMPs-2	248 (247;250) $p_2 = 0,041$ $p_3 = 0,715$	612 (610;614) $p_1 = 0,034$ $p_3 = 0,033$	254 (252;257)
MMPs-7	3,4 (3,1;3,6) $p_2 = 0,021$ $p_3 = 0,715$	10,2 (9,7;11,1) $p_1 = 0,021$ $p_3 = 0,022$	3,8(3,6;4,0)
MMPs-9	395 (393;397) $p_2 = 0,031$ $p_3 = 0,755$	862 (860;864) $p_1 = 0,043$ $p_3 = 0,022$	396 (394;398)

Примечание: данные представлены в виде медианы и межквартильного размаха. Достоверности p1, p2, p3 приведены в соответствии с межгрупповыми сравнениями.
Note: Here and below: data are presented as median and interquartile range. Significances p1, p2, p3 are given in accordance with intergroup comparisons.

In patients included in group 1, the levels of TIMP-1, MMPs-2, MMPs-7 and MMPs-9 did not change compared with the values obtained after PDT.

By the third day after surgery, in patients treated only by the surgical method, there were no statistically significant changes in the level of TIMP-1 and MMPs. Patients who received combined treatment showed a statistically significant increase in the amount of TIMP-1 to the level observed in donors. In these patients, a decrease in the concentration of all studied MMPs was noted, however, compared with the data of donors, their values were statistically significantly higher.

By the fifth day after surgical treatment, there were no statistically significant changes in laboratory parameters in patients of group 2. In patients of group 1 treated with the combined method, it was noted that the values of MMPs-2, MMPs-7 and MMPs-9 decreased statistically significantly and did not differ from the values recorded in the group of healthy donors.

There were no significant changes in the studied parameters in patients with SCSC in both observation groups on the seventh postoperative day; they did not differ statistically significantly from the data observed on the fifth day after surgical treatment.

By the tenth day after the operation, no statistically significant changes were obtained in patients who underwent neoadjuvant PDT. In group 2, there was an increase in the TIMP-1 index and, as a result, a decrease in the levels of the studied MMPs. However, the concentrations of MMPs remained statistically significantly higher than those of donors, their values began to correspond to the results established before the start of surgical treatment.

In the late postoperative period, there were no changes in the analyzed parameters in patients of both groups, all the studied parameters corresponded to the data obtained on the tenth day after the operation.

Thus, as a result of the study, it was found that surgical removal of the tumor without neoadjuvant PDT does not restore the studied parameters. They remained statistically significantly elevated both in the immediate and late postoperative periods. However, the implementation of combined treatment made it possible to increase the level of TIMP-1 statistically significantly before the start of the surgical stage, which naturally led to a decrease in the number of MMPs-2, MMPs-7 and MMPs-9. During dynamic observation, a complete recovery of the TIMP-1 level was determined, which, in turn, contributed to an increase in the number of all MMPs.

During the study, it was found that the TIMP-1 index in group 1 before the start of the surgical stage of treatment was 679 ng/ml, by the 10th day of the postoperative period – 785 ng/ml, in group 2 – 567.3 ng/ml and 345 .1 ng/ml, respectively. The evaluation of the results of the study was carried out by the method of non-parametric statistical analysis in order to establish the reliability of differences in the studied groups using the Mann-Whitney and Kolmogorov-Smirnov criteria. Mann-Whitney test: U = 251.500; Z = 2.927316 ($p = 0.003419$); Kolmogorov-Smirnov criterion: Max Neg Difference = 0.00; Max Pos Difference = 0.433333 ($p < 0.01$).

The initial level of MMPs-2 in group 1 was 312 ng/ml, by day 10 of the postoperative period it was 248 ng/ml; in group 2 – 616 ng/ml and 612 ng/ml, respectively. Mann-Whitney test: U = 117.0000; Z = 4.915821 ($p = 0.000001$); Kolmogorov-Smirnov criterion: Max Neg Difference = 0.00; Max Pos Difference = 0.60000 ($p < 0.001$). The level of MMPs-7 in group 1 was 4.1 ng/ml and 3.4 ng/ml; in group 2 – 10.4 ng/ml and 10.2 ng/ml, respectively. Mann-Whitney test: U = 125.0000; Z = 4.797546 ($p = 0.000002$); Kolmogorov-Smirnov criterion: Max Neg Difference = 0.00; Max Pos Difference = 0.60000 ($p < 0.001$). The level of MMPs-9 in group 1 was 412 ng/ml and 395 ng/ml; in group 2 – 864 ng/ml and 862 ng/ml, respectively. Mann-Whitney test: U = 251.5000; Z=2.927316 (p=0.000001); Kolmogorov-Smirnov criterion: Max Neg Difference = 0.00; Max Pos Difference = 0.60000 ($p < 0.001$). There is a strong feedback ($r = – 0.87$) between the TIMP-1 and MMPs-2, MMPs-7 and MMPs-9 in the blood.

One of the most important criteria for evaluating the effectiveness of cancer treatment is survival, absence of recurrence and disease progression. These indicators were studied in patients included in the 1st and 2nd observation groups. Considering the fact that SCSC was diagnosed at the T1-2N0M0 stage in the patients included in our study, no lethal cases from the underlying disease were recorded during the period of dynamic observation. Fatal outcomes were noted in 12 (6.5%) patients from comorbidities, mainly from cardiovascular events. We consider it necessary to note that all the deceased patients were from group 2, in which only surgical treatment was performed without the use of PDT.

When analyzing other indicators, it was found that metastasis was detected in 19 (10.3%) patients with SCSC in terms of 3 to 7 years. In all cases, metastases in regional lymph nodes were diagnosed, which required chemotherapy. Lymphogenic metastases were predominantly detected in 16 (8.6%) patients of group 2. In the complex treatment group, metastases were found only in 3 (1.6%) patients ($p < 0.05$). It is obvious that the use of the PDT method, and then the implementation of a surgical intervention in the treatment of patients with early stage SCSC, can reduce the risk of lymphogenous metastasis in the long-term period. Relapse of the disease was observed in 15 (8.1%) patients: in group 1 – in 4 (2.2%), in group 2 – in 11 (9.5%) ($p<0.05$). Thus, combined treatment, including PDT before the surgical stage, is an effective method for the treatment of patients with localized SCSC and can be recommended for widespread use.

Discussion

It has been established that changes in TIMP-1, MMPs-2, MMPs-7 and MMPs-9 are recorded already at the early stages of SCSC. Surgical treatment did not lead to the restoration of the initial level of indicators, they remained statistically significantly increased both in the immediate and late postoperative periods. It is possible that SCSC produces substances that reduce the amount of TIMP-1, which, in turn, leads to an increase in the amount of MMPs-2, MMPs-7 and MMPs-9 in the blood. It is known that tissue collagenases MMPs-2 and MMPs-9 hydrolyze type IV collagen, the basis of the basal lamina at the dermoepidermal junction, promoting tumor invasion. In addition, the destruction of type IV collagen contributes to deep damage to epithelial cells from membrane destruction to vascular invasion. MMPs-2 and MMPs-9 also release a number of angiogenic factors, including VEGF, which is considered the main polyclonal inducer of angiogenesis. The destruction of vascular collagen contributes to the disruption of the vascular wall, which leads to endothelial dysfunction [14]. Studies by

foreign scientists [15] have convincingly shown that carcinogenesis is accompanied by imbalance of oncogenes and prooncogenes. These processes lead to hypoxia, induction of angiogenesis (creation of a tumor vascular bed), hydrolysis of the basement membrane and extracellular matrix due to the ability of metalloproteinases to decompose almost all of their components (all types of collagens, elastin, proteoglycans, laminin, and others); tumor progression and metastasis.

The results of our study show that the use of PDT before surgical treatment in patients with early stage SCSC contributes to the normalization of the level of TIMP-1, which leads to the normalization of the level of MMPs-2, MMPs-7 and MMPs-9 in the blood. This prevents damage to the endothelium of the vascular wall both in the immediate and long-term period after treatment [16]. It should be noted that the removal of the tumor without the use of PDT did not lead to correction of the level of metalloproteinases: both before and after surgical treatment, an increase in these indicators was noted. It is possible that surgical treatment without the use of PDT does not lead to the elimination of the causes that induce the development of SCSC. However, this issue requires further research.

Conclusion

The study shows that in patients with the initial stage of SCSC, changes in the parameters of metalloproteinases in the blood serum are recorded, which is manifested by a decrease in the level of TIMP-1 and an increase in MMPs-2, MMPs-7 and MMPs-9. These changes are a trigger for the destruction of vascular collagen and disruption of the integrity of the vascular wall. PDT contributes to the normalization of the levels of TIMP-1 and MMPs-2, MMPs-7 and MMPs-9 in the blood, indirectly prevents damage to the endothelium of the vascular wall and prevents changes in hemostasis.

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