ORIGINAL ARTICLES

PHOTODYNAMIC THERAPY IN TREATMENT OF SQUAMOUS CELL CARCINOMA OF ORAL CAVITY WITH CHLORINE e6 PHOTOSENSITIZER WITH LONG-TERM FOLLOW UP

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Abstract

Photodynamic therapy is an effective method for treating superficial forms of malignant neoplasms, characterized by a minimal risk of damage to normal tissues. In this study, we presented our experience of treating cancer of the oral mucosa using photodynamic therapy, and analyzed the immediate and long-term results of treatment. 38 patients with squamous cell carcinoma of oral cavity mucosa, with a depth of invasion no more than 7 mm, were included in the study. All patients underwent photodynamic therapy with chlorine e6 based photosensitizer. Photosensitizers were administered intravenously 3 hours before irradiation, at a dosage of 1 mg/kg of the patient's weight. Photodynamic therapy was performed with the following parameters: P – 1.0 W, Ps – 0.31 W/cm^2, E – 300 J/cm^2. The area of one irradiation field ranged 1.0-2.0 cm^2. Treatment effect was evaluated by RECIST 1.1. Overall survival, cancer-specific survival, and disease-free survival were calculated using Kaplan-Meier curves. Evaluation of adverse events was made by CTCAE 5.0 criteria. At 35 (92.1%) out of 38 cases, complete regression was observed after photodynamic therapy. Among them in 3 out of 35 patients relapse was diagnosed in 11.5 to 43.2 months. The total number of patients who didn't respond to treatment was 6 (15.8%). Follow-up period was 4.2-87.3 months. (mean 42.9). 34 (89.5%) out of 38 patients are alive, 1 (2.6%) died from progression, and three died from other causes. The 5-year overall survival rate was 82.1%, cancer-specific survival rate was 97.0%, and disease-free survival rate was 81.1%. Among the factors significantly ($p < 0.05$) influencing relapse-free survival: depth of invasion < 5 mm (p – 0.013) and the presence of leukoplakia (p – 0.007). When assessing cancer-specific survival, factors worsening the prognosis were: age >70 years (p – 0.034) and the presence of leukoplakia (p – 0.007). Photodynamic therapy is an alternative treatment method of oral cancer superficial lesions, in case of proper assessment of primary lesion and in case of possibility of full irradiation of the tumor. Moreover, after using photodynamic therapy, the underlying connective-muscular structures are preserved, which promotes rapid healing with minimal scarring, the functions of the affected organ remain intact, and cosmetic defects do not form.

Key words: photodynamic therapy, squamous cell carcinoma of the oral cavity, leukoplakia, prognosis factors for oral cancer, survival rate for oral cancer.

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For citations: Panaseykin Y.A., Kapinus V.N., Filonenko E.V., Polkin V.V., Sevrukov F.E., Smirnova M.A., Isaev P.A., Ivanov S.A., Kaprin A.D. Photodynamic therapy in treatment of squamous cell carcinoma of oral cavity with chlorine e6 photosensitizer with long-term follow up, *Biomedical Photonics*, 2024, vol. 13, no. 1, pp. 28–38. doi: 10.24931/2413–9432–2023–13-1-28–38.

РЕЗУЛЬТАТЫ ЛЕЧЕНИЯ БОЛЬНЫХ РАКОМ ПОЛОСТИ РТА ПРИ ПОМОЩИ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ С ФОТОСЕНСИБИЛИЗАТОРОМ НА ОСНОВЕ ХЛОРИНА e6

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Фотодинамическая терапия является эффективным методом лечения поверхностных форм злокачественных новообразований, характеризующимся минимальным риском повреждения нормальных тканей. В данном исследовании мы представили опыт лечения рака слизистой оболочки полости рта при помощи фотодинамической терапии, проанализировали непосредственные и отдаленные результаты лечения. В группу были включены 38 пациентов с плоскоклеточным раком слизистой оболочки полости рта с глубиной инвазии не более 7 мм. Всем пациентам выполнена фотодинамическая терапия с фотосенсибилизатором на основе хлорина е6. Фотосенсибилизатор вводили внутривенно за 3 ч до облучения, в дозировке 1 мг/кг веса пациента. Параметры облучения: плотность мощности на выходе волокна – 1,0 Вт, плотность мощности – 0,31 Вт/см^2, световая доза – 300 Дж/см^2. Площадь одного поля облучения составляла 1,0 – 2,0 см^2. Эффект от лечения оценивали по системе RECIST 1.1. Общая выживаемость, канцер-специфичная выживаемость и безрецидивная выживаемость были определены при помощи кривых Каплан-Майера. Оценка нежелательных явлений произведена по критериям CTCAE 5.0. У 35 (92,1%) из 38 пациентов получена полная регрессия опухолевого очага после ФДТ, из них рецидив заболевания выявлен у 3 из 35 пациентов в сроки от 11,5 до 43,2 мес. Общее количество пациентов, не ответивших на лечение, составило 6 (15,8%) человек. Общий период наблюдения пациентов составил 4,2-87,3 мес (в среднем 42,9 мес). 34 (89,5%) из 38 пациентов живы, 1 (2,6%) умер от прогрессирования заболевания, трое погибли по другим причинам. 5-летний показатель общей выживаемости составил 82,1%, канцер-специфичной выживаемости – 97,0%, безрецидивная выживаемость составила – 81,1%. Среди факторов достоверно ($p < 0,05$) влияющих на безрецидивную выживаемость: глубина инвазии < 5 мм (p 0,013) и наличие лейкоплакии (p 0,007). При оценке канцер-специфичной выживаемости факторами, ухудшающими прогноз, стали: возраст >70 лет (p 0,034) и наличие лейкоплакии (p 0,007). Фотодинамическая терапия является альтернативным методом лечения поверхностных очагов рака полости рта, при адекватной оценке распространенности первичного очага и возможности полноценного облучения опухоли. При этом после применения ФДТ сохраняются подлежащие соединительно-мышечные структуры, что способствует быстрому заживлению с минимальным рубцовым процессом, остаются сохранными функции пораженного органа и не формируются косметические дефекты.

Ключевые слова: фотодинамическая терапия, плоскоклеточный рак полости рта, лейкоплакия, факторы прогноза рака полости рта, выживаемость при раке полости рта.

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Для цитирования: Панасейкин Ю.А., Капинус В.Н., Филоненко Е.В., Полькин В.В., Севрюков Ф.Е., Смирнова М.А., Исаев П.А., Иванов С.А., Каприн А.Д. Результаты лечения больных раком полости рта при помощи фотодинамической терапии с фотосенсибилизатором на основе хлорина е6 // Biomedical Photonics. – 2024. – Т. 13, № 1. – С. 28–38. doi: 10.24931/2413–9432–2024–13–1-28–38.

Introduction

Currently, the main method of treatment of oral squamous cell cancer (SCC) is surgery [1]. Surgical treatment allows adequate staging of the cancer process and identification of prognostically unfavorable factors requiring adjuvant treatment [2]. However, even in initial oral cavity SCC (T1-T2), a reconstructive-plastic stage is performed in 86%. According to a meta-analysis, in the surgical treatment of oral cavity SCC, small defects are replaced with local flaps in 45% of cases. If necessary, in 41%, microsurgical free flap transplantation is used [3]. Such extensive surgical interventions undoubtedly increase surgical trauma and rehabilitation time. The quality of speech, the act of swallowing deteriorates, and the cosmetic result is not always satisfactory, which in turn reduces the quality of life [4-6].

An alternative to surgical treatment of oral SCC is chemoradiation therapy in a stand-alone option [7]. The difficulties of radiation treatment of oral cavity SCC are associated with the fact that radiation eradication of the tumor usually requires the administration of total doses exceeding the tolerance of the surrounding normal tissues. This leads to adverse events such as mucositis, osteomyelitis, dysgeusia, hyposalivation, and radioinduced oncopathologies [8].

Photodynamic therapy (PDT) can be used as an independent technique for radical treatment of oral cavity SCC (T1-T2) with comparable antitumor results with conventional treatment methods. Many adverse events associated with surgical and chemoradiotherapy treatment are minimized or absent [9-13]. In a retrospective meta-analysis comparing the results of treatment of oral cavity SCC with surgery and PDT, the oncologic results were comparable, but in the PDT group there was a significant improvement in the quality of life [11]. The use of PDT is especially relevant in severe, somatically-challenged patients for whom other treatment methods are contraindicated. It is possible to achieve complete resorption of the primary focus and treatment of combined pathology of the oral mucosa –

leukoplakia [14]. The use of PDT does not limit the further use of traditional methods, such as surgical treatment, chemoradiation therapy or immunotherapy [15].

Photosensitizers (PS) based on the active substance chlorin e6 are licensed and actively used in the treatment of precancerous diseases, oncopathology of skin and mucous membranes [16, 17]. Chlorin e6 activation is achieved by local exposure to light radiation with a wavelength of 660-670 nm. This induces intracellular cytotoxic effects, such as the formation of free oxygen radicals, the effects of cellular hypoxia, and systemic immune response. The effective light penetration depth of PDT is approximately 10 mm [18]. This limits the use of PDT as a radical treatment for oral cancer with a depth of invasion (DI) of the primary focus greater than 5-7 mm [19, 20].

Numerous advantages of PDT, such as minimal toxicity of surrounding healthy tissues due to selective accumulation of PS in the tumor; absence of limiting doses of PS and light exposure and, as a consequence, the possibility of multiple repetition of the procedure; convenience of application in case of multiple lesions and better cosmetic results due to preservation of collagen fibers structure, which contributes to the formation of normotrophic scars; and the possibility of combination with other methods, make the PDT a valuable option [21, 22].

In a meta-analysis of 43 clinical trials of PDT for oral cancer, complete regression was observed in 94.4% and the 5-year survival rate was 84.2% [11]. Also, a comparison of surgical treatment and PDT in the initial stages of oral cancer (T1-T2) showed no significant superiority of either technique. The PDT group included 126 patients with T1 and 30 patients with T2 oral SCC, while the surgical group included 58 patients with T1 and 33 patients with T2, respectively. The complete tumor response to treatment, at T1 was 86% and 76% for PDT and surgery, respectively. At T2, it was 63% for PDT and 78% for surgery [9].

In another systematic meta-analysis including 900 patients with head and neck SCC, complete response to PDT was found in 741 cases (82%). Jiao Lin et al. argue that PDT is an effective technique for the treatment of superficial foci of head and neck SCC, but point out the need for optimization of treatment regimens and further studies to evaluate the efficacy of PDT [23].

In this clinical study, we present our own results of PDT use in T1-T2 stages of oral cavity SCC.

Materials and Methods

The prospective study included 38 patients who came to the A. Tsyb Medical Radiological Research Centre (MRRC) – the branch of the FSBI "National Medical Research Radiological Centre" (NMRRC) of the Ministry of Health of the Russian Federation from May 2016 to September 2023 for oral cavity SCC. All patients were diagnosed with primary oral cavity SCC (T1-T2). The main inclusion criterion was a depth of invasion (DI) of less than 7 mm. The DI of the primary focus was determined by ultrasound, CT and MRI (Fig. 1). Exclusion criteria were: tumor invasion depth more than 7 mm, presence of regional or distant metastases, technical impossibility to include all necessary tissue volume in the irradiation field due to anatomical features of the affected area.

There were 21 (55.3%) men and 17 (44.7%) women in the group, aged 37 to 83 (average 61) years at the time of treatment. Localization of the tumor process: lateral surface of the tongue – 16 (42.1%), floor of the oral cavity – 11 (28.9%), lip mucosa – 5 (13.2%), cheek – 3 (7.9%), alveolar process – 2 (5.3%), retromolar space – 1 (5.3%). The depth of invasion of the primary focus ranged from 0 (in situ cancer) to 7 mm (mean 3.4 mm), among them T1 – 28 (73.7%) tumors, of which 5 (13.2%) were cancer in situ and T2 – 10 (26.3%) cases. The depth of invasion was <0mm in 5 (13.2%) cases, 1-5 mm in 26 (68.4%) cases and 5-7 mm in 7 (18.4%) cases. Visible tumor sizes ranged from 2x3 to 35x15 mm, with the total tumor area ranging from 0.06 to 5.25 cm^2.

Characteristics of the primary focus was the following: superficial form – 24 (63,2%), ulcerated form – 4 (10,5%) cases, exophytic focus – 7 (15,8%), endophytic focus – 4 (10,5%) (Fig. 2). In 5 (13.2%) patients cancer developed on the background of leukoplakia (Fig. 3). General characteristics of the patients are presented in Table 1.

None of the patients were diagnosed with regional (cN0) and distant metastasis (cM0) according to clinical and instrumental examination. Staging was performed according to the UICC TNM system of 8th edition [24].

This clinical trial was approved by the local ethical committee of A. Tsyb MRRC (Ethical Committee Meeting Minutes No. 294 dated 11.07.2018). All patients signed informed voluntary consent.

Two chlorin e6-based preparations – photolon and photoran – were used as PSs, and were administered by intravenous drip at a dose of 1.0 mg/kg 3 h before PDT.

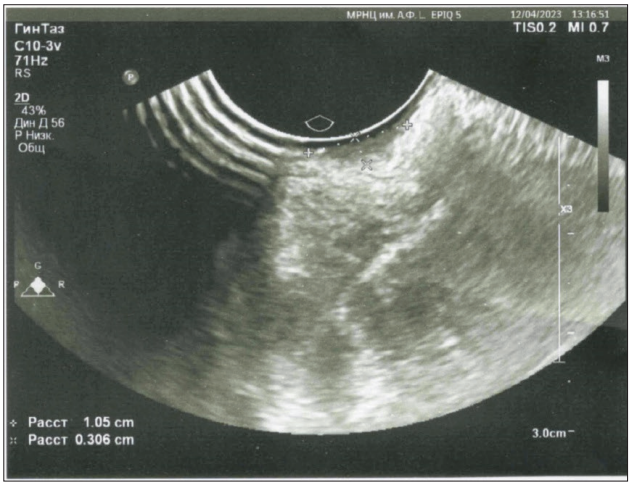

Рис. 1. УЗ отображение опухоли языка с определением глубины инвазии.
Fig. 1. US of tongue cancer with depth of invasion.

Таблица 1
Клинические характеристики пациентов
Table 1
Patient's clinical characteristics

Характеристика Characteristic	Количество пациентов (%) Number of patients (%)
Пол: Gender: Мужской Male Женский Female	 21 (55,3%) 17 (44,7%)
Возраст: Age: 30–59 60–69 70–79 80–89	 13 (34,2%) 17 (44,7%) 6 (15,8%) 2 (5,3%)
Локализация опухоли: Tumor localization Язык (боковая поверхность) Tongue (lateral surface) Дно полости рта Floor of the mouth Слизистая губы Mucous lips Щека Cheek Альвеолярный отросток Alveolar ridge Ретромолярное пространство Retromolar region	 16 (42,1%) 11 (28,9%) 5 (13,2%) 3 (7,9%) 2 (5,3%) 1 (2,6%)
Т категория T stage T1 T2	 28 (73,7%) 10 (26,3%)
Глубина инвазии Depth of invasion <0 (опухоль не определяется) <0 (tumor not detected) ≥1mm ≤5mm >5mm ≤7mm	 5 (13,2%) 26 (68,4%) 7 (18,4%)
Площадь опухоли: Tumor area: <1cm^2 1-2 cm ^{2} ≥2 cm^2	 25 (65,8%) 8 (21,1%) 5 (13,2%)
Тип опухоли: Tumor type: Поверхностная Superficial Язвенная Ulcerative Экзофитная Exophytic Эндофитная Endophytic	 24 (63,2%) 4 (10,5%) 6 (15,8%) 4 (10,5%)
Фоновое заболевание: Background disease: Лейкоплакия Leukoplakia Отсутствует Absent	 6 (15,8%) 33 (84,2%)

Irradiation was performed in a darkened room using a remote laser device "Latus-2" (wavelength 662 nm) with flexible quartz light guides (Fig. 4).

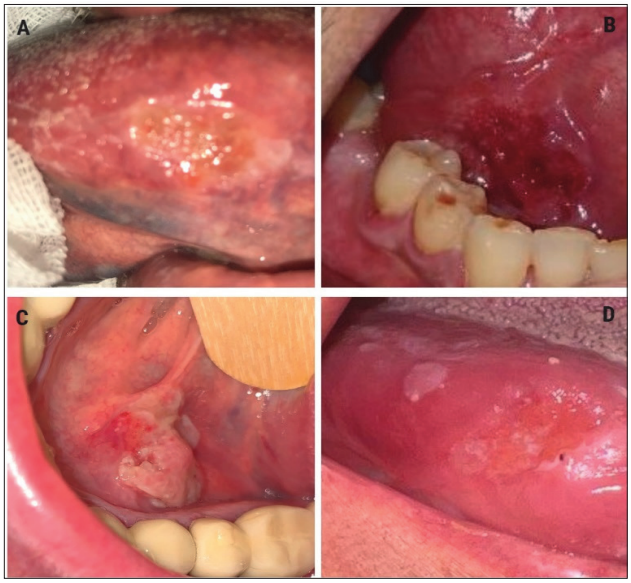

Рис. 2. Типы очагов: a – поверхностный; b – язвенный; c – экзофитный; d – эндофитный.
Fig. 2. Types of lesions: a – superficial; b – ulcerative; c – exophytic; d – endophytic.

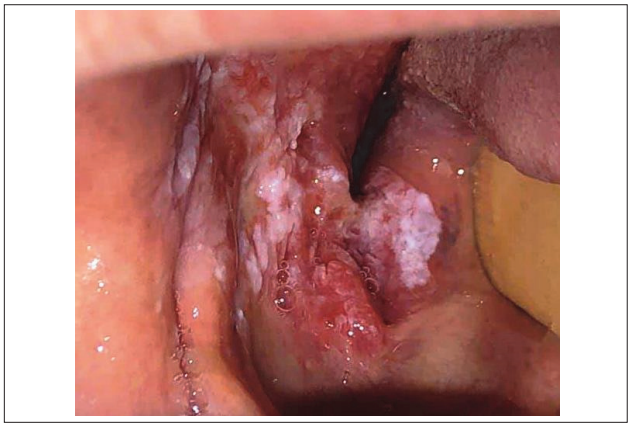

Рис. 3. Плоскоклеточный рак полости рта на фоне лейкоплакии.
Fig. 3. Squamous cell carcinoma of oral cavity with leukoplakia.

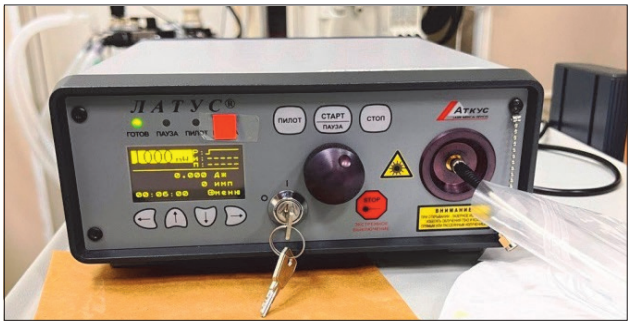

Рис. 4. Источник лазерного излучения аппарат «Латус-2» (662 нм).
Fig. 4. Source of laser irradiation «Latus-2» (662 nm).

The irradiation field included an area 5-10 mm away from the visible edges of the tumor mass. Surrounding tissues were covered with dark light-tight material to protect from damage to healthy tissues during PDT session (Fig. 5).

PDT parameters: power at the fiber output – 1.0 W, power density – 0.31 W/cm^2, light dose – 300 J/cm^2. The area of one irradiation field was 1.0 – 2.0 cm^2. In case of a large tumor focus size or presence of concomitant pathology in the form of leukoplakia, irradiation with two or more fields was performed in order to include all necessary tissues in the irradiation volume.

PDT was performed under local or general anesthesia if it was necessary to perform surgical interventions on the pathways of regional lymph drainage (biopsy of a sentinel lymph node or prophylactic lymphadenectomy).

Within 36 h after PS injection patients avoided direct sunlight and were in a darkened room (under the light not more than 1000 lux). A follow-up after the PDT in the clinic was from 3 to 7 days.

Adverse events were evaluated according to the CTCAE 5.0 criteria. Evaluation for adverse events was performed during the first 5 days after PDT and subsequently, during follow-up examinations at 4 weeks, 3, 6, 12 months and then once a year.

The first clinical and instrumental examination was performed 4 weeks after PDT with evaluation of the immediate response. In case of suspicion of residual tumor presence, biopsy was performed. Thereafter, patients underwent routine examination at 3, 6, and 12 months, respectively, and once a year thereafter.

The immediate response to treatment was evaluated as follows: complete response (CR) – complete regression of tumor focus, partial response (PR) – presence of residual tumor tissue in the PDT zone, disease progression (DP) – tumor enlargement after treatment. The distant result was evaluated in terms of more than 3 months with previously achieved CR on treatment. The distant result included: local recurrence (LR) – recurrence in the area of primary focus, regional recurrence (RR) – metastases to lymph nodes of the neck, distant metastases (DM).

Overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) were determined using Kaplan-Meier curves. Both progression by primary focus and progression by locoregional and distant metastases were considered in the analysis of RFS. Log-rank analysis was also performed to identify prognostically unfavorable factors. The analysis included: sex, age, tumor localization, tumor size, tumor type, and presence of background disease. Statistical significance was determined at $p < 0.05$.

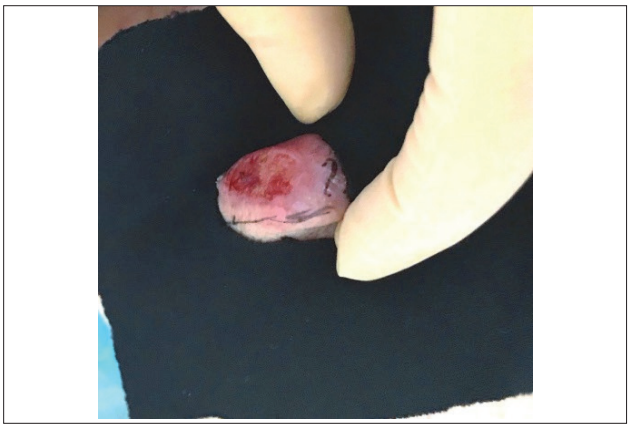

Рис. 5. Опухолевый очаг на нижней губе и защитный экран для здоровых тканей.
Fig. 5. Tumor lesion of lower limb with protective screen.

Results

Effectiveness of PDT

Initial signs of necrosis after PDT were observed immediately after the procedure, in the form of demarcation of the treatment zone due to vascular stasis. On 3-6 days after PDT a necrotic scab was formed, which was independently rejected on 10-15 days. Further, independent wound healing was observed within 1 month (Fig. 6).

At the first follow-up examination, 3 months later, 35 (92.1%) of the 38 patients had CR, and three patients had PR (7.9%). During the follow-up period, 3 of the 35 patients who had previously reported immediate CR had a recurrence between 11.5 and 43.2 months after treatment. In one case, the recurrence was both in the primary site and metastasis to regional lymph nodes,

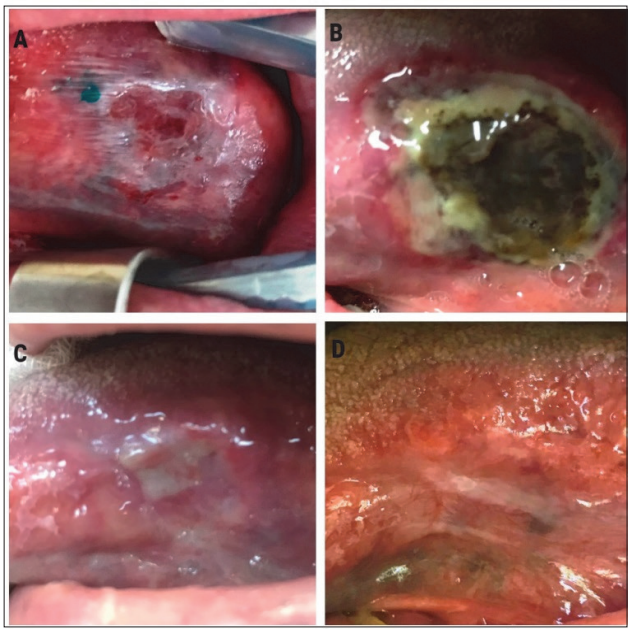

Рис. 6. Клинические изменения в зоне проведения ФДТ: a – через 10 мин после ФДТ; b – 5 сут после ФДТ; c – 20 сут после ФДТ; d – 3 мес после ФДТ.
Fig. 6. Clinical changings in PDT zone: a – 10 min after PDT; b – 5th day after PDT; c – 20th day after PDT; d – 3 months after PDT.

in another case the recurrence was only in the primary site, and in the third patient only regional recurrence was detected. Thus, the total number of patients who did not respond to treatment was 6 (15.8%). All 6 patients who did not respond to treatment underwent surgical treatment followed by adjuvant chemoradiation therapy. The total patient follow-up period was 4.2-87.3 months (mean 42.9 months), during this period 34 (89.5%) of 38 patients were alive, 1 (2.6%) died of disease progression, and three died of causes unrelated to oral cancer (Table 2).

At 5 years after treatment, the overall survival rate (OS) was 82.1%, the cancer-specific survival rate (CSS) was 97.0%, and the disease-free survival rate (DFS) rate was – 81.1% (Fig. 7).

We used log-rank analysis of such clinical and demographic factors as sex, age, focus location, T category, DI of the primary tumor, tumor area and type,

Таблица 2
Результаты лечения методом ФДТ
Table 2
Results of treatment by PDT

Клиническая характеристика Clinical characteristics	Количество пациентов (%) Number of patients (%)
Непосредственный ответ на лечение: Immediate response to treatment:	
Полный ответ (ПО) Full response (FR)	35 (92,1%)
Частичный ответ (ЧО) Partial response (PR)	3 (7,9%)
Прогрессия заболевания (ПЗ) Disease progression (PD)	0
Отдаленные результаты: Long-term results:	
Локальный рецидив (ЛР) Local recurrence (LR)	2 (5,3%)
Регионарный рецидив (РР) Regional recurrence (RR)	2 (5,3%)
Отдаленные метастазы (ОМ) Distant metastases (DM)	0
Причины смертности: Causes of mortality:	
Смерть от прогрессии Death by progression	1 (2,6%)
Другие причины Other reasons	3 (7,9%)
Лечение неполного ответа/рецидива: Treatment of incomplete response/relapse:	
Хирургия (первичный очаг) Surgery (primary site)	5 (13,2%)
Хирургия (шейная диссекция) Surgery (neck dissection)	2 (5,3%)
Лучевая терапия Radiation therapy	6 (15,8%)
Паллиативная химиотерапия Palliative chemotherapy	1 (2,6%)

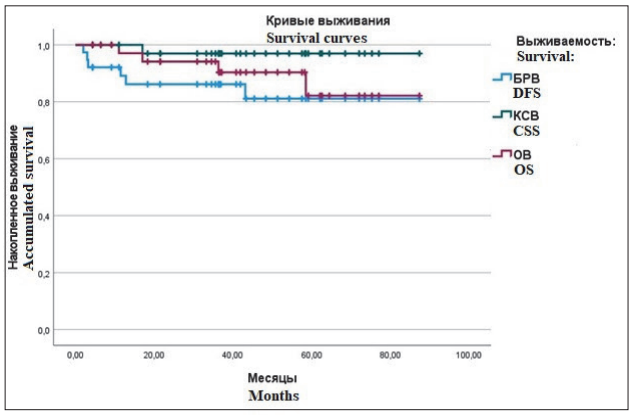

Рис. 7. Кривые Каплан-Майера по анализу общей выживаемости (ОВ), безрецидивной выживаемости (БРВ) и канцер-специфичной выживаемости (КСВ).
Fig. 7. Kaplan-Mayer curves in overall survival (OS) rate analysis, disease-free survival rate (DSS) и cancer-specific survival rate (CSS).

and the presence of leukoplakia to identify reliable prognostic factors in terms of OS, CSS, and DFS.

Statistical analysis revealed no significant ($p < 0.05$) difference in overall survival according to any clinical and demographic characteristics.

However, a significant difference was detected when analyzing cancer-specific survival for patients over 70 years of age. The 5-year CSS for patients over 70 years of age was 87.5%, versus 100% for those under 70 years of age (p 0.034). Another significant prognostic factor for worsening CSS was the presence of leukoplakia. The 5-year cancer-specific survival rates were 83.3% in the presence and 100% in the absence of leukoplakia (p 0.007).

In the analysis of disease recurrence, the presence of leukoplakia and depth of invasion were significant factors for prognosis. Thus, the recurrence-free survival rate was 57.1% for invasion depths greater than 5 mm versus 90.3% for invasion depths of 0 to 5 mm (p 0.013). The 5-year recurrence-free survival rate was 100% in patients with cancer in situ, in whom no invasive growth was detected according to the examination data (invasion depth 0 mm).

The second factor of recurrence was the presence of leukoplakia. In the presence of leukoplakia, 50% of patients developed recurrence after treatment, in its absence – the risk of recurrence was 90.6% (p 0.007) (Fig. 8-11). The summary data on DFS are summarized in Table 3.

Adverse events

The most common early adverse event was pain in the PDT area. This adverse event was observed in 35 out of 38 patients (92,1%) with various degrees of severity. The majority (25 out of 35) had insignificant soreness (grade 1), which did not affect daily activity and did not require drug correction. Seven of 35 patients had

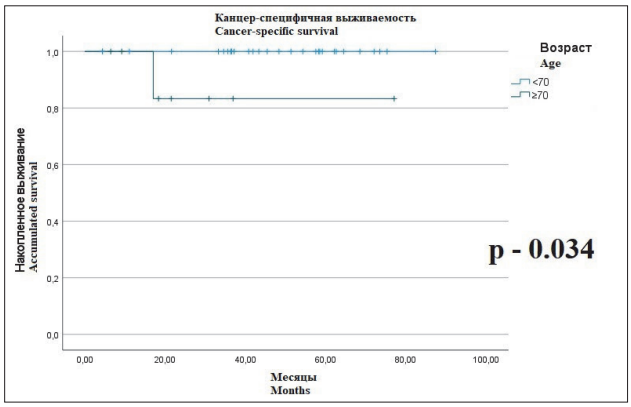

Рис. 8. Кривые Каплан-Майера по оценке возрастного фактора на канцер-специфичную выживаемость.
Fig. 8. Kaplan-Mayer curves in evaluation of age factor, affecting to cancer-specific survival.

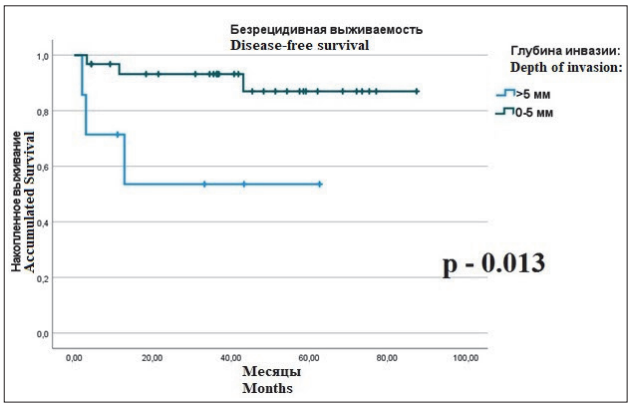

Рис. 10. Кривые Каплан-Майера по оценке фактора глубины инвазии на безрецидивную выживаемость.
Fig. 10. Kaplan-Mayer curves in evaluation of depth of invasion, affecting to disease-free survival rate.

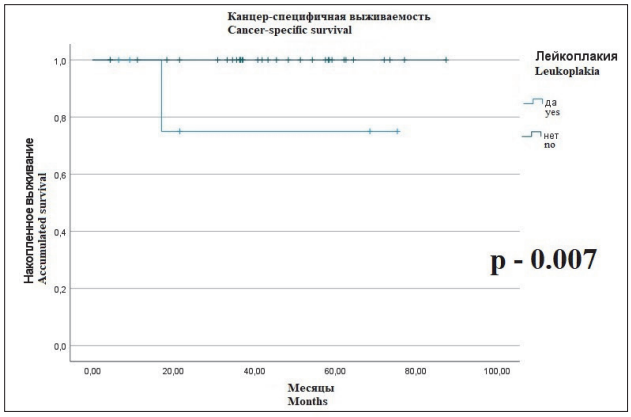

Рис. 9. Кривые Каплан-Майера по оценке фактора наличие лейкоплакии на канцер-специфичную выживаемость.
Fig. 9. Kaplan-Mayer curves in evaluation of leukoplakia present, affecting to cancer-specific survival.

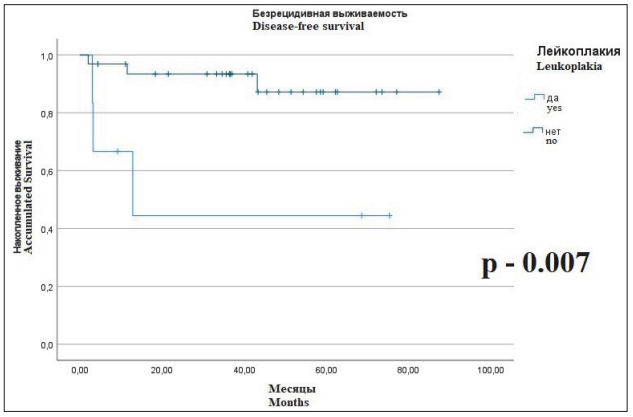

Рис. 11. Кривые Каплан-Майера по оценки наличие лейкоплакии на безрецидивную выживаемость.
Fig. 11. Kaplan-Mayer curves in evaluation of leukoplakia present, affecting to disease-free survival rate.

moderate pain (grade 2), which was managed with non-steroidal anti-inflammatory drugs. Severe pain (grade 3) was noted in 3 cases, requiring the use of narcotic drugs. This adverse event started on the 1-2 day after PDT and was resolved on the 6-10 day.

Another undesirable phenomenon was local edema of oral mucosa in the PDT area, observed in 50% of cases, in 19 out of 38 patients. Mainly (in 11 out of 19 patients) the edema was insignificant (grade 1), not affecting the functionality of the organ and did not require medication correction. In 8 out of 19 cases the edema was moderate (grade 2). Glucocorticosteroid administration in the postoperative period was required to restore the nutritional function and to stop the threat of respiratory failure through the upper respiratory tract. This phenomenon started on the 1st day after PDT and resolved on the 5th-6th day (Table 4).

In the treatment of mucosal cancer of the alveolar outgrowth in the area of PDT, bare bone site was observed in the area of PDT, with independent epithelization observed at 3-6 months after PDT. There were no other adverse events, including phototoxicity associated with PDT.

Таблица 4
Нежелательные явления после ФДТ
Table 4
Adverse events after PDT

Нежелательные явления Adverse events	Количество пациентов (%) Number of patients (%)
Боли в области ФДТ: Pain in the PDT area: Grade 1 Grade 2 Grade 3	35 (92,1%) 25 (65,8%) 7 (18,4%) 3 (7,9%)
Отек слизистой полости рта: Swelling of the oral mucosa: Grade 1 Grade 2	19 (50%) 11 (28,9%) 8 (21,1%)

Discussion

Our study on the use of PDT with chlorine-type PCs in T1-T2 stages of oral cancer showed good functional and aesthetic results of treatment, without mucosal scar

Таблица 3
Анализ безрецидивной выживаемости, в зависимости от клинических характеристик
Table 3
Analysis of disease-free survival according to clinical characteristics

Характеристика Characteristic	1-летняя безрецидивная выживаемость 1st year disease-free survival	2-летняя безрецидивная выживаемость 2nd year disease-free survival	P значимость (логарифмический тест) P significance (log test)
Пол: Gender: Мужской Male Женский Female	 90,45 (19/21) 84,6 (11/13)	 85,7 (18/21) 81,8 (9/11)	 0.757
Возраст: Age: <70 ≥70	 92,6 (25/27) 71,4 (5/7)	 88,9 (24/27) 60,1 (3/5)	 0.274
Локализация опухоли: Tumor localization Язык (боковая поверхность) Tongue (lateral surface) Дно полости рта Floor of the mouth Слизистая губы Mucous lips Щека Cheek Альвеолярный отросток Alveolar ridge Ретромолярное пространство Retromolar space	 84,6 (11/13) 81,8 (9/11) 100 (5/5) 100 (2/2) 100 (2/2) 100 (1/1)	 84,6 (11/13) 72,7 (8/11) 100 (5/5) 100 (1/1) 100 (2/2) 0 (0/1)	 0.332
Т категория: T stage: T1 T2	 91,7 (22/24) 80 (8/10)	 91,3 (21/23) 66,7 (6/9)	 0.184
Глубина инвазии: Depth of invasion: <0 (опухоль не определяется) <0 (tumor not detected) 1-5 mm 5-7 mm	 100 (4/4) 91,7 (22/24) 66,7 (4/6)	 100 (3/3) 91,3 (21/23) 50 (3/6)	 0.038
Площадь опухоли: Tumor area: <2 cm^2 ≥2 cm^2	 89,7 (26/29) 80 (4/5)	 85,2 (23/27) 80 (4/5)	 0.887
Тип опухоли: Tumor type: Поверхностная Superficial Язвенная Ulcerative Экзофитная Exophytic Эндофитная Endophytic	 100 (21/21) 66,7 (4/6) 66,7 (2/3) 75 (3/4)	 94,7 (18/19) 66,7 (4/6) 66,7 (2/3) 75 (3/4)	 0.329
Фоновое заболевание: Background disease: Лейкоплакия Leukoplakia Отсутствует Absent	 60 (3/5) 93,1 (27/29)	 40 (2/5) 92,6 (25/27)	 0.007

formation (Fig. 6C). Presumably this result is due to the preservation of tissue matrix components (collagen and elastin), while cellular vascular elements are damaged by PDT. It is believed that preservation of tissue architecture provides the best conditions for normal tissue regeneration and leads to superior healing with less scar formation [25, 26].

Of 38 patients with stage T1-T2 of oral mucosal cancer, complete response to the treatment was obtained in 35 (92.1%) cases up to 3 months after treatment. The obtained 5-year overall and cancer-specific survival rates were 82.1% and 97.0%, respectively, which is a reasonably good result. Such treatment results are comparable to those of PDT treatment with other PSs (complete response rate of 88.2%), surgery (5-year overall survival rate of 69.7-93.8%), and radiation therapy (5-year overall survival rate of 51.5-84.0%) [10, 27, 28]. Gluckman [29] and Biel [30] reported local recurrence in 16-36% after achieving a complete response in oral cancer for which PDT was performed. In our study, 2 out of 35 patients who achieved a complete response to treatment developed local recurrence. The risk of developing local recurrence was 5.7% after complete response. The overall 5-year recurrence-free survival rate was 81.1%.

We also investigated various clinical and demographic characteristics to identify unfavorable prognostic factors for recurrence. PDT is usually used for relatively small tumor foci. In our study, we primarily relied on the depth of tumor invasion rather than the area of the primary focus. Thus, the study included patients with superficial, relatively large (up to 5.3 cm^2) tumor foci, but with a shallow depth of invasion (up to 7 mm). At the same time, the data analysis did not show a statistically significant difference in the development of recurrence depending on the area of the primary focus. Thus, one patient in the distant period developed a relapse (at 43.2 months) in the area adjacent to the site of previously performed PDT. Thus, recurrence can develop regardless of the size of the primary focus. In such cases differential diagnostics between the primary tumor recurrence and the development of synchronous oncopathology of the oral cavity is difficult. Such a fact is explained by the so-called "malignization field" theory described by Slaughter in 1953 [31]. This theory assumes that squamous cell cancer does not arise from an isolated cell, but rather as a tendency towards anaplastic processes involving many cells simultaneously. This theory is partly supported by the fact that in our study one of the proven prognostic factors for recurrence was the presence of leukoplakia as a facultative precancerous lesion characterized by cellular dysplasia (Table 3) [32]. Nevertheless, PDT may be the treatment of choice for multifocal, superficial tumors because it can be repeated as often as necessary without loss of normal tissue functionality and without accumulation of toxic effects. In addition, conventional treatment remains as an option [26, 33, 34].

PDT has a high selectivity of PS accumulation in tumor tissues, which leads to minimal damage to healthy tissues. According to most researchers [35-37], the selectivity of PS accumulation in tumors with respect to healthy tissue can range from 2:1 to 15:1. In the cell, PSs mainly accumulate in mitochondria and lysosomes [38]. Minimal accumulation in the cell nucleus avoids the development of genetically therapy-resistant cells [39].

Since the 8th revision of TNM [24], it is the depth of invasion rather than the size of the primary focus that has become the determining factor in assessing the incidence and prognosis of oral cancer. In our study, it was also statistically significantly shown that the risk of recurrence increased with invasion depth greater than 5 mm. This fact is explained by the physical properties of PDT laser radiation, the penetrating ability of which is limited [40].

Conclusion

This study has shown that PDT with PS of chlorine series is an alternative method of treatment of superficial foci of oral cavity cancer in case of adequate assessment of the primary focus prevalence and possibility of full-fledged tumor irradiation. In this case, after PDT application, the underlying connective-muscular structures are preserved, which contributes to rapid healing with minimal scarring, the functions of the affected organ remain intact, and no cosmetic defects are formed.

REFERENCES

1. Kaprin A.D., Starinsky V.V., Shakhzadova A.O. Clinical recommendations of the Association of Oncologists of Russia. *Malignant neoplasms of the oral cavity*, 2020, pp. 18-19
2. Cooper J.S., Zhang Q., Pajak T.F., et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int. J. Radiat. Oncol. Biol. Phys*, 2012, vol. 84(5), pp. 1198-205.
3. Kansy K., Mueller A.A., Mücke T., et al. A worldwide comparison of the management of T1 and T2 anterior floor of the mouth and tongue squamous cell carcinoma - Extent of surgical resection

ЛИТЕРАТУРА

1. Каприн А.Д., Старинский В.В., Шахзадова А.О. Клинические рекомендации ассоциации онкологов России // Злокачественные новообразования полости рта. – 2020. – С. 18-19.
2. Cooper J.S., Zhang Q., Pajak T.F., et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck // Int. J. Radiat. Oncol. Biol. Phys. – 2012. – Vol. 84(5). - P. 1198-205.
3. Kansy K., Mueller A.A., Mücke T., et al. A worldwide comparison of the management of T1 and T2 anterior floor of the mouth and tongue squamous cell carcinoma - Extent of surgical resection

and reconstructive measures. *J. Craniomaxillofac Surg*, 2017, vol. 45(12), pp. 2097-2104.
4. Ochoa E., Larson A.R., Han M., et al. Patient-Reported Quality of Life After Resection With Primary Closure for Oral Tongue Carcinoma. *Laryngoscope*, 2021, vol. 131(2), pp. 312-318.
5. Biazevic M.G., Antunes J.L., Togni J., et al. Immediate impact of primary surgery on health-related quality of life of hospitalized patients with oral and oropharyngeal cancer. J. *Oral Maxillofac Surg*, 2008, vol. 66, pp. 1343-1350.
6. Chandu A., Smith A.C., Rogers S.N. Health-related quality of life in oral cancer: a review. *J Oral Maxillofac Surg*, 2006, vol. 64, pp. 495-502.
7. Shah J.P., Gil Z. Current concepts in management of oral cancer – Surgery. *Oral Oncol*, 2009, vol. 45, pp. 394-401.
8. Agarwal P., Upadhyay R., Agarwal A. Radiotherapy complications and their possible management in the head and neck region. *Indian J Dent Res*, 2012, vol. 23(6), pp. 843.
9. de Visscher S.A., Melchers L.J., Dijkstra P.U., et al. mTHPC-mediated photodynamic therapy of early stage oral squamous cell carcinoma: a comparison to surgical treatment. *Ann Surg Oncol*, 2013, vol. 20(9), pp. 3076-3082.
10. Toratani S., Tani R., Kanda T., et al. Photodynamic therapy using Photofrin and excimer dye laser treatment for superficial oral squamous cell carcinomas with long-term follow up. *Photodiagnosis Photodyn Ther*, 2016, vol. 14, pp. 104-110.
11. Ibarra A.M.C., Cecatto R.B., Motta L.J., et al. Photodynamic therapy for squamous cell carcinoma of the head and neck: narrative review focusing on photosensitizers. *Lasers Med Sci,* 2022, vol. 37(3), pp. 1441-1470.
12. Cerrati E.W., Nguyen S.A., Farrar J.D., Lentsch EJ. The efficacy of photodynamic therapy in the treatment of oral squamous cell carcinoma: a meta-analysis. *Ear Nose Throat J*, 2015, vol. 94(2), pp. 72-79.
13. Karakullukcu B., Stoker S.D., Wildeman A.P., et al. A matched cohort comparison of mTHPC-mediated photodynamic therapy and trans-oral surgery of early stage oral cavity squamous cell cancer. *Eur Arch Otorhinolaryngol*, 2013, vol. 270(3), pp. 1093-1097.
14. Panaseykin Y.A., Kapinus V.N., Filonenko E.V., et al. Photodynamic therapy treatment of oral cavity cancer in patients with comorbidities. *Biomedical Photonics*, 2022, Vol. 11(4), pp. 19-24.
15. Panaseykin Y.A., Filonenko E.V., Sevrukov F.E., et al. Possibilities of photodynamic therapy in the treatment of malignant tumors of the oral cavity. *Biomedical Photonics*, 2021, vol. 10(3), pp. 32-38.
16. Kapinus V. N., Kaplan M. A., Yaroslavtseva-Isaeva E. V., and coauthors A. Application of chlorin E6-photodynamic therapy of basal cell skin cancer. *Research and Practice in Medicine*, 2021, vol. 8(4), pp. 33-43.
17. Gondivkar S.M., Gadbail A.R., Choudhary M.G., et al. Photodynamic treatment outcomes of potentially-malignant lesions and malignancies of the head and neck region: A systematic review. *J Investig Clin Dent*, 2018, pp. 9-10.
18. Kapinus V. N., Kaplan M.A., Yaroslavtseva-Isayeva E. V., et al Photodynamic therapy for head and neck basal cell skin cancer with additional interstitial laser irradiation. *Biomedical Photonics*, 2018, vol. 6, pp. 20-26.
19. Shevchenko O.V., Korshunova O.V., Plekhova N.G. Study of the cytotoxic effect of a molecular conjugate based on chloride e6. *Medical and pharmaceutical journal "Pulse",* 2022, vol. 24(11), pp. 18-22.
20. Senge M.O., Brandt J.C., Temoporfin (Foscan®, 5,10,15,20-tetra(m-hydroxyphenyl)chlorin)--a second-generation photosensitizer. *Photochem Photobiol*, 2011, vol. 87(6), pp. 1240-1296.
21. Copper M.P., Triesscheijn M., Tan I.B., et al. Photodynamic therapy in the treatment of multiple primary tumors in the head and neck, located to the oral cavity and oropharynx. *Clin Otolaryngol*, 2007, vol. 32, pp. 185-189.

and reconstructive measures // J. Craniomaxillofac Surg. – 2017. – Vol. 45(12). – P. 2097-2104.
4. Ochoa E., Larson A.R., Han M., et al. Patient-Reported Quality of Life After Resection With Primary Closure for Oral Tongue Carcinoma // Laryngoscope. – 2021. – Vol. 131(2). – P. 312-318.
5. Biazevic M.G., Antunes J.L., Togni J., et al. Immediate impact of primary surgery on health-related quality of life of hospitalized patients with oral and oropharyngeal cancer // J. Oral Maxillofac Surg. – 2008. – Vol. 66. – P. 1343-1350.
6. Chandu A., Smith A.C., Rogers S.N. Health-related quality of life in oral cancer: a review // J Oral Maxillofac Surg. – 2006. – Vol. 64. - P. 495-502.
7. Shah J.P., Gil Z. Current concepts in management of oral cancer – Vsurgery // Oral Oncol. – 2009. – Vol. 45. – P. 394-401.
8. Agarwal P., Upadhyay R., Agarwal A. Radiotherapy complications and their possible management in the head and neck region // Indian J Dent Res. –2012. – Vol. 23(6). – P. 843.
9. de Visscher S.A., Melchers L.J., Dijkstra P.U., et al. mTHPC-mediated photodynamic therapy of early stage oral squamous cell carcinoma: a comparison to surgical treatment // Ann Surg Oncol. – 2013. – Vol. 20(9). – P. 3076-3082.
10. Toratani S., Tani R., Kanda T., et al. Photodynamic therapy using Photofrin and excimer dye laser treatment for superficial oral squamous cell carcinomas with long-term follow up // Photodiagnosis Photodyn Ther. – 2016. – Vol. 14. – P. 104-110.
11. Ibarra A.M.C., Cecatto R.B., Motta L.J., et al. Photodynamic therapy for squamous cell carcinoma of the head and neck: narrative review focusing on photosensitizers // Lasers Med Sci . – 2022. – Vol. 37(3). – P. 1441-1470.
12. Cerrati E.W., Nguyen S.A., Farrar J.D., Lentsch EJ. The efficacy of photodynamic therapy in the treatment of oral squamous cell carcinoma: a meta-analysis // Ear Nose Throat J. – 02.2015. – Vol. 94(2). – P. 72-79.
13. Karakullukcu B., Stoker S.D., Wildeman A.P., et al. A matched cohort comparison of mTHPC-mediated photodynamic therapy and trans-oral surgery of early stage oral cavity squamous cell cancer // Eur Arch Otorhinolaryngol. – 2013. – Vol. 270(3). – P. 1093-1097.
14. Panaseykin Y.A., Kapinus V.N., Filonenko E.V., et al. Photodynamic therapy treatment of oral cavity cancer in patients with comorbidities // Biomedical Photonics. – 2022. – Vol. 11(4). – P. 19-24.
15. Panaseykin Y.A., Filonenko E.V., Sevrukov F.E., et al. Possibilities of photodynamic therapy in the treatment of malignant tumors of the oral cavity // Biomedical Photonics. – 2021. – Vol. 10(3). – P. 32-38.
16. Капинус В. Н., Каплан М. А., Ярославцева-Исаева Е. В., и соавт. А. Применение хлорин Е6-фотодинамической терапии базально-клеточного рака кожи // Исследования и практика в медицине. – 2021. – Т. 8, № 4. – С. 33-43.
17. Gondivkar S.M., Gadbail A.R., Choudhary M.G., et al. Photodynamic treatment outcomes of potentially-malignant lesions and malignancies of the head and neck region: A systematic review // J Investig Clin Dent. – 2018. – P. 9-10.
18. Kapinus V. N., Kaplan M.A., Yaroslavtseva-Isayeva E. V., et al Photodynamic therapy for head and neck basal cell skin cancer with additional interstitial laser irradiation // Biomedical Photonics. – Vol. - 2018. – Vol. 6. – P. 20-26.
19. Шевченко О.В., Коршунова О.В., Плехова Н.Г. Изучение цитотоксического действия молекулярного конъюгата на основе хлорина е6 // Медико-фармацевтический журнал «Пульс» . – 2022. – Т. 24, № 11. – С. 18-22.
20. Senge M.O., Brandt J.C., Temoporfin (Foscan®, 5,10,15,20-tetra(m-hydroxyphenyl)chlorin)--a second-generation photosensitizer // Photochem Photobiol. – 2011. – Vol. 87(6). – P. 1240-1296.
21. Copper M.P., Triesscheijn M., Tan I.B., et al. Photodynamic therapy in the treatment of multiple primary tumors in the head and neck, located to the oral cavity and oropharynx // Clin Otolaryngol. – 2007. – Vol. 32. – P. 185-189.

22. Hopper C. Photodynamic therapy: a clinical reality in the treatment of cancer. *Lancet Oncol*, 2000, vol. 1, pp. 212-219.
23. Lin J., Guangcheng N., Tingting D., et al. Photodynamic Therapy for Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. *International Journal of Photoenergy*, 2021, pp. 1-14.
24. Brierley J. D., Gospodarowicz M. K., Wittekind C. TNM Classification of malignant tumor. *Eighth Edition*, 2017, pp. 36-39.
25. Grant W.E., Speight P.M., Hopper C., et al. Photodynamic therapy: an effective, but non-selective treatment for superficial cancers of the oral cavity. *Int. J. Cancer*, 1997, vol. 71, pp. 937-942.
26. Hopper C., Kübler A., Lewis H., et al. mTHPC-mediatedphotodynamic therapy for early oral squamous cell carcinoma. *Int. J. Cancer*, 2004, pp. 138-146.
27. Luryi A.L., Chen M.M., Mehra S., et al. Treatmentfactor associated with survival in early-stage oral cavity cancer. Analysis of 6830 cases from the National Cancer Date Base. *JAMA Otolaryngol. Head NeckSurg*, 2015, vol. 141, pp. 593-598.
28. Umeda M., Komatubara H., Ojima Y., et al. A comparison of brachytherapy and surgery for treatment of stage I-II squamous cell carcinoma of the tongue. *Int. J. Oral Maxillofac. Surg*, 2005, vol. 34, pp. 739-744.
29. Gluckman J.L., Hematoporphyrin photodynamic therapy: is there truly a future in head and neck oncology? Reflection on a 5-years' experience. *Laryngoscope*, 1991, vol. 101, pp. 36-42.
30. Biel M.A., Photodynamic therapy and the treatment of head and neck neoplasia. *Laryngoscope*, 1996, vol.108, pp. 1259-1268.
31. Slaughter D., Southwick W., Smejkal W., Field cancerization in oral stratifiedsquamous epithelium: clinical implications multicentric origin. *Cancer*, 1953, pp. 963-968.
32. de Visscher J.G.A.M., van der Meij E.H. Witte afwijking van het mondslijmvlies: leukoplakie [White lesions of the oral mucosa: leukoplakia]. *Ned Tijdschr Tandheelkd*, 2023, vol. 130(5), pp. 232-236.
33. Pass H.I., Photodynamic therapy in oncology: mechanisms and clinical use. J. *Natl. Cancer Inst*, 1993, vol. 85, pp. 443-456.
34. Grant W.E., Hopper C., Speight P.M., et al. Photodynamictherapy of malignant and premalignant lesions in patients with 'fieldcancerization' of the oral cavity. *J. Laryngol. Otol*, 1993, vol. 107, pp. 1140-1145.
35. Chadha R., Jain D.V.S., Aggarwal A. et al. Binding constants of inclusion complexes of nitroimidazoles with βcyclodextrins in the absence and presence of PVP. *Thermochim. Acta*, 2007, vol. 459, pp. 111-115.
36. Douillard S., Olivier D., Patrice T. In vitro and in vivo evaluation of Radachlorin(R) sensitizer for photodynamic therapy. *Photochem. Photobio. Sci.*, 2009, vol. 8(3), pp. 405-13.
37. Chan Thi Hai Yen, Ramenskaya G.V., Oborotova N.A. Photosensitizers of the chlorine series in PDT of tumors. *Russian Biotherapeutic Journal*, 2009, vol. 4.
38. Moan J., Berg K., Kvam E., et al. Intracellular Localization of Photosensitizers, In Ciba Foundation Symposium 146. *Photosensitizing Compounds: Their Chemistry, Biology and Clinical Use (eds G. Bock and S. Harnett)*, 1989, pp. 95-111.
39. Agostinis P., Berg K., Cengel K.A., et al. Photodynamic therapy of cancer: An update. *CA: A Cancer Journal for Clinicians*, 2011, vol. 61, № 4, pp. 250-281.
40. Mosaddad S.A., Mahootchi P., Rastegar Z., et al. Photodynamic Therapy in Oral Cancer: A Narrative Review. *Photobiomodul Photomed Laser Surg.*, 2023, vol. 41(6), pp. 248-264.

22. Hopper C. Photodynamic therapy: a clinical reality in the treatment of cancer // Lancet Oncol . – 2000. – Vol. 1. – P. 212-219.
23. Lin J., Guangcheng N., Tingting D., et al. Photodynamic Therapy for Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis // International Journal of Photoenergy. – 2021. – P. 1-14.
24. Brierley J. D., Gospodarowicz M. K., Wittekind C. TNM Classification of malignant tumors // Eighth Edition. – 2017. – P. 36-39.
25. Grant W.E., Speight P.M., Hopper C., et al. Photodynamic therapy: an effective, but non-selective treatment for superficial cancers of the oral cavity // Int. J. Cancer. – 1997. – Vol. 71. – P. 937-942.
26. Hopper C., Kübler A., Lewis H., et al. mTHPC-mediatedphotodynamic therapy for early oral squamous cell carcinoma // Int. J. Cancer. – 2004. – P. 138-146.
27. Luryi A.L., Chen M.M., Mehra S., et al. Treatmentfactor associated with survival in early-stage oral cavity cancer. Analysis of 6830 cases from the National Cancer Date Base // JAMA Otolaryngol. Head NeckSurg. – 2015. – Vol. 141. – P. 593-598.
28. Umeda M., Komatubara H., Ojima Y., et al. A comparison of brachytherapy and surgery for treatment of stage I-II squamous cell carcinoma of the tongue // Int. J. Oral Maxillofac. Surg. –2005. – Vol. 34. – P. 739-744.
29. Gluckman J.L., Hematoporphyrin photodynamic therapy: is there truly a future in head and neck oncology? Reflection on a 5-years' experience // Laryngoscope. – 1991. – Vol.101. – P. 36-42.
30. Biel M.A., Photodynamic therapy and the treatment of head and neck neoplasia // Laryngoscope. – 1996. – Vol.108. – P. 1259-1268.
31. Slaughter D., Southwick W., Smejkal W., Field cancerization in oral stratifiedsquamous epithelium: clinical implications multicentric origin // Cancer. – 1953. – P. 963-968.
32. de Visscher J.G.A.M., van der Meij E.H. Witte afwijking van het mondslijmvlies: leukoplakie [White lesions of the oral mucosa: leukoplakia] // Ned Tijdschr Tandheelkd. – 2023 . – Vol. 130(5). – P. 232-236.
33. Pass H.I., Photodynamic therapy in oncology: mechanisms and clinical use // J. Natl. Cancer Inst. – 1993. – Vol. 85. – P. 443-456.
34. Grant W.E., Hopper C., Speight P.M., et al. Photodynamictherapy of malignant and premalignant lesions in patients with 'fieldcancerization' of the oral cavity // J. Laryngol. Otol. – 1993. – Vol. 107. – P. 1140-1145.
35. Chadha R., Jain D.V.S., Aggarwal A. et al. Binding constants of inclusion complexes of nitroimidazoles with βcyclodextrins in the absence and presence of PVP // Thermochim. Acta. – 2007 – Vol. 459. – P. 111-115.
36. Douillard S., Olivier D., Patrice T. In vitro and in vivo evaluation of Radachlorin(R) sensitizer for photodynamic therapy // Photochem. Photobio. Sci. – 2009. – Vol. 8(3). – P. 405-13.
37. Чан Тхи Хай Иен, Раменская Г. В., Оборотова Н. А. Фотосенсибилизаторы хлоринового ряда в ФДТ опухолей // Российский биотерапевтический журнал. – 2009. – №4.
38. Moan J., Berg K., Kvam E., et al. Intracellular Localization of Photosensitizers, In Ciba Foundation Symposium 146 // Photosensitizing Compounds: Their Chemistry, Biology and Clinical Use (eds G. Bock and S. Harnett). – 1989. – P. 95-111.
39. Agostinis P., Berg K., Cengel K.A., et al. Photodynamic therapy of cancer: An update // CA: A Cancer Journal for Clinicians. – 2011. – Vol. 61, № 4. – P. 250-281.
40. Mosaddad S.A., Mahootchi P., Rastegar Z., et al. Photodynamic Therapy in Oral Cancer: A Narrative Review // Photobiomodul Photomed Laser Surg. – 2023. – Vol. 41(6). – P. 248-264.