ORIGINAL ARTICLES

PALLIATIVE TREATMENT WITH THE USE OF PHOTODYNAMIC THERAPY OF PATIENTS WITH MALIGNANT TUMORS OF PANCREATOBILIARY ZONE COMPLICATED BY OBSTRUCTIVE JAUNDICE

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Abstract

The paper presents the results of a complex palliative treatment using photodynamic therapy of patients with pancreatobiliary malignancies complicated by obstructive jaundice. In the main group, which included 22 patients, palliative comprehensive treatment was performed using local and systemic photodynamic therapy of pancreatobiliary neoplasms complicated by obstructive jaundice. In the comparison group, consisting of 165 patients, palliative complex treatment of complications was performed without the use of photodynamic therapy. The used photosensitizers were chlorin-based fotoditazin (21 patients) and radachlorin (1 patient). The first step was a systemic PDT. In the course of infusion through a peripheral access into the cubital vein, blood was irradiated externally by laser with monochromatic light with a wavelength of 662–665 nm and a light dose of 1200–1400 J/cm^2. As the second stage of the treatment, 3–5 hours after the end of the infusion, an intraductal PDT was carried out by irradiation with monochromatic light with a wavelength of 662 nm and a light dose of 220 J/cm^2. After the use of local and systemic photodynamic therapy, a statistically significant decrease in the size of the tumor focus in patients with pancreatic malignant neoplasms was established within a week after treatment in the main group according to the ultrasound examination of the abdominal cavity. Restoration of bile excretion into the intestine was noted in 100% of patients with malignant neoplasms of the bile duct and head of the pancreas. We also note an increase in median survival of patients in the main group to 5.9 months compared with 4.7 months in the comparison group.

Keywords: malignant tumors of the pancreatobiliary zone, obstructive jaundice, photodynamic therapy.

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ПАЛЛИАТИВНОЕ ЛЕЧЕНИЕ С ПРИМЕНЕНИЕМ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ ПАЦИЕНТОВ СО ЗЛОКАЧЕСТВЕННЫМИ НОВООБРАЗОВАНИЯМИ ПАНКРЕАТОБИЛИАРНОЙ ЗОНЫ, ОСЛОЖНЕННЫМИ МЕХАНИЧЕСКОЙ ЖЕЛТУХОЙ

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Резюме

В работе представлены результаты комплексного паллиативного лечения с применением фотодинамической терапии (ФДТ) больных со злокачественными новообразованиями (ЗНО) панкреатобилиарной зоны, осложненными механической желтухой. В основной группе, включавшей 22 больных, было проведено паллиативное комплексное лечение с применением локальной и системной ФДТ новообразований панкреатобилиарной зоны, осложненных механической желтухой. В группе сравнения, состоявшей из 165 больных,

было проведено паллиативное комплексное лечение осложнений без применения ФДТ. В качестве фотосенсибилизатора использовали препараты хлоринового ряда: фотодитазин (у 21 пациента) и радахлорин (1 пациент). Первым этапом проводили системную ФДТ. В процессе инфузии через периферический доступ в кубитальную вену надвенно проводили лазерное облучение крови монохроматическим светом с длиной волны 662–665 нм и световой дозой 1200–1400 Дж/см^2. По истечении 3–5 ч с момента окончания инфузии вторым этапом осуществлялась локальная внутрипротоковая ФДТ путем облучения монохроматическим светом с длиной волны 662 нм и дозой света 220 Дж/см^2. На фоне применения локальной и системной ФДТ в основной группе в течение недели после лечения установлено статистически значимое уменьшение размеров опухолевого очага у больных с ЗНО поджелудочной железы по данным ультразвукового исследования брюшной полости, отмечено восстановление выведения желчи в кишечник у 100% больных с ЗНО желчевыводящих протоков и головки поджелудочной железы. Установлено увеличение медианы выживаемости пациентов опытной группы до 5,9 мес по сравнению с 4,7 мес в контрольной группе.

Ключевые слова: злокачественные новообразования панкреатобилиарной зоны, механическая желтуха, фотодинамическая терапия.

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Introduction

Malignant neoplasms of the pancreatobiliary zone remain a significant cause of death in the structure of oncological diseases of the Russian population. The standardized prevalence of pancreatic malignancy in 2018 was 13.5 cases per 100,000 population, and the prevalence of gall bladder and extrahepatic bile duct malighnancy was 5.9 cases per 100,000 population [1]. The prognostic median survival in non-resectable patients with a high risk of surgical treatment, according to the Harrel concordance index, is 3.7 months [2]. The mortality rate within a year from the diagnosis in patients with malignant disease of the pancreatic head was 66.9% in 2018, in those with gall bladder and extrahepatic bile ducts malignancy, 65.6% [1].

The modern approach to the treatment of patients with pathology of the pancreatobiliary zone is the use of a combined method with the leading role of surgical treatment. At the same time, it is essential to prevent complications of malignant diseases of the pancreatobiliary zone, the most common of which are mechanical jaundice and purulent cholangitis. At the time of detection and diagnosis, fewer than 20% of patients are operable, so the vast majority of patients receive palliative treatment [3-7].

In recent years, photodynamic therapy (PDT) has been used to treat patients with pancreatobiliary cancer [8, 9]. The first clinical study of the effectiveness of PDT in the treatment of locally advanced pancreatic tumors was perrformed in 2002 by S. G. Bown et al. The authors used the photosensitizer (PS) mesotetrahydroxyphenyl chloride in 16 patients with a tumor diameters from 2.5 to 6 cm. The median survival rate of patients after PDT was 9.5 months, and the 1-year survival rate from the moment of diagnosis was 44%. In 2 patients with tumor invasion into the gastroduodenal artery, gastrointestinal bleeding was observed, which was conservatively stopped, and 3 patients developed duodenal obstruction [10].

Of considerable interest is the research by M. T .Huggett et al., which included 15 patients with locally advanced pancreatic head cancer [11]. The average size of the tumor was 4.0 cm. The authors used Verteporfin as the PS. As a result of the treatment, no signs of tumor progression were observed in 11 patients 1 month after PDT, and in 6 patients 3 months after PDT. The median survival after PDT increased from 3-6 months to 8.8 months, and the survival from the moment of diagnosis reached 15.5 months. The side effects after local PDT included, in 3 patients, mild to moderate abdominal pain, and 1 patient had diarrhea.

More than 80% of patients with pancreatic head cancer and bile duct malignancies have local or remote metastatic lesions [3-7]. PDT in combination with surgical treatment has a great potential in eliminating complications, reducing tumor size, and improving patient survival [8, 9].

The purpose of this study was to evaluate the effectiveness of PDT in complex palliative treatment of patients with pancreatobiliary cancer complicated by mechanical jaundice.

Materials and methods

The comparative prospective study included 187 patients with mechanical jaundice of tumor origin who received treatment in the period from 2013 to 2019.

The main group consisted of 22 patients with pancreatobiliary malignancy who received complex palliative treatment with PDT. All the patients signed an informed consent for PDT. In 13 patients (59.1%), stage IV of the disease was established, stage III in 3 (13.6%), stage IIa in 5 (22.7%), and stage Ib in 1 (4.6%). In 21 (95.5%) patients, the process was found to be inoperable, and 1 (4.5%) patient underwent nominally radical surgical treatment. In

18 patients with stage III, IIa, Ib of the malignant process, surgical interventions were impossible due to decompensation of concomitant diseases of the cardiovascular or urinary systems, or liver failure. 1 patient was given 5 courses of PDT at intervals of 1 to 6 months, and another patient received 2 courses at the interval of 6 months.

In the comparison group, which included 165 patients with pancreatobiliary tumors, palliative complex treatment without PDT was performed in the period from 2013 to 2016. 44 patients (26.67%) were diagnosed with stage IV of the disease, 27 (16.36%) with stage III, 12 (7.27%) with stage IIb, 48 (29.09%) with stage IIa, 32 (19.39%) with stage Ib, 2 (1.21%) with stage Ia.

Comparative analysis of the topography of the pancreatobiliary zone in both groups of patients revealed no statistically significant differences (Table 1). According to the paired sample t-test, there were no statistically significant differences in gender, age, or duration of the disease between the compared groups.

In the main group, 5 (22.7%) patients had mild, 6 (27.3%) moderate, and 11 (50.0%) had severe mechanical jaundice. In the comparison group, there were 36 (21.8%) patients with mild, 33 (20.0%) with moderate, and 96 (58.2%) with severe mechanical jaundice. The severity of jaundice was assessed according to the classification of mechanical jaundice suggested by M. I. Bykov et al. [12].

In the main group, 4 (18.2%) patients had blood leukocytosis, 8 (36.4%) had purulent cholangitis. In 9 (40.9%) patients, clinical and laboratory signs of renal dysfunction with creatinine elevation above 106 mmol/l in men and 90 mmol/l in women were detected, accompanied by oliguria in all patients.

The comparison group included 75 (46.0%) patients with purulent cholangitis. In 73 (44.8%) patients, blood leukocytosis was observed, in 27 (16.6%), clinical and laboratory signs of renal dysfunction were detected with a rise in creatinine above 106 mmol/l in men and 90 mmol/l in women, accompanied by oliguria in 25 (15.3%) patients, and anuria in 2 (1.2%).

According to abdominal ultrasound, the largest sizes of pancreatic tumors before treatment in patients of the compared groups did not significantly differ (Table 2).

Complex treatment in both groups involved palliative surgical interventions, including percutaneous

Таблица 1
Топография злокачественных новообразований панкреатобилиарной зоны
Table 1
The pattern of the disease in patients with acute complications of tumors of the pancreatobiliary zone

Злокачественное новообразование Malignant neoplasm	Группа больных Group of patients				p
	основная (n – 22) main (n – 22)		сравнения comparison (n – 165)		
	абс. число abs. number	%	абс. число abs. number	%	
Желчных протоков, в том числе: Bile ducts, including:	5	22,73	60	36,81	> 0,1
внутрипеченочных intrahepatic	1	4,55	18	11,04	> 0,1
внепеченочных extrahepatic	1	4,55	21	12,88	> 0,1
желчного пузыря gallbladder	0	0,00	8	4,91	> 0,1
ампулы Фатерова сосочка Ampulla of Vater	3	13,64	13	7,98	> 0,1
Поджелудочной железы, в том числе: Pancreas, including:	17	77,27	105	64,42	> 0,1
головки head	17	77,27	104	63,80	> 0,1
тела и хвоста body and tail	0	0,00	1	0,61	> 0,1

Таблица 2
Сравнительная характеристика наибольших размеров злокачественных новообразований поджелудочной железы в двух группах до лечения по данным ультразвукового исследования брюшной полости (Me (Q_1; Q_3), в мм)
Table 2
Comparative characteristics of the largest sizes of pancreatic malignancies before treatment according to ultrasound examination of the abdominal cavity (Me (Q1; Q3), in mm)

Метод исследования Method of examination	Максимальный размер образования, мм Maximal size of tumor, mm		
	основная группа main group	группа сравнения comparison group	p
	Me (Q_1; Q_3)	Me (Q_1; Q_3)	
УЗИ Ultrasound	40,40 (35,38; 46,50)	42,66 (39,36; 45,95)	>0,1

Примечание: Me – медиана, Q_1, Q_3 – нижний и верхний квартили
Note: Me is the median, Q1, Q3 are the lower and upper quartiles

catheterization of the bile ducts (right and left lobular ducts, external-internal drainage, antegrade and retrograde stenting, etc.) under ultrasound and x-ray control in order to stop mechanical jaundice and impose bypass biliodigestive anastamoses, as well as detoxification, antispasmodic, hepatoprotective, infusion, and antibacterial therapy.

In the main group, 5 (22.7%) patients underwent a single drainage of the bile ducts, while 17 (77.37%) had it twice. During primary bile duct drainage, 20 (91.0%) patients had external bile duct drainage (19 on the right, 1 on the right and left), 1 (4.5%) had external gall bladder drainage, and 1 (4.5%) had bilobate external bile duct drainage. For the second time, 17 (77.3%) patients had external drainage replaced by external-internal drainage, 2 (9.1%) had hepaticojejunostomy, and 1 (4.5%) underwent conditionally radical gastropancreatoduodenal resection. Subsequently, antegrade stenting of the bile ducts was performed in 11 (50.0%) patients. In the postoperative period on the 7th to 30th days, all the patients underwent PDT.

In the comparison group, 39 (23.6%) patients had external drainage of the bile ducts, 24 (14.5%) had external drainage of the gallbladder, and 2 (1.2%) had bilobate external drainage of the bile ducts. In 80 (48.5%) patients, hepaticojejunostomy was used, choledochojejunoanastomosis in 4 (2.4%), and transhepatic drainage of the bile ducts was performed on 32 (19.4%). During repeated drainage in 4 (2.4%) patients, secondary procedure was performed to transform the external drainage into the external-internal one.

Palliative local and systemic PDT was performed in all patients of the main group, with the use of the following photosensitizers:

1. 21 patients underwent PDT ith photoditazine (OOO "VETA-GRAND", Russia), of which 20 had a single course, and 1 had a double course. The infusion was performed by intravenous drip-feed at the dose of 1 mg/kg of body weight. The calculated dose was dissolved in 200-500 ml of 0.9% normal saline depending on the patient's hemodynamic parameters and administered by intravenous drip-feed for 30-40 minutes;
2. in 1 patient, PDT was performed with Radachlorin (OOO "RADA-PHARMA", Russia); 5 courses were administered. The infusion was performed by intravenous drip-feed at the dose of 1 mg/kg of body weight. The calculated dose was dissolved in 200-500 ml of 0.9% normal saline depending on the patient's hemodynamic parameters and administered by intravenous drip-feed for 30-40 minutes.

At the first stage, a systemic PDT was performed. During the infusion, through peripheral access into the cubital vein supravenously, blood was irradiated with monochromatic light with a wavelength of 662-665 nm and an exposure dose of 1200-1400 J/cm^2 with "LAMI-Helios", a specialized dual-frequency programmable laser device (OOO "Novyie Khirurgicheskiye Technologii", Russia). In accordance with TU 9444-001-53807582-2010, the radiation power was 0.7 W, and the radiation power density was 0.22 W/cm^2.

After 3-5 hours since the completion of the infusion, the second stage was implemented, which was local photodynamic therapy by irradiation with monochromatic light with a wavelength of 662 nm at a dose of 220 J/cm^2 with "LAMI-Helios", a specialized dual-frequency programmable laser device with power of 0.7 W and power density of 0.22 W/cm^2 using percutaneous transhepatic antegrade access and/or endoscopically with video esophagoscopy/duodenoscopy via retrograde access depending on the nature of the patient's disease: in patients with malignant tumors of extra- and intra-

Таблица 3
Сравнительная характеристика наибольших размеров злокачественных новообразований головки поджелудочной железы у пациентов основной группы по данным ультразвукового исследования и МСКТ с внутривенным болюсным контрастированием брюшной полости в динамике (Me (Q1; Q3), в мм)
Table 3
Comparative characteristics of the largest sizes of malignant neoplasms of the head of the pancreas in the main group according to ultrasound and MSCT with intravenous bolus contrasting of the abdominal cavity in dynamics (Me (Q1; Q3), in mm)

Метод исследования Method of examination	Максимальный размер образования, мм Maximal size of tumor, mm		
	до ФДТ before PDT	3–7 дней после ФДТ 3–7 day after PDT	p
	Me (Q_1; Q_3)	Me (Q_1; Q_3)	
УЗИ Ultrasound	39,50 (33,50; 48,50)	35,50 (30,00; 44,00)	< 0,05
МСКТ с внутривенным болюсным контрастированием MSCT with intravenous bolus contrasting	39,00 (32,00; 44,78)	34,00 (27,50; 38,75)	0,438

Примечание: Me – медиана, Q_1, Q_3 – нижний и верхний квартили
Note: Me is the median, Q1, Q3 are the lower and upper quartiles

hepatic biliary ducts and gall bladder, only through the antegrade access, patients with malignant tumors of hepaticopancreatic ampulla and pancreas, first, through antegrade, and then via retrograde access.

All patients of the main group with pancreatic malignancies had the size of their neoplasm determined before PDT, as well as within 1 week after PDT, with the use of instrumental methods of examination, including ultrasound and multispiral computed tomography (MSCT) with intravenous bolus contrast.

The Shapiro-Wilk test was used to analyze the distribution of the studied indicators. The test results showed an abnormal distribution of all the studied indicators. Statistical evaluation of the results was performed with nonparametric Wilcoxon test for related samples. The survival rate of patients in the study groups was analysed with the Kaplan–Meier estimator, and a log-rank test was used to compare the survival curves. The critical level of the study results significance was assumed to be $p<0.05$. Statistical data was obtained with the use of SigmaPlot 11.0 statistical program (registration number 775050001).

Results and discussion

In both groups, the clinical manifestations of mechanical jaundice were stopped. The assessment of the biliary tree patency after PDT revealed, in all patients of the main group, that bile excretion in the intestine was restored, the feces had normal color, the urine became light yellow, the skin itching disappeared, the skin jaundice decreased, there were no side effects of allergic origin or postoperative complications from the complex treatment. In the comparison group, 131 postoperative complications were observed among 165 patients.

The analysis of the largest size of the pancreatic head malignant tumor in the main group according to abdominal ultrasound and MSCT with intravenous bolus contrast enhancement performed as follow-up showed a statistically significant reduction in the size of the tumor according to the results of abdominal ultrasound, from 39.50 mm to 35.50 mm (Table 3).

A comparative study revealed a statistically significant decrease in the size of the neoplasm according to abdominal ultrasound 1 week after treatment; no statistically significant decrease or increase in the size of the neoplasm was found according to abdominal MSCT with intravenous contrast enhancement.

In the compared groups, the Kaplan–Meier estimator was used to perform a comparative assessment of patient survival. The highest average overall long-term survival was found in patients of the main group who were followed for a year or more (Table 4). The survival curves of the studied groups were compared with a log-rank criterion, which revealed that the average overall survival in the main group of patients was higher than in the comparison group ($p < 0.05$) (Fig. 1).

Thus, these results confirm the data obtained from the study by M. T. Huggett et al. [11] concerning an increase in the median survival rate of patients. The proposed new method of local and systemic photodynamic therapy in combination with complex treatment of patients with pancreatobiliary malignancy allowed for the improvement in the quality of life of the patient, with high safety and no surgical complications, increase the overall survival rate and reduce the risk of complications due to the slower growth of the neoplasms. At the moment, PDT is the therapy of choice for patients who are not recommended radical surgical treatment and who are unable to tolerate other types of palliative treatment satisfactorily due to their high toxicity. This is especially important for patients with pancreatobiliary malignancy, since more than 80% of them have local or remote metastatic lesions. PDT has a great potential in combination with the surgical method in eliminating complications, reducing the size of the tumor, increasing survival; unlike chemo- and radiation therapy, PDT does not involve immunosuppression and the risk of systemic complications.

Clinical observation

The patient, aged 75, was admitted to the affiliated hospital of the Departmental and Hospital Surgery Subdepartment named after Professor I. I. Neymark with a course of Continuing Professional Education in surgery, with complaints of dark urine, discolored stool, jaundice of the skin, itching, aching in the right hypochondrium.

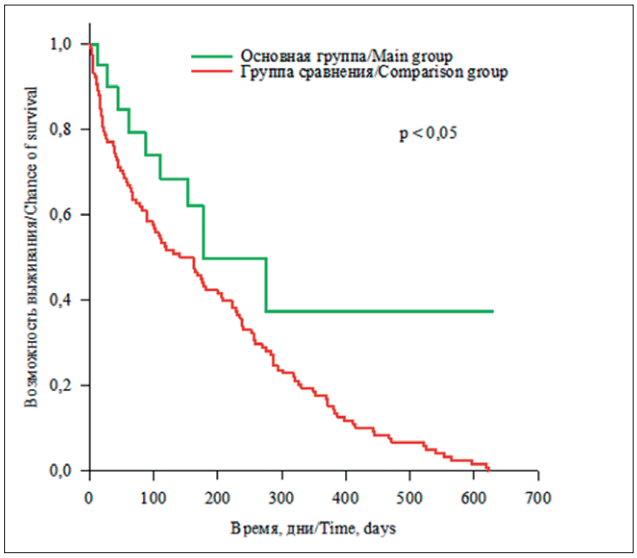

Рис. 1. Кривые выживаемости больных после комплексного лечения, включавшего фотодинамическую терапию (основная группа) и без нее (группа сравнения)
Fig. 1. Survival curves of patients after the complex treatment including photodynamic therapy (main group) and without it (comparison group)

He considers himself ill for 5 months, since he noticed the above symptoms. The jaundice was determined to be mechanical, of tumor genesis. The patient underwent external drainage of the bile ducts under ultrasound control

Таблица 4
Сравнительная характеристика групп больных со злокачественными новообразованиями панкреатобилиарной зоны по показателям выживаемости (Me (Q_1; Q_3), в днях)
Table 4
Comparative characteristics of patient groups in terms of survival (Me (Q1; Q3), in days)

Группа Group	Медиана выживания, дни Median of survival, days	Стандартная ошибка Standard error	95% доверительный интервал 95% confidence interval	p
	Me (Q_1; Q_3)			
Основная Main (n – 22)	177 (275; 87)	59,09	61,17–292,83	0,042
Сравнения Comparison (n – 165)	141 (287;38)	29,87	82,45–199,55	

Примечание: Me – медиана, Q_1, Q_3 – нижний и верхний квартили.
Note: Me is the median, Q1, Q3 are the lower and upper quartiles.

on the right, with cholangiography. According to cholangiography data, the expansion of intrahepatic ducts and ductus hepaticocholedochus was present, with a break at the level of the middle third of the ductus hepaticocholedochus. The mechanical jaundice was relieved.

After 1 month in the emergency hospital, the patient had a cholecystectomy due to acute destructive cholecystitis, biliary stone extraction, and a biopsy of the tumor in the ductus hepaticocholedochus. Pathoanatomic conclusion on intraoperative biopsy: cancer of the common bile duct mucosa (adenocarcinoma) T3N1M0 (according to intraoperative data).

Subsequently, the patient, in a state of moderate severity, was admitted to the affiliated hospital of the Departmental and Hospital Surgery Subdepartment named after Professor I. I. Neymark with a course of Continuing Professional Education in surgery. The skin was jaundiced, heart rate: 70 bpm, blood pressure: 110/60 mm Hg, the size of the liver according to Kurlov: 9x8x6 cm, peritoneal signs: negative, feces: acholic, urine: dark yellow.

Complete blood count at admission: hemoglobin: 154 g/l, hematocrit: 48.2%, WBC: 4.8x10^9/l, ESR: 10 mm/h. Biochemical blood analysis at admission: total bilirubin: 118 mmol/l, indirect: 5 mmol/l, direct: 113 mmol/l, AST: 67 U/l, ALT: 128 U/l, alkaline phosphatase: 449 U/l, alpha-amylase: 85 mg/l, total protein: 67 g/l, creatinine: 99 mmol/l, fasting glucose: 5.3 mmol/l, sodium: 136 mmol/l, potassium: 4.9 mmol/l.

Abdominal ultrasound findings: liver: Oblique Y-Dimension: 170 mm; thickness of the right lobe: 136 mm; Craniocaudal dimension: 116 mm; thickness of the left lobe: 80 mm; thickness of the caudate lobe: 23 mm. No space-occupying lesions were found in the liver. The diameter of the portal vein is 12 mm; the IVC diameter is 14 mm. Intrahepatic ducts are expanded: segmental to 5 mm, lobular to 9 mm. The ductus hepaticocholedochus is expanded to 15 mm and is bluntly broken off at the level of the head of the pancreas; its course is non-linear. The maximum size of the head is 30 mm; body: 20 mm, the tail: 25 mm. The Wirsung's duct was not dilated. Conclusion: biliary hypertension syndrome, low block level. The increase in the size of the liver.

The patient underwent antegrade and retrograde cholangiography prior to complex treatment, which provided a visualization of a tumor stricture in the area of the common hepatic duct after the confluence zone of the lobular ducts (Fig. 2a). The procedures performed included endoscopic papillosphincterotomy, stenting of the common bile duct, local and systemic PDT. Retrograde cholangiography and choledochoscopy were performed after complex therapy with PDT based on Radachlorin, according to the method outlined above (Fig. 2b, c). Retrograde cholangiography performed in the follow-up after the complex treatment showed a recovered lumen of the common bile duct, with restored borders and patency. Retrograde choledochoscopy performed on the patient after the complex treatment visualized the restored patency of the common bile duct and a reduced size of the neoplasm in the choledochus.

The complete blood count at discharge: hemoglobin: 140 g/l, hematocrit: 45.4%, WBC: 5.48x10^9/l, ESR: 34

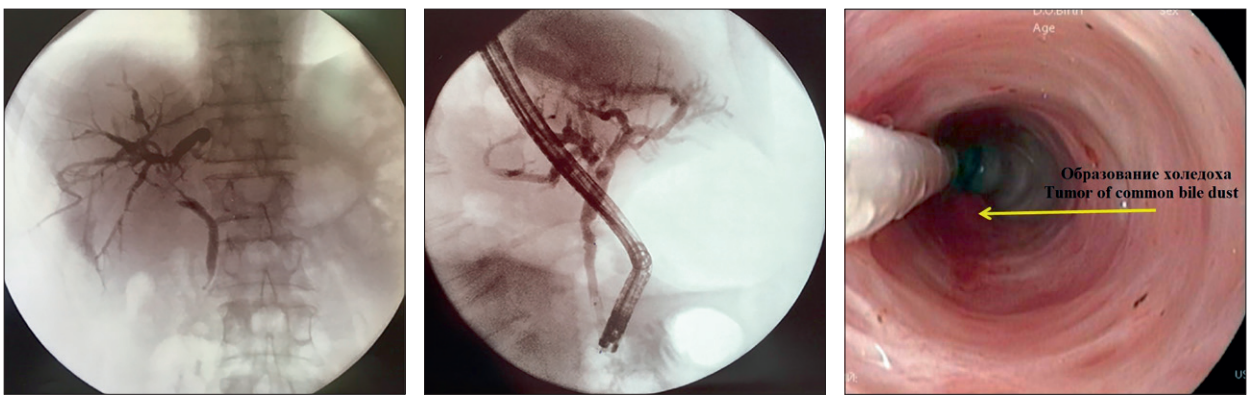

Рис. 2. Результаты исследований, полученные в ходе терапии пациента:
а – андеградная и ретроградная холиангиография до проведения комплексного лечения с применением фотодинамической терапии;
b – ретроградная холангиография после проведения комплексного лечения с применением фотодинамической терапии;
c – холедохоскопия после проведения комплексного лечения с применением фотодинамической терапии

Fig. 2. The results of the study conducted during the patient's therapy
a – antegrade and retrograde cholangiography before the complex treatment using photodynamic therapy;
b – retrograde cholangiography after the complex treatment using photodynamic therapy;
c – retrograde patient choledochoscopy after the complex treatment using photodynamic therapy

mm/h. Biochemical blood analysis at discharge: total bilirubin: 11 mmol/l, indirect: 6 mmol/l, direct: 5 mmol/l, AST: 14 U/l, ALT: 19 U/l, alkaline phosphatase: 158 U/l, alpha-amylase: 98 mg/l, total protein: 67 g/l, urea: 5.2 mmol/l, creatinine: 79 mmol/l, fasting glucose: 7.04 mmol/l, sodium: 145 mmol/l, potassium: 4.5 mmol/l.

The patient was discharged for outpatient observation and treatment, in a satisfactory condition.

Conclusion

Palliative treatment with PDT of the pancreatobiliary zone malignant tumors complicated by mechanical jaundice allowed to restore the lumen of the bile ducts, which stopped the clinical presentation of life-threatening complications.

Palliative treatment with PDT of malignant neoplasms of the pancreatic head complicated by mechanical jaundice made it possible to reduce the largest size of the neoplasm within a week (according to abdominal ultrasound) and to increase the survival rate of patients who are not recommended radical surgical treatment.

The findings of our study indicate the good prospects of further research into the possibilities of the use of PDT in the complex treatment of this severe category of patients.

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APPLICATION OF PHOTODYNAMIC THERAPY IN COMPLEX TREATMENT OF PURULENT DISEASES OF THE HAND

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Abstract

For many years, the treatment of purulent diseases of the hand has stayed relevant. Despite the progress in modern medicine, this pathology retains its prevalence and, most importantly, is often found in patients of the working age, which determines the socio-economic importance of the search for new approaches to the treatment of purulent diseases of this localization. In the purulent surgery department of State Clinical hospital № 4, a study and treatment of two groups of patients were carried out: patients with phlegmons and felons of the hand with open management of postoperative wounds using traditional treatment methods (antibiotic therapy, immobilization, dressings with antiseptic solutions and ointments, the use of wound enzymes) and with the use of photodynamic therapy (PDT) in the postoperative period. PDT was performed on the second or third day after opening the phlegmon or felon using an ATKUS-2 semiconductor laser (AO "Poluprovodnikovye pribory", Russia) with an output power of 1 to 2 W, an operating wavelength of 660 ± 0.03 nm and an energy density between 20 and 25 J/cm^2 after application of the photosensitizer based on chlorin e_6 to the treated wound area. The article describes the technique of PDT in patients with purulent diseases of the hand. It was found that it is optimal to perform PDT as early as possible after the operation period, but not earlier than on the second day after the operation, because earlier dressing is especially painful in the absence of sutures and can lead to bleeding from a postoperative wound when the dressing is removed. The effectiveness of treatment in the studied groups was evaluated: the terms of inpatient healing in the groups were compared; the dynamics of the course of the wound process was analyzed. When comparing the results of the two groups, a significant acceleration in the healing of the postoperative wounds was noted in patients for whom PDT was used – 5 days (1.4 times) faster compared to treatment according to the generally accepted technique. The early appearance of granulations and the antibacterial effect of this procedure are noted, which significantly improves the treatment outcome for this pathology. This makes the use of PDT relevant and appropriate in the complex treatment of purulent diseases of the hand

Keywords: photodynamic therapy, purulent diseases of the hand, drainage system, photosensitizer, necroectomy.

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ПРИМЕНЕНИЕ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В КОМПЛЕКСНОМ ЛЕЧЕНИИ ГНОЙНЫХ ЗАБОЛЕВАНИЙ КИСТИ

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Резюме

Многие годы не теряют актуальности вопросы лечения гнойных заболеваний кисти. Несмотря на прогресс в современной медицине, данная патология сохраняет свою распространенность и, что наиболее важно, часто встречается у пациентов трудоспособного возраста, что обуславливает социально-экономическую важность поиска новых подходов к лечению гнойных заболеваний данной локализации. На базе отделения гнойной хирургии ГБУЗ ГКБ № 4 проведено исследование и лечение двух групп больных: пациентов

с флегмонами и панарициями кисти при открытом ведении послеоперационных ран при применении традиционных методик лечения (антибактериальная терапия, иммобилизация, повязки с антисептическими растворами и мазями, применение раневых ферментов) и с применением в послеоперационном периоде фотодинамической терапии (ФДТ). ФДТ выполняли на вторые-третьи сутки после вскрытия флегмоны или панариция с использованием полупроводникового лазерного аппарата «АТКУС-2» (АО «Полупроводниковые приборы», Россия) с выходной мощностью от 1 до 2 Вт, рабочей длиной волны 660±0,03 нм и плотностью энергии от 20 до 25 Дж/см^2 после аппликации на обрабатываемую раневую область фотосенсибилизатора на основе хлорина e_6.
В статье описана методика проведения ФДТ у пациентов с гнойными заболеваниями кисти. Установлено, что оптимально проводить ФДТ в максимально ранние сроки после операционного периода, но не ранее, чем на вторые сутки после операции, так как перевязка в более ранние сроки особенно болезненна в условиях отсутствия швов и может привести к кровотечению из послеоперационной раны при удалении повязки. Проведена оценка эффективности лечения в исследуемых группах: выполнены сравнение сроков стационарного заживления в группах, проведен анализ динамики течения раневого процесса. При сравнении результатов терапии отмечено достоверное ускорение в 1,4 раза (на 5 суток) заживления послеоперационных ран у пациентов, у которых применялась ФДТ, по сравнению с лечением по общепринятой методике. Отмечено раннее появление грануляций и антибактериальный эффект ФДТ, что существенно улучшает результат лечения данной патологии. Это делает применение ФДТ актуальным и целесообразным в комплексном лечении гнойных заболеваний кисти.

Ключевые слова: фотодинамическая терапия, гнойные заболевания кисти, дренажно-промывная система, фотосенсибилизатор, некрэктомия.

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ORIGINAL ARTICLES

Introduction

The problem of treating panaritium and hand phlegmons remains complex and relevant, despite the progress achieved by modern medical science. Among the primary patients who go to the surgeon with purulent diseases, patients with panaricia and phlegmon of the hand make up from 15% to 31% [1], 50% to 85.5% of them being people of working age. It is noted that men develop this disease more often than women [2]. Temporary disability caused by purulent diseases of fingers and hands entails economic losses which are many times higher than those related with purulent processes of other localizations.

According to the literature, 17-60% of patients with bone panaritium undergo phalange amputation. Up to 48% of minor hand injuries are complicated by suppuration, which makes microtrauma one of the leading factors in the development of a severe purulent process on the fingers and hand [1, 2].

Very often, pain in purulent inflammatory pathology of the hand is felt constantly, which leads to a serious deterioration of the patients' quality of life. Due to the violation of the function of the hand and the peculiarities of the course of the pathological process, purulent diseases of the hand result in a sharp decline in the effectiveness and quality of professional activity [3, 4].

In the surgical treatment of purulent pathology of fingers and hands, the method of choice is the one developed and implemented in the 1990s by the Department of General Surgery of the Pediatric Department of Russian National Research Medical University (under the supervision of Prof. A. P. Chadaev), the main principles of which are optimal access, adequate necrectomy and installation of a drainage and irrigation system (DIS) in the wound, with the imposition of primary stitches on the skin at the stage of surgery completion. However, in the case of extensive injuries to the hand, it is often not possible to fully close the wound defect, so there is a need for open wound management. In addition, there are a number of medical contraindications to applying DIS and maintaining a wound under primary sutures, such as bite wounds and crushed wounds [1-5]. Open management of hand wounds leads to a higher number of hospital bed days. At the same time, the risk of secondary infection increases, and there is a need for frequent dressings, which in the absence of stitches are very painful. Thus, it is necessary to find more new effective methods of treating wounds in the early postoperative period.

Photodynamic therapy (PDT), widely used worldwide for the treatment of purulent diseases, is one of the promising methods of treatment of purulent wounds of various localities [6-9].

PDT is a method of treating oncological diseases, as well as certain skin diseases (psoriasis, ichthyosis, pustular diseases, etc.) or infectious diseases, inflammatory diseases of the mucous membranes (including chronic periodontitis), based on the use of photosensitizers and laser radiation of a certain wavelength [10-16]. At the beginning of the XX century, scientists G. Raab and G. Tappeiner found that some dyes, which are harmless or slightly poisonous to infusoria in the dark, kill them very quickly in the light. This phenomenon was called the

photodynamic effect. The effect is observed only in the presence of oxygen in the environment [17, 18].

Hardly any information is found in domestic and foreign literature concerning the use of PDT in the treatment of purulent diseases of the hand.

The purpose of this work was to study the effectiveness of PDT-based treatment and traditional therapy methods for patients with purulent diseases of the hand in open management of postoperative wounds.

Materials and methods

The results of treatment of 86 patients with purulent diseases of the fingers and hands admitted to the the Department of purulent surgery of the City Clinical Hospital No. 4 of Moscow for the period from December 2017 to December 2018 were analysed. The age of patients ranged from 19 to 64 years, 78 (90.7%) of them being of employable age. Deep forms of panaritium occurred in 51 (59.3%) patients, phlegmons of the hand in 31 (36.0%), phlegmons of the hand with a transition to the forearm, in 4 (4.7%). The hand that most often (in 90% of the patients) was affected was the right hand. The most common concomitant pathologies in the patients were type II diabetes mellitus, in 10 (20%) cases, cardiovascular diseases, in 8 (16%), multiple drug use, 3 (6%), systemic lupus erythematosus, 1 patient. In terms of the causal factor, non-industrial injuries prevailed (45%), followed by bitten wounds (30%), industrial injuries (10%), post-injection phlegmons (5%), and wounds of unknown origin (10%).

Depending on the treatment method, the patients were divided into two comparable groups by age and gender, forms of the disease, and the duration of the disease before admission to the hospital. The main group consisted of 43 patients who underwent PDT after the opening of the suppurative focus; the control group consisted of 43 patients who were treated according to the generally accepted method.

All patients had a standard examination before the study, which included an assessment of clinical and laboratory data, radiography of the damaged hand, and ultrasound examination of the soft tissues of the hand. According to the indications, tetanus vaccination was administered (tetanus toxoid and tetanus serum according to the scheme), and wound components underwent bacteriological and histological examination at various times of the treatment.

At the first stage, patients in both groups were treated surgically. Purulent focus dissection, necrectomy and drainage were performed under local conductor anesthesia corresponding to the level of the infectious lesion.

Patients of the control group were subsequently subject to the standard combined treatment, which included antibacterial therapy, analgesics, daily dressings with antiseptics, physiotherapy (UHF, ultraviolet irradiation, magnetotherapy).

Рис. 1. Проведение сеанса фотодинамической терапии гнойной раны кисти
Fig. 1. Conducting a session of photodynamic therapy of the purulent wound of the hand

PDT was administered to the main group of patients in the postoperative period. A PDT session was administered as early as possible: on the second (less often on the third) day after the opening of the suppurative focus, in the context of open wound management. In the earlier postoperative period, the appointment of a PDT session is not recommended, since there is a high risk of bleeding from the wound upon the removal of the dressing; in addition, wound dressing in the first day is quite painful. The number of PDT courses varied from 1 to 2, depending on the area of damage to the hand and the dynamics of wounds cleaning.

A PDT session consisted of the following stages. A bandage with a photosensitizer based on e_6 chlorine (PS) was applied to the wound for 20 to 30 minutes. The amount of PS was calculated based on the dosage of 1 ml per 3-5 cm^2 of the treated surface. Then the wound was washed with saline solution to remove the residual PS. Activation of PS was performed immediately after the completion of the drug exposure and the removal of PS residues by light exposure to the wound surface with laser radiation with an output power of 1-2 W, at a wavelength of 660±0.03 nm, and energy density from 20 to 25 J/cm^2 (Fig. 1). The treatment was performed with "ATKUS-2" device (AO "Poluprovodnikovyie Pribory", Russia). The irradiation time for external light supply provided

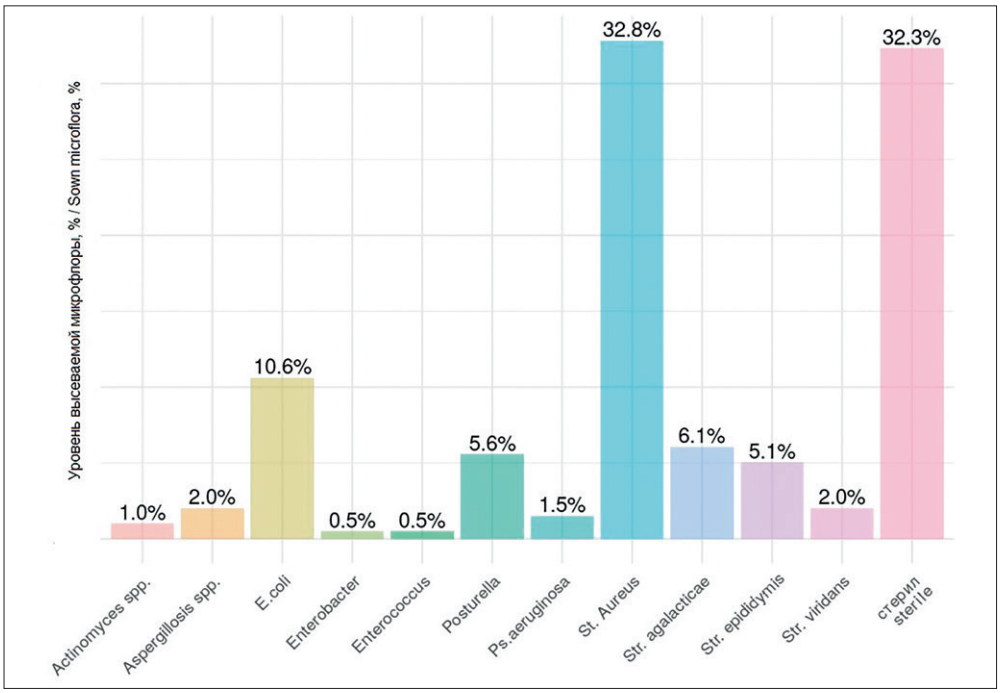

Рис. 2. Микрофлора раны при первичном посеве
Fig. 2. Wound microflora after the initial seeding

with optic fiber guides with a polished end was determined by the formula [19, 20]:

$$T\,(\text{s}) = E_s\,(\text{J/cm}^2) / P_s\,(\text{W/cm}^2),$$

where T is the irradiation time, E_s – is the required light dose (energy density), and P_s is the power density.

The cases administered PDT were observed to have a wound cleansing process, a reduction of microcirculatory disorders, and a reinforcement of previously suppressed sequential reparative processes: macrophage reaction, collagen synthesis, scarring and epithelization. Maturing granulation tissue with vertical vessels, fibroblasts, and pronounced fibrillogenesis was determined on days 6 -7. To assess the bacterial landscape of the wound, the wound contents were inoculated in a sterile test tube with a nutrient medium before and after the PDT session. The biological material was collected with a sterile cotton swab and then transferred to nutrient media in Petri dishes. Histological examination of the wound edge tissues was performed on days 2, 3 and 6 after PDT sessions in order to assess the dynamics of inflammation and determine the timing of the granulation tissue emergence.

Statistical processing of the obtained data was performed by variation statistics with the definition of Student test with 2017 Microsoft Office (Word, Excel). The mean values were compared, including the determination of measurement error and the reliability of differences in the length of hospital stay and time of wound healing between the study groups. Differences were assessed as significant at $p<0.05$.

Results

The duration of inpatient treatment of patients with purulent wounds of the hand depended on the origin of the wound, the depth of the lesion, and the time of hospitalization from the moment of the injury. In the traditional therapy group, the average duration of inpatient treatment was 13±1 days, complete wound healing was observed 17±1 days after the surgery; 30% of patients required repeated necrectomy, lavage of the purulent necrotic focus. In patients who underwent PDT in the postoperative period, the duration of inpatient treatment was 7±1 days ($p = 0.03$), and complete wound healing was observed after 12 days.

The primary bacterial seeding of wound discharge performed during surgical treatment revealed Staphylococcus aureus in 1/3 of the patients (32.8%) which was confirmed by the results of laboratory studies and coincides with earlier data from other authors [1, 2, 21]. The results of inoculations with no growth of microorganisms may be due to anaerobic microflora, which is not possible to plate with conventional methods of sample collection for inoculation.

The microbiological study of intraoperative inoculations before PDT produced the following data: *Staphylococcus aureus*: 32,8%; *Streptococcus agalacticae*: 6,1%; *Streptococcus epididymis*: 5,1%; *Streptococcus viridans*: 2,0%; *Esherichia Coli*: 10,6%; *Enterobacter*: 0,5%; *Enterococcus*: 0,5%; *Posturela*: 5,6%; no growth: 32,3% (Fig. 2).

In part of the inoculations, the associated microflora was found to be *Candida albicans* (10.4%).

The antimicrobial effect of PDT was revealed by bacteriological research: in the inoculations produced after the completion of PDT courses, the growth of microorganisms detected during primary bacteriological studies was absent in all observations.

According to the clinical findings and the histological data, on the 2nd and 3rd days after PDT, the wound became cleared of purulent necrotic masses, and on the 5th day, granulation tissue appeared. Visual examination found that the amount of discharge from the wound in patients after PDT significantly decreased, the hyperemia of the wound edges and edema decreased by day 2 after the course of PDT, the quantity of fibrinous overlay was significantly lower than in patients of the control group, and the use of wound enzymes was no longer required.

After PDT, an analgesic effect was observed in all patients, which was expressed in a significant decrease in pain syndrome when subjectively evaluated on the standard pain scale. During the second dressing in both groups, the pain syndrome was 8-9 points, and immediately after the PDT session, the indicator decreased to 5-6 points and then progressively decreased to 1 point as assessed during dressing on the 5th day. In patients who did not undergo PDT, the pain syndrome on the 5th day remained at the level of 4-5 points.

The advantages of using this technique in the treatment of purulent wounds of the hand can also include the absence of additional destructive tissue lesions in the wound, the possibility of affecting deeply located tissues.

After PDT, amputation of the affected phalanges or repeated necrectomy were not required. During PDT, there was almost no bleeding during subsequent dressings.

No allergic reactions to the introduction of PS were observed. During the PDT session, the patient experienced no pain syndrome. No hyperthermia and no local inflammatory reaction were observed during the PDT session and after it.

As an example of the effective use of PDT in the treatment of hand phlegmon, we present the following clinical observation.

Patient K., 42 years old.

He was hospitalized in the Department of purulent surgery of the City Clinical Hospital No. 4 from December 5 to December 11, 2017 with a diagnosis of phlegmon of the back of the left hand.

Complaints on admission: pain in the left hand, hyperthermia.

According to the patient, 3 days before admission, he injured his left hand in a fight, and a day later he noted signs of inflammation. He was hospitalized in a purulent surgery unit. On admission: hyperthermia 38.9°C, state of moderate severity.

The clinical findings at admission (Fig. 3a): the back of the left hand is swollen, hyperemic, in the projection of the third intermetacarpal space, a wound of 2.0x4.0 cm in size is observed, with pronounced perifocal edema and hyperemia. Palpation of the back of the hand discovered a sharp pain, and a fluctuation was determined. Movements in the third and fourth metacarpophalangeal joints are limited and painful. Regional lymph nodes are not enlarged.

Рис. 3. Клиническая картина флегмоны левой кисти:
a – до операции;
b – после некрэктомии и вскрытия флегмоны;
c – через 2-е сут после проведения ФДТ;
d – на 12-е сутки после операции (амбулаторный этап лечения)

Fig. 3. The clinical picture of the phlegmon of the left hand:
a – before the operation;
b – after the necrectomy and phlegmon autopsy;
c – 2 days after the PDT;
d – on the 12th day after the operation (outpatient treatment)

Рис. 4. Рентгенограмма при поступлении (а и б – разные проекции)
Fig. 4. X-ray upon admission (a and б – different projections)

The x-ray of the hand dated 05.12.2017 (Fig. 4) shows no destructive or traumatic changes of the bone.

The ultrasound of the soft tissues of the left hand performed at admission showed an infiltration of tissues, with many accumulations of liquid.

The clinical and laboratory data were as follows: leukocytosis: up to 25,000 g/l, RBC: 4.04 million, hemoglobin: 136 g/l, hematocrit-38%, left shift in neutrophil band cells, ESR: 35 mm/h, blood glucose level: 5.2 mmol/l. On the day of admission, the patient underwent surgery, including incisions and necrectomy. However, in the postoperative period, inflammatory phenomena persisted, as well as purulent discharge from the wound, edema of the back of the hand, hyperthermia up to 38.3 C° (Fig. 3b).

Inoculations from the wounds found *Staphylococcus aureus* and *Escherichia coli* sensitive to the 3rd and 4th generation cephalosporins.

On the 2nd day after the operation (07.12.17), the patient was prescribed PDT with PS based on e_6 chlorine with an exposure of 15 min. The wound was irradiated with ATKUS-2 device for 4.5 minutes at a laser power of 2 W, a wavelength of 660±0.03 nm, and an energy density of 25 J/cm^2. During the session, the patient noted a tingling sensation in the area of the wound. After the session, the patient noted a decrease in pain, and the visual inspection after the completion of the PDT session showed that the amount of discharge from the wound decreased.

In the tissue sample taken from the wound edge before PDT, there are foci of necrosis and tissue edema (Fig. 3b). On the first day after the PDT session, a decrease in inflammatory phenomena was noted at histological examination; on the second day, fresh granulations were visualized in the wound, and no purulent discharge was detected (Fig. 3c), which was also confirmed by the results of inoculation of the wound content.

In the Department, the patient received analgesic therapy and daily aseptic dressings. Physical therapy was not administered.

The patient's condition at discharge was satisfactory. The postoperative wound was without signs of inflammation, the bottom of the wound was covered with red coarse granulations, there was no discharge, the wound

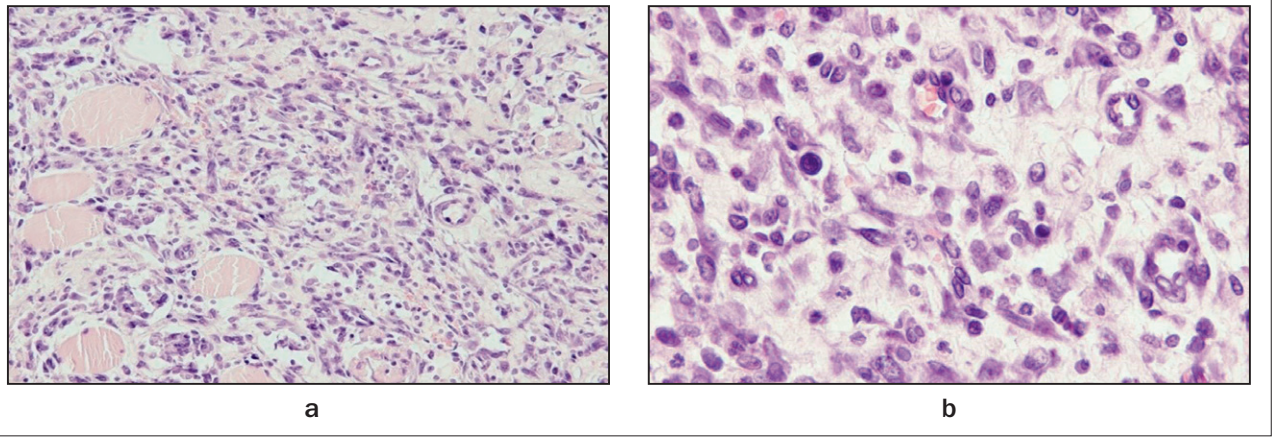

Рис. 5. Биоптат ткани, взятой из края раны пациента К. (окраска гематоксилином и эозином):
а – до курса ФДТ: фрагменты некротически измененных мышечных волокон и фибринозно-лейкоцитарного слоя; отек, полнокровие сосудов глубоких отделов раны, островки формирующейся грануляционной ткани (увеличение х120);
b – на вторые сутки после курса ФДТ: макрофаги и отдельные неориентированные фибробласты вблизи сосудистых элементов (увеличение х200)
Fig. 5. Tissue biopsy taken from the edge of the wound of patient K. (stained with hematoxylin and eosin):
a – before the PDT course: fragments of necrotic altered muscle fibers and fibrinous-leukocyte layer; edema, vascular congestion in the deep sections of the wound, islets of forming granular tissue (magnification x120);
b – on the second day after the PDT course: macrophages and individual non-oriented fibroblasts near vascular elements (magnification x200)

became completely clean. The edges of the wound are without inflammation, with signs of epithelization. The patient was discharged for outpatient treatment on the 5th day after the surgery. Plastic surgery to close the wound defects was not required, as the wounds healed (Fig. 3d).

Conclusion

The developed method of the use of PDT in the complex treatment of purulent diseases of the hand with open wound management has a positive effect on the course of the wound healing process, helps to accelerate purification and reduce the healing time of wounds by 1.4 times, reduces the duration of inpatient treatment by 1.8 times compared to the traditional method, and contributes to good functional results. The new method of PDT use improves the immediate and long-term results of patients treatment, which is of great socio-economic significance.

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EXPERIENCE OF USING AN EXCIMER LAMP EQUIPPED WITH UVB DOSE CONTROL SYSTEM IN DERMATOLOGY

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Abstract

Intermediate ultraviolet (UVB) therapy is considered a relatively safe method of treating skin diseases with an autoimmune component in development compared to medical drug methods, including PUVA therapy. This is due to the small depth of penetration of the rays of this wavelength range into skin, which provides a purely local effect on the human body. Excimer lamps are an alternative to the expensive excimer laser for phototherapy of psoriasis or vitiligo. However, for effective phototherapy using UVB lamps, the distance from an emitter to a patient's skin must be considered. In this paper, we report on treatment of patients using an excimer lamp, the control unit of which is equipped with an optical system for controlling of ultraviolet radiation dose, which allows automatically calculating the time for a set UVB dose. The article describes the results of phototherapy using an excimer lamp of several cases of psoriasis, vitiligo and other forms of dermatitis with a good therapeutic and cosmetic effect. When using an excimer lamp, not a single case of exacerbation of dermatological diseases was established.

Keywords: psoriasis, vitiligo, atopic dermatitis, phototherapy, UVB, excimer lamp, UV dose

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ОПЫТ ПРИМЕНЕНИЯ ЭКСИМЕРНОЙ ЛАМПЫ, ОСНАЩЁННОЙ СИСТЕМОЙ КОНТРОЛЯ UVB ДОЗЫ, В ДЕРМАТОЛОГИИ

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Резюме

UVB терапия считается относительно безопасным способом лечения кожных заболеваний с аутоиммунным компонентом в развитии в сравнении с медикаментозными методами, включая ПУВА терапию. Это обусловлено малой глубиной проникновения лучей данного диапазона длин волн в кожный покров, что обеспечивает сугубо локальное воздействие на организм человека. Эксимерные лампы являются альтернативой дорогостоящему эксимерному лазеру при фототерапии псориаза и витилиго. Однако для эффективной фототерапии с использованием UVB ламп необходимо учитывать расстояние от излучателя до кожи пациента. В данной работе сообщается о лечении больных с использованием эксимерной лампы, блок управления которой снабжён оптической системой контроля дозы ультрафиолетового излучения, что позволяет автоматически производить расчёт времени сеанса для заданной UVB дозы. В статье приведено описание результатов фотолечения с использованием эксимерной лампы нескольких случаев псориаза, витилиго и других форм дерматитов с хорошим терапевтическим и косметическим эффектом. При использовании эксимерной лампы не установлено ни одного случая обострения дерматологических заболеваний.

Ключевые слова: псориаз, витилиго, атопический дерматит, фототерапия, UVB, эксимерная лампа, доза ультрафиолетового излучения

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Introduction

In modern medicine, drug-based immunocorrection drugs are traditionally used for the complex treatment of immune system-related dermatological diseases and for the prevention of their recurrence. The chronic persistent nature of dermatoses with an immune component in pathogenesis requires long-term use of this group of drugs. However, taking into account the need for their lifelong use, there is a high risk of developing a wide range of side effects, as well as the tolerance syndrome to the drug [1], so today UV physiotherapy of skin diseases is considered the safest and most popular method of treating various forms of psoriasis [2], vitiligo [3] and other forms of dermatoses.

Experimental studies conducted in the early 80's of the last century showed high efficiency of phototherapy with the use of UVB irradiation (280-315 nm range) [4]. It has been proved that rays with a wavelength of more than 315 nm (UVA) are ineffective in the treatment of psoriasis, and short-wave radiation of the UVC range causes mutations and is carcinogenic, since it is within the absorption bands of DNA and RNA [5]. UVB therapy is a relatively safe treatment method due to the minimal impact of radiation on the human body. The rays of this wavelength range are completely dispersed in the epidermis [6], initiating photobiological reactions that contribute to the improvement of the skin [7].

Along with the spectral composition of the ultraviolet radiation, an important parameter in the process of phototherapy, which has a significant impact on the effectiveness of treatment, is the level of the ultraviolet dose when irradiating the patient's skin [8]. It is believed that the optimal effectiveness and safety of phototherapy in the treatment of psoriasis and/or vitiligo is achieved with the value of the minimum erythema dose (MED), which reflects the level of the patient's skin sensitivity to UVB radiation. A well-known technique for the determination of a patient's MED is used, which was described by P. Asawanonda et al. [8]. With a UVB dose below MED, phototherapy may be ineffective, and irradiation of the skin with a dose higher than MED will lead to a burn of the patient's skin, which may provoke an exacerbation of the disease [9].

Excimer lasers, which can generate coherent and directed radiation at a wavelength of 308 nm, are often used as a source of UVB radiation. Laser radiation produced by the decomposition of an exciplex XeCl* molecule has stable spectral and energy characteristics and is easily dosed, which makes excimer lasers a traditional choice for dermatological applications [10]. The disadvantages of the XeCl laser include the large size and weight of the device, the small area of the radiating surface, the need for maintenance, and the high cost of installation; in addition, the gas mixture used in the laser contains a hazardous dose of chlorine.

Phototherapy of large areas affected with dermal diseases is often provided with low-pressure fluorescent mercury lamps, which emit narrow-band ultraviolet with a band peak of about 311 nm. The configuration of UVB emitters based on such lamps is diverse: from portable lamps for home use to UV booths. However, mercury UVB lamps are characterized by a strong dependence of the radiation intensity on the temperature of the walls of the quartz envelope and a significant decrease in the radiation power over their relatively short service life (no more than 1,500 hours) [11], which significantly affects the accuracy of calculating the UVB dose with the use of these lamps.

The gas mixture of excimer lamps does not contain metal vapors, so the temperature of the flask walls of such lamps has little effect on their radiation power [12], and the use of an electrodeless system [13] of an excimer lamp can provide a service life of more than 8,000 hours [14]. Thus, excimer lamps do not need warming up before use and provide highly stable ultraviolet radiation.

Unfortunately, the use of semiconductor LEDs developed for UVB phototherapy (UVB LED) is not widespread, because there are problems with a rapid decline of the power of such LEDs, which reduces the efficiency of the semiconductor device [15].

Unlike lasers, all lamps developed for UVB therapy are characterized by a significant decrease in the intensity of radiation when the distance from the emitter to the irradiated surface increases, and for the calculation of the UVB dose received by the patient during a phototherapy session, it is necessary to take into account the distance to the patient's skin. It is obvious that the accuracy of distance measurement and the constancy of the distance will determine the actual UVB dose and the effectiveness of treatment in general.

Materials and methods

91 patients with the winter form of vulgar (plaque) psoriasis were treated, including 24 patients with I - III Fitzpatrick skin phototypes, 55 with vitiligo, and 12 with atopic dermatitis. Before the treatment, informed consent was obtained from the patients.

All patients were treated with an excimer lamp [16] developed in the Optical Radiation Laboratory of Immanuel Kant Baltic Federal University, where two XeCl emitters based on a barrier discharge were used as a source of UVB rays [17]. A distinctive feature of this device is the possibility of complete automatic no-touch control of the level of UV radiation dose received by the patient.

Results

The results of treatment of patients with psoriasis

The group of patients with psoriasis included 24 patients: 13 (54.2%) men and 11 (44.8%) women. The average age of patients was 34 (ranging from 21 to 48 years).

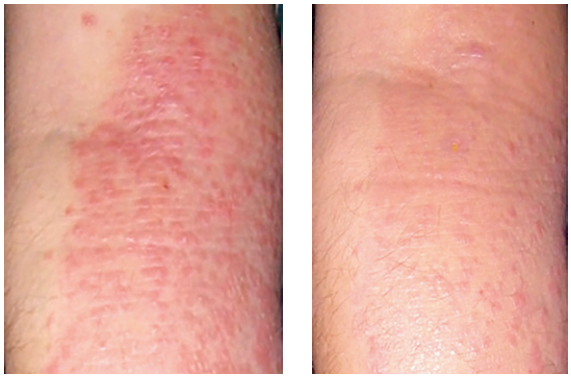

Рис. 1. Очаг псориаза на правой сгибательной внутренней поверхности верхней конечности:
a – до лечения;
b – после 6-го сеанса фототерапии
Fig. 1. Right bending inner surface of an upper limb:
a – before the treatment;
b – after the 6th session of phototherapy

The duration of psoriasis from its onset was from 1 to 19 years. All patients were treated on an outpatient basis in accordance with the described method. The initial UVB dose was from 0.1 to 0.3 J/cm^2. The course of treatment included 12 sessions held at regular intervals 3 times a week: Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. Each subsequent dose of the therapy session was increased by 0.1J/cm^2, which brought the final radiation dose within the range of 1.2-1.4 J/cm^2. Positive results in the form of plaques flattening and decreased inflammation activity were observed from the 6th session of the therapy. A persistent effect, expressed in maintaining the institutional stage of psoriasis, was persistent in all patients over the 8 months of the follow-up after the completion of therapy.

Clinical observation # 1. Male, 54 y. o. Diagnosis: plaque psoriasis. The PASI value before the start of therapy was 18 (Fig. 1a). After the final session of excimer lamp therapy, the patient had a clinical decrease in erythema, the plaques flattened, and the peeling on their surface was resolved (Fig. 1b). The PASI index was found to be 8. Observation of the patient for the next 6 months showed no signs of relapsing psoriasis: slight dyschromia persisted in the former areas of rash.

Clinical observation # 2. Male, 48 y. o. Diagnosis: plaque psoriasis, extensive, advanced stage. Disease history: he has been suffering from psoriasis for 20 years, and for a long time, he was treated with narrow-band phototherapy on a UV 1000 KL unit (Herbert Waldmann GmbH & Co, Germany) at a wavelength of 311 nm, which gave a temporary effect. He received treatment with Apremilast for 1 year, without any improvement. Clinical findings: the process is widespread, the skin of the lower extremities and the lower leg area features multiple flat papular elements of pinkish-red color, ranging in size from a pinhead to a small coin, infiltrated, dense, rising above the level of healthy skin, prone to coalescence and peripheral growth, grouped in plaques (Fig. 2a). Papules are covered with abundant easily separated scales of silvery-white color. The isomorphic reaction and the triad of psoriatic clinical sings are positive.

After the final series of excimer lamp therapy sessions, the patient had significantly flatter plaques, and the peeling on their surface was resolved (Fig. 2b).

Fig. 3 shows the results of the ultrasound examination of the patient's psoriatic plaque before treatment and 1 month after its start. The studies were performed with

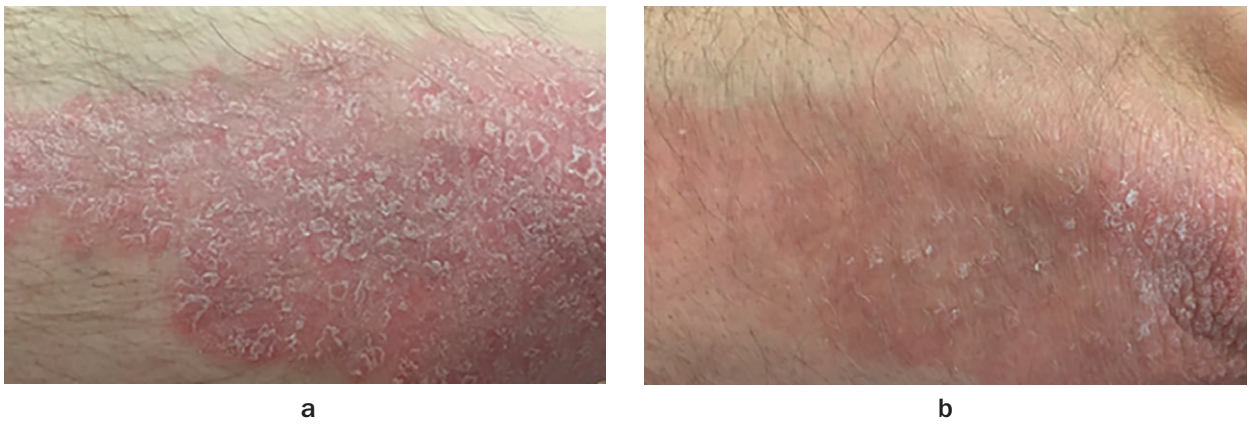

Рис. 2. Очаг псориаза на левой наружной поверхности верхней конечности:
a – до лечения;
b – после 12-го сеанса фототерапии
Fig. 2. Left outer surface of the upper limb:
a – before the treatment;
b – after the 12th session of phototherapy

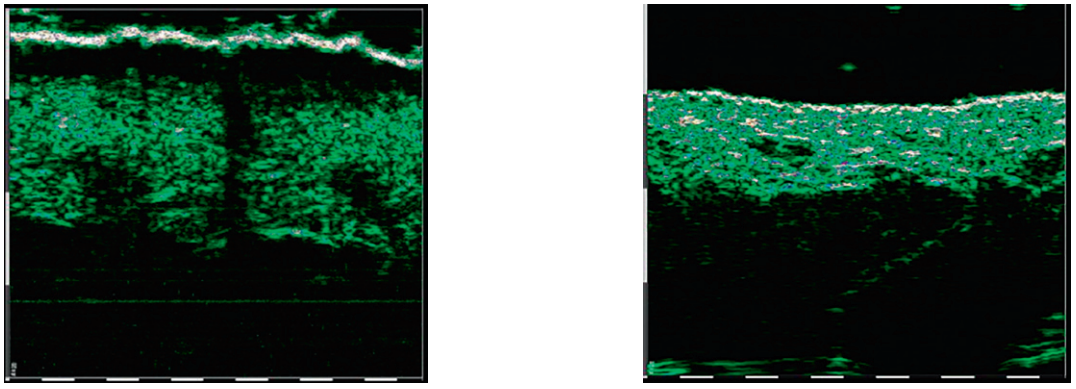

Рис. 3. Данные ультразвукового исследования псориатической бляшки:
a – до лечения;
b – спустя 1 мес после начала лечения
Fig. 3. Left outer surface of the upper limb:
a – before the treatment;
b – a month after the start of the treatment

DUB SkinScanner unit (Taberna pro medicum GmbH, Germany).

The results of treatment of patients with vitiligo

The second group of patients included in the study was represented by 55 patients with vitiligo, including 28 (51%) men and 27 (49%) women. The average age of patients was 33 (ranging from 14 to 62). The duration of the disease was from 8 months to 12 years. All patients received treatment on an outpatient basis. Sessions were held 3 times a week with a minimum, individually set irradiation exposure. The initial UVB dose was 0.2 to 0.5 J/cm^2. The dose of each subsequent therapy session was increased by 0.1 J/cm^2, so that the dose of the final irradiation session was within the range of 1.7-2.0 J/cm^2. The total number of sessions was individual and did not exceed 16. The sessions were held at regular intervals 3 times a week: Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. In the majority of the patients, active repigmentation of vitiligo foci began from the 4th session. Further monitoring of patients with vitiligo showed a persistent positive effect that remained for 12 months.

Clinical observation # 3. Woman, 45 y. o. Diagnosis: vitiligo. Disease history: the patient has had it for 20 years. She did not receive any treatment. Clinical findings: on the skin of the upper and lower extremities; on the forearms and shins, there are multiple milky-white depigmented spots of irregular shape with clear borders, prone to peripheral growth and coalescence.

After the completion of the series of UVB therapy sessions with an excimer lamp, the patient had a significant clinical repigmentation of the lesions.

The results of treatment of patients with atopic dermatitis

The third follow-up group consisted of 12 patients with atopic dermatitis, including 5 (42%) men and 7 (58%) women. The average age of the patients was 17 years old (ranging from 12 to 26). The duration of the disease ranged from 1 year to 26 years. The initial UVB dose for patients with atopic dermatitis was from 0.1 to 0.2 J/cm^2. Patients received 10 therapy sessions, which were conducted at equal intervals 3 times a week: Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. Each subsequent dose of therapy was increased by 0.1 J/cm^2, so that the dose of the last session of irradiation was at a dose of 1.0 - 1.1 J/cm^2. A positive effect in the form of smoothing of lichenized foci was observed from the fourth or fifth irradiation sessions. The follow-up of the patients for a year after the completion of therapy did not reveal episodes of exacerbation of dermatosis.

Clinical observation # 4. Girl, 13 y. o. Diagnosis: atopic dermatitis in the exacerbation phase. History of the disease: atopic dermatitis from early childhood, exacerbations twice a year in autumn and spring. The last exacerbation was within 1.5 months. Clinical findings: the process is widespread, involving the skin of the face, neck, upper and lower extremities, and the corpus, there are multiple erythematous and erythematous/papular foci of red color with fuzzy borders, symmetrical, prone to coalescence. Against the background of erythema, there are erosions covered with serous crusts (Fig. 5a). There are pronounced manifestations of lichenification (the skin is rough to the touch, thickened, flaky, the skin pattern is exaggerated). Multiple excoriations are observed. The dermographism in the foci is white.

The result of treatment: the inflammatory process

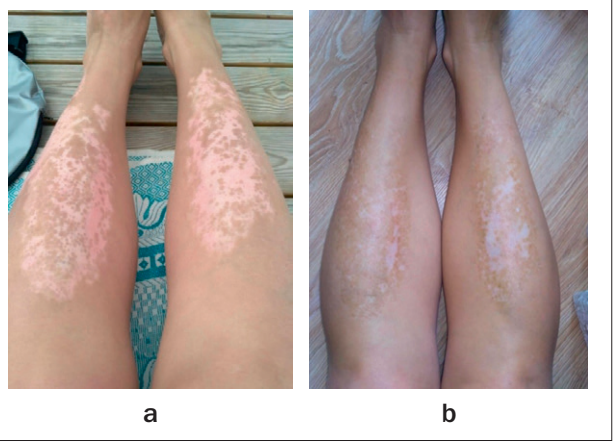

Рис. 4. Очаги витилиго на голенях:
a – до лечения;
b – после 15-го сеанса фототерапии
Fig. 4. Lower legs of a patient:
a – before the treatment;
b – after the 15th session of phototherapy

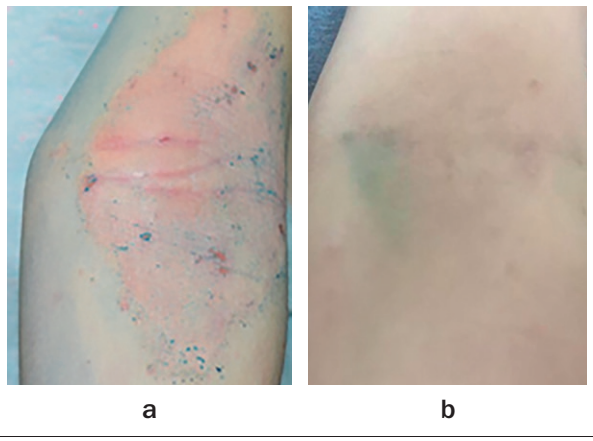

Рис. 5. Атопический дерматит на сгибательной стороне локтевого сустава:
a – до лечения;
b – после 10-го сеанса фототерапии
Fig. 5. Bending side of an elbow joint:
a – before the treatment;
b – after the 10th session of phototherapy

stopped, reducing peeling, itching, dryness of the skin (Fig. 5b).

Conclusion

The use of a device that automatically monitors the level of UV radiation dose received by the patient makes UVB therapy of patients with autoimmune skin diseases safe and effective. We have not found any cases of exacerbation of dermatological diseases after the use of the method.

The short interval of the procedure (from 10 seconds to several minutes) allows the device to be actively used in outpatient settings on a large number of patients, and makes the use of an excimer lamp equipped with a UVB dose control system a highly cost-effective method, taking into account the cost of the procedure.

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THE USE OF CONTRAST ENHANCEMENT IN THE ULTRASOUND DIAGNOSIS OF SIMPLE AND COMPLEX KIDNEY CYSTS

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Abstract

In developed countries, the main methods of research and dynamic monitoring of cystic kidney formations are CT and MRI, but their use is impossible in patients with severe concomitant diseases, as well as in the presence of metal structures, pacemakers, etc. Additionally, taking into account the high dose of radiation exposure when using CT obtained by the patient during dynamic observation, the development of alternative methods is relevant. These include, but not limited to, ultrasound using contrast enhancement, which can be used as an alternative or additional method in primary diagnosis or in the dynamic observation of cystic kidney formations. In the article, the authors provide their own experience with the use of an ultrasound contrast medium for the diagnosis and dynamic observation of complex kidney cysts, as well as the introduction of ultrasound observation using a contrast medium to classify patients according to Bosniak M.A.

The study included the results of the use of contrast enhanced ultrasound (CEUS) in 28 patients with various cystic formations of the kidneys. The patients were previously divided into two groups: the first consisted of 13 patients with simple cysts, the second – 15 with suspected complex cysts. As a result of the study, the patients were distributed as follows: 15 patients were classified as Bosniak type I, 7 patients – as type II, 3 - type III, 3 - type IV. The studied CEUS method is simple and effective. The specificity of the method was 78.57%, the accuracy of the method was 85.71%, the predictive value of the positive result was 81.25%, and the predictive value of the negative result was 91.66%. CEUS helps to quickly and accurately conduct differential diagnosis between a simple cyst and a complex one, as well as classify cysts according to M.A. Bosniak.

Keywords: contrast enhanced ultrasound, CEUS, contrast agent, Bosniak classification.

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ИСПОЛЬЗОВАНИЕ КОНТРАСТНОГО УСИЛЕНИЯ ПРИ УЛЬТРАЗВУКОВОМ ИССЛЕДОВАНИИ ПРОСТЫХ И СЛОЖНЫХ КИСТ ПОЧЕК

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Резюме

В развитых странах основными методами исследования и динамического наблюдения за кистозными образованиями почек являются КТ и МРТ, однако их применение невозможно у пациентов с тяжелыми сопутствующими заболеваниями, а также при наличии в организме металлоконструкций, кардиостимуляторов и т.д. Дополнительно принимая во внимание высокую дозу лучевой нагрузки при использовании КТ, получаемой пациентом при динамическом наблюдении, является актуальной разработка альтернативных методик. К относится ультразвуковое исследование с применением контрастного усиления (КУУЗИ), которое может использоваться как альтернативный или дополнительный метод в первичной диагностике или в динамическом наблюдении кистозных образований почек. В статье авторы приводят собственный опыт применения при ультразвуковом исследовании контрастного препарата для диагностики и динамического наблюдения сложных кист почек, а также внедрения этой технологии для распределения пациентов по классификации M.A. Bosniak.

В основу исследования вошли результаты применения КУУЗИ у 28 пациентов с различными кистозными образованиями почек. Предварительно пациенты были разделены на две группы: первую составили 13 пациентов с простыми кистами, вторую – 15 пациентов с подозрением на сложные кисты. В результате исследования было получено следующее распределение пациентов по M.A. Bosniak: 15 отнесены к I категории, 7 – ко II, 3 – к III, 3 – к IV. Исследуемый метод КУУЗИ отличается простотой и эффективностью. Специфичность метода составила 78,57%, точность метода – 85,71%, прогностичность положительного результата – 81,25%, прогностичность отрицательного результата – 91,66%. КУУЗИ помогает быстро и качественно провести дифференциальную диагностику между простой кистой и сложной, а также классифицировать кисты по M.A. Bosniak.

Ключевые слова: УЗИ с контрастным усилением, контрастный препарат, классификация M.A. Bosniak.

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Introduction

Cystic kidney disease is fairly common, with the occurrence rate in people under the age of 40 from 5% to 20%, and exceeding 30% in patients older than 60 or 70. During ultrasound examination of the kidneys, specialists often encounter complex cysts: they are distinguished by the presence of partitions, calcinates, thick contents, a solid component, as well as thickened walls.

Currently, computer tomography (CT) and magnetic resonance imaging (MRI) are the standard for differential diagnosis of benign and malignant kidney formations. The introduction and use of a contrast agent allows for the visualization of the solid component, the septum, calcinates, and other inclusions that accumulate contrast in cystic formations, which makes it possible to determine which patients require surgery. According to the degree of severity of partitions and their location, cysts are assigned to one of the four main groups in accordance with the classification developed by M. A. Bosniak and adopted in 1986 Kidney cysts classification by M. A. Bosniak [1-3], in its simple version, can be presented as a table (Table 1).

The authors distinguish between 4 categories of kidney cysts based on the presence of multiple partitions, filling with the contrast agent, as well as the presence or absence of calcinates and a solid component [5]. Cysts assigned to group III and IV require surgical treatment since the probability of the presence of a malignant lesion is high, 92% and 100%, respectively [6-9]. When CEUS is performed, these cysts accumulate the contrast agent in the walls, partitions, have a solid contrasting component, or feature all of the above at the same time.

Not so long ago, contrast agents (CA) were introduced to the ultrasound imaging procedure. Contrast-enhanced ultrasound technique (CEUS) is developing. The technology has found intensive application in the diagnosis of heart and liver diseases, and by 2008 recommendations for extrahepatic use of CA were issued [10-12].

The purpose of this research is to determine the diagnostic significance of the use of contrast agent for ultrasound, as well as to evaluate the possibility of using CEUS for the follow-up of simple and complex kidney cysts.

Materials and methods

In the period from 2017 to 2018, we used contrast enhancement ultrasound to examine 28 patients with various cystic kidney formations. In most patients with simple cysts, CEUS was performed in connection with another cancer as the principal disease or in order to confirm the presence of liver metastases. The study included cysts ranging in size from 15 mm to 35 mm. Larger cysts were screened out. Not all patients with the studied cysts were further examined with other diagnostic methods, including CT with contrast enhancement and MRI with contrast enhancement. Contrasting for ultrasound was performed with a SonoVue CA (Bracco Swiss S. A., Switzerland) based on sulfur hexafluoride on a Philips Epiq 7 unit (Philips, Netherlands), with a 1-5 MHz convex transducer. Initially, all patients underwent ultrasound of the kidneys without contrast enhancement, then 2.4 ml of SonoVue was injected into the vein via an ulnar catheter. During the study, a video recording was performed for 3 minutes. After the study, the organ and formations were evaluated both visually and with QLAB software (Philips, Netherlands).

The accumulation of contrast in unchanged kidney tissue and in the walls of cysts was evaluated, special attention being paid to the partitions in the lumen of anechoic formations, as well as to complex cysts, in which blood flow appeared in the modified partitions and walls in the arterial phase.

Results and discussion

During the study, we identified the following conventional groups of patients with the use of contrast enhanced ultrasound diagnostics (Fig. 1).

Таблица 1
Классификация кистозных образований почки по M.A. Bosniak [4]
Table 1
Classification of kidney cystic formations according to M.A. Bosniak [4]

Категория по Bosniak Category by Bosniak	Особенности Features	Результат исследования Study results
I	Простая, доброкачественная с тонкой стенкой, не содержит септ, очагов обызвествлений и солидных компонентов. По плотности соответствует воде и не контрастируется. Simple benign with a thin wall, does not contain septa, foci of calcifications or solid components. The density corresponds to water and does not contrast	Доброкачественная киста. Benign cyst
II	Доброкачественная киста, в которой могут быть немногочисленные тонкие септы. В стенке или септах возможны мелкие очаги обызвествления. Гомогенное гипоинтенсивное по сравнению с паренхимой образование диаметром <3 см, с четкими границами, не накапливающее контраст. A benign cyst in which there may be a few thin septa. Small foci of calcification are possible in the wall or septa. Homogeneous hypointense (compared to parenchyma) formation with a diameter of <3 cm, with clear boundaries, without contrast	Доброкачественная киста. Benign cyst
IIF	В кистах, относящихся к этой категории, может быть больше тонких септ. Возможно незначительное усиление септ и стенки кисты, а также минимальное утолщение их. В кисте могут быть относительно крупные очаги обызвествления, имеющие нодулярную структуру, но не накапливающие контрастное вещество. Мягкотканные элементы, усиливающие сигналы, отсутствуют. К этой категории относятся также расположенные полностью интраренально кистозные образования диаметром ≥3 см, не накапливающие контрастное вещество, имеющие четко очерченные границы и повышенную плотность. The cysts belonging to this category may contain more thin septa. A slight strengthening of the septa and cyst walls, as well as their minimal thickening. The cyst may contain relatively large foci of calcification with a nodular structure, but not accumulating contrast medium. Soft tissue features amplifying the signals are absent. This category also includes fully intrarenal cystic formations with a diameter of ≥3 cm that do not accumulate contrast medium and have clearly defined borders and increased density	Необходимо наблюдение больного. Иногда возможно злокачественное перерождение. Observation is necessary. Malignant degeneration is sometimes possible
III	Кистозные образования с неровными утолщенными стенками или септами, в которых может накапливаться контрастное вещество (контрастное усиление). Cystic formations with uneven thickened walls or septa, in which contrast medium can accumulate (contrast enhancement)	Показано хирургическое лечение или наблюдение в динамике. Более чем в 50% случаев кисты III категории бывают злокачественными. Surgical treatment or observation in dynamics. In more than 50% of cases, category III cysts are malignant
IV	Явно злокачественные кисты, содержащие мягкотканный компонент, для которого характерно контрастное усиление. Obviously malignant cysts containing a soft tissue component, which is characterized by contrast enhancement	Рекомендуется хирургическое удаление. В основном это злокачественные новообразования. Surgical removal is recommended. These are mainly malignant neoplasms

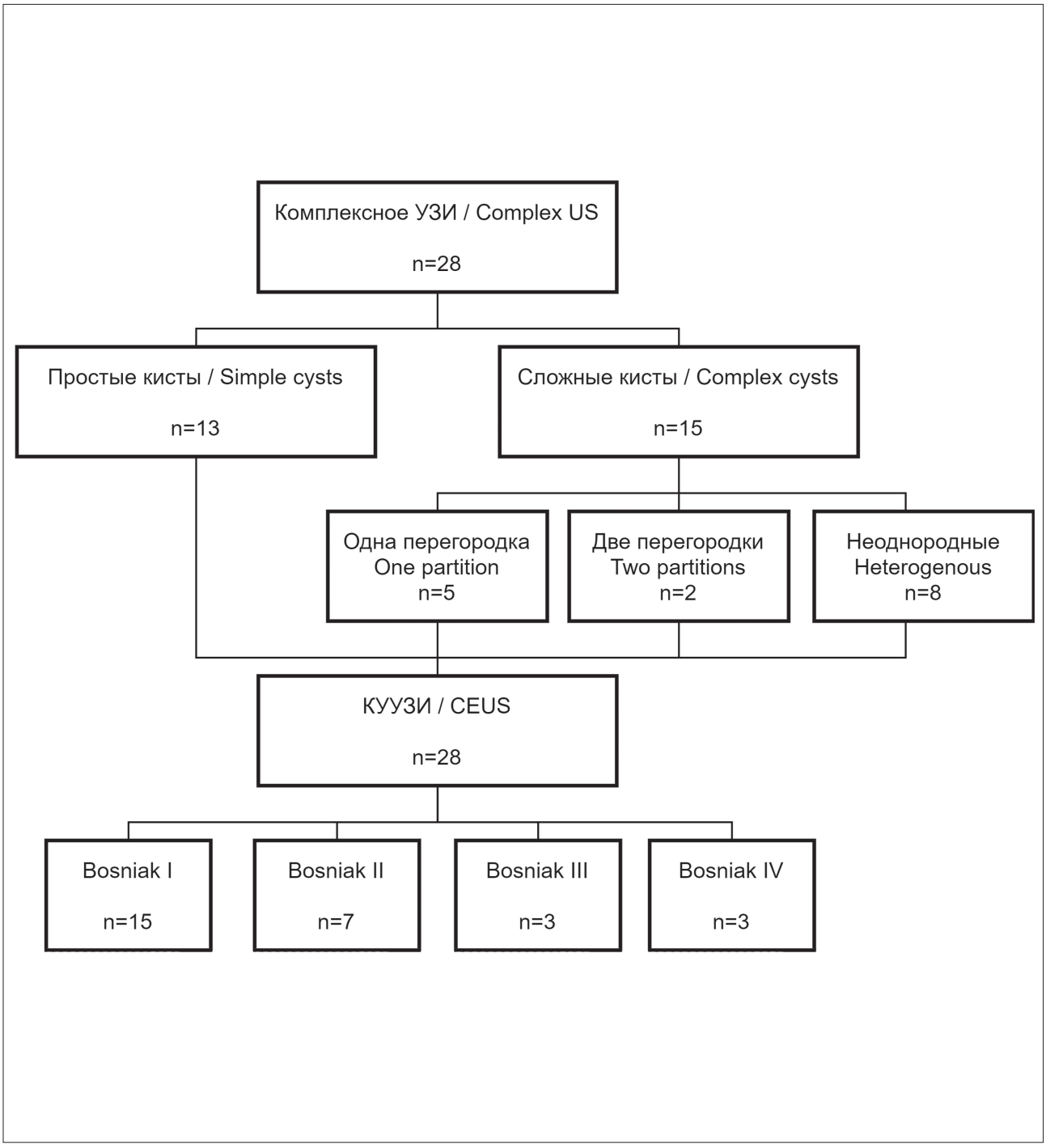

Рис. 1. Группы пациентов с кистами почек до и после КУУЗИ
Fig. 1. Groups of patients with renal cysts before and after CEUS

In the first group, consisting of 13 (46.42%) patients, contrast enhancement was administered primarily for the diagnosis of secondary liver damage. The study unexpectedly revealed some simple cysts in the kidneys. Cysts were visualized as simple thin-walled anechoic formations of a benign nature. They had no partitions. Their contents were determined to be liquid. During CUSI, no additional inclusions were found in the lumen of the cysts. All 13 patients were classified by us as category I according to the M. A. Bosniak classification.

The second group consisted of 15 (53.58%) patients who, as a result of ultrasound examination in the gray scale and other methods of kidneys examination, were found to have clearly visualized additional

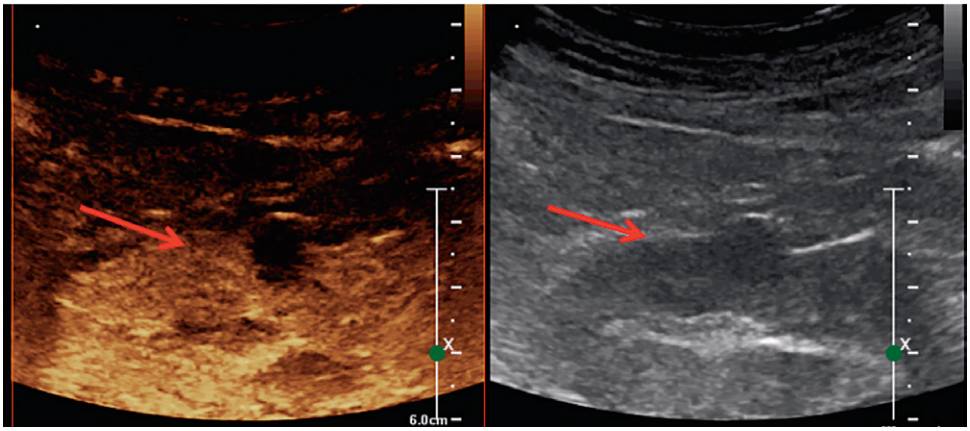

Рис. 2. Контрастирование в артериальную фазу простой кисты
При исследовании в стандартном режиме у пациента заподозрено солидное образование. При использовании контрастного препарата в артериальную фазу визуализировано неконтрастное образование, которое нами было описано как простая киста по классификации Bosniak I

Fig. 2. Left outer surface of the upper limb
When examined in standard mode, a solid formation was suspected. When using a contrast agent, a non-contrast formation is visualized in the arterial phase, which we ascribe as a simple cyst according to the Bosniak I classification

structures in the cyst, or the presence of partitions was suspected.

Among the patients who were suspected of having complex cysts during standard ultrasound, CEUS revealed a thin septum in the cyst in 7 cases. All the formations had clear contours, the partitions did not contrast, 5 patients had one thin partition in their cysts, and 2 patients had two partitions. In the process of CEUS, the partitions did not accumulate contrast, but became clearly visible. We have assessed this phenomenon as "apparent false contrasting". All these patients with single septa in cysts were classified as Bosniak category II.

Upon the administration of contrast, 3 patients were found to have a complex cyst with multiple partitions, uniformly thickened, partially accumulating the contrast agent. The same result was obtained by CT with contrast enhancement. In one case, the septum featured a calcinate up to 2 mm in size. All 3 patients were assigned to category III according to the M. A. Bosniak classification and assigned rigorous follow-up.

In 5 patients, cysts with thick curved septa and suspected solid components were visualized during a standard ultrasound examination. Among them, in one observation, the cyst was found to have an unevenly thickened capsule up to 3.5 mm in size. We initially considered the capsule to be a tumor change, but it did not display contrast in either the arterial or the venous phase. The patient was observed to have a low-grade fever and moderate pain in the lumbar region on the left. Due to the suspicion of inflammatory changes, surgical treatment was performed. Histological examination of the removed tissue did not reveal a tumor. Based on the results of ultrasound, we initially considered this case as belonging to Bosniak category III. After a negative histological report for the presence of a tumor process was received, the patient was reassigned to category I.

In another observation, a solid formation with a partially thickened capsule was suspected during a standard ultrasound. CEAS visualized a simple cyst that remained contrast-negative throughout the study. This case was considered by us as a simple cyst and classified as I by Bosniak. The patient was assigned for a follow-up (Fig. 2).

In the other three observations, both with a gray scale image and with the introduction of contrast, the formations looked like cystic solid tumors with pronounced contrast in irregular-shaped partitions and the solid inclusions. This group of patients underwent surgery. Histological examination of the surgical material led to the diagnosis of cystic kidney cancer. The patients were classified to category IV by Bosniak (Fig. 3, 4).

As a result of the study, we obtained the following results of the patient distribution in accordance with M. A. Bosniak's classification: 15 are classified as category I, 7 as category II, 3 as category III, and 3 as category IV (Fig. 1).

As a result of the analysis of the standard mode ultrasound findings, 2 out of the 28 patients examined were suspected of having a cyst with the signs of a complex one. Thus, the sensitivity of the method was 92.85%. During CEUS, contrasting, including false contrasting, was registered in 6 patients. Thus, the specificity of the method was 78,57%, its accuracy 85,71%, positive predictive value: 81.25%, negative predictive value: 91,66%.

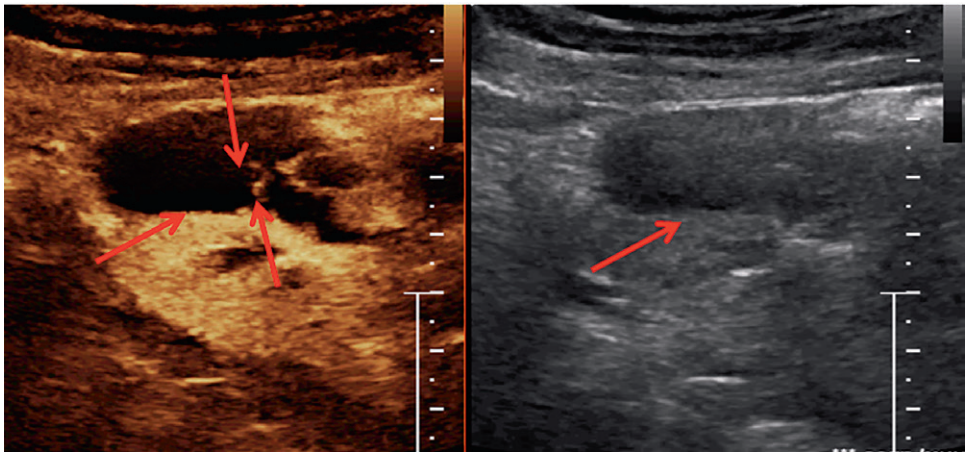

Рис. 3. Контрастирование сложной кисты. Артериальная фаза.
У пациента со сложной кистой и перегородками при многократном КТ исследовании возникало сомнение в постановке стадии по Bosniak. При использовании контрастного препарата SonoVue визуализируется сложная киста с тремя контрастируемыми перегородками. Нами эта сложная киста была расценена как Bosniak IV

Fig. 3. Complex cyst contrast. Arterial phase.
In a patient with a complex cyst and septa, multiple CT scans gave doubts to assigning a Bosniak stage. When using the SonoVue contrast agent, a complex cyst with three contrasting partitions can be seen. We classified this complex cyst as Bosniak IV

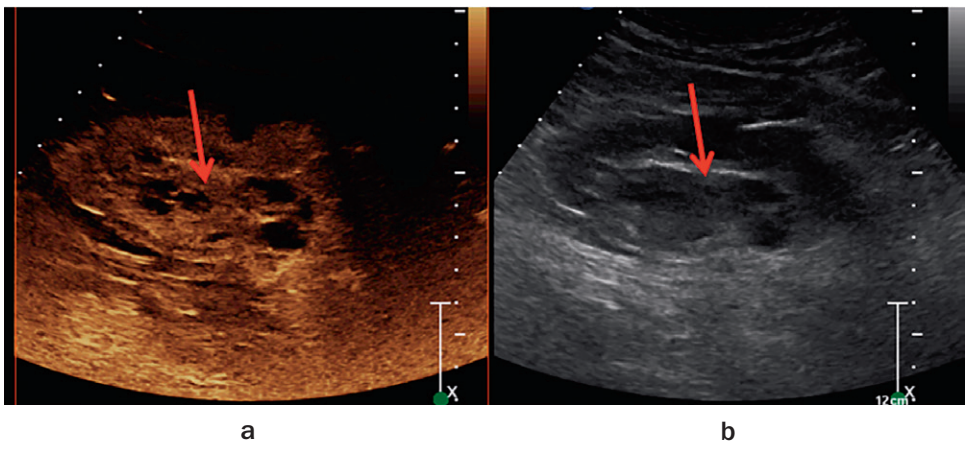

Рис. 4. Контрастирование опухоли почки с кистозным компонентом. Артериальная фаза.
У пациента с опухолью почки дополнительно при УЗИ с применением контрастного препарата визуализирован кистозный компонент с контрастируемыми перегородками.

Fig. 4. Kidney tumor with a cystic component contrast. Arterial phase.
In a patient with a kidney tumor, an additional cystic component with contrasting septa can be seen by using ultrasound with contrasting agent

Conclusion

The results of the study indicate that ultrasound with contrast enhancement can be performed as an additional method of investigation when obtaining questionable results or as a diagnostic tool for follow-up of complex kidney cysts. CEUS allows to identify the kidney cysts walls, which cannot be visualized with ultrasound in standard mode. The technique helps to conduct a quick and effective differential diagnosis between a solid formation and a usual cyst. According to the accumulation of contrast agent in cysts, patients can be put into categories according to M. A. Bosniak's classification, and the decision is then taken whether to perform surgical treatment or place the patient under dynamic observation.

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PHOTODYNAMIC THERAPY OPPORTUNITIES FOR THE TREATMENT OF ERYTHROPLASIA OF QUEYRAT

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Abstract

The review is dedicated to the analysis of the effectiveness of the treatment of erythroplasia of Queyrat (EQ) using photodynamic therapy (PDT). Particular attention is paid to the relationship between EQ and human papillomavirus (HPV) infection. The data of various researchers are presented, confirming the correlation between the development of the EQ and the HPV infection, however, it is noted that due to the small number of studies it is difficult to draw reliable conclusions on the presence and strength of this connection. The mechanisms of PDT involved in the implementation of both the antitumor effect in the treatment of EQ and the antiviral effect against HPV are considered. The data of 12 clinical studies and observations of the results of PDT of the EQ conducted in recent years are analyzed. An analysis of literature data showed that in the treatment of EQ, one of the two photosensitizers is usually used locally: 5-aminolevulinic acid or 5-aminolevulinic acid methyl ester. The treatment parameters in all the analyzed studies were similar: exposure to the ointment for 3–5 hours followed by irradiation with a light dose of 37–105 J/cm^2. The number of PDT courses in different studies varied from 1 to 19. The effectiveness of treatment varied widely in different studies and clinical observations. Most studies have demonstrated high efficacy of PDT with complete regression in 36–83% (100% in one study) and a relapse-free follow-up period of up to 51 months. However, there were also individual clinical observations of patients in whom the treatment with the method of PDT was ineffective. It is possible that the described results were associated with improperly selected regimes of PDT or a large lesion area. Most authors especially note a very good cosmetic effect and a complete absence of scars after the treatment. Thus, PDT is an effective and promising method for the treatment of EQ that requires, however, a more thorough development of the application regimen and a deeper study of the antitumor and antiviral components of the mechanism of action.

Keywords: 5-aminolevulinic acid, aminolaevulinic acid methyl ester, photodynamic therapy, erythroplasia of Queyrat.

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ВОЗМОЖНОСТИ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ ПРИ ЭРИТРОПЛАЗИИ КЕЙРА

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Резюме

Обзор посвящен анализу эффективности лечения эритроплазии Кейра методом фотодинамической терапии (ФДТ). Особое внимание уделено вопросам взаимосвязи эритроплазии Кейра с инфицированием вирусом папилломы человека (ВПЧ). Приведены данные исследований, подтверждающие корреляцию между развитием заболевания и инфицированием ВПЧ, отмечено, что в связи с небольшим количеством исследований сложно делать достоверные выводы о наличии и силе этой связи. Рассмотрены механизмы ФДТ, участвующие в реализации как противоопухолевого эффекта при лечении эритроплазии Кейра, так и противовирусного действия в отношении ВПЧ. Проанализированы данные 12 клинических исследований и наблюдений результатов ФДТ при эритроплазии Кейра,

проведенных в последние годы. Установлено, что при лечении заболевания, как правило, используют местно один из двух фотосенсибилизаторов: 5-аминолевулиновую кислоту (5-АЛК) или ее метиловый эфир. Параметры лечения во всех исследованиях были близки: экспозиция мази продолжительностью от 3 до 5 ч с последующим облучением со световой дозой 37 - 105 Дж/см^2. Количество курсов ФДТ в разных исследованиях составляло от 1 до 19. Эффективность лечения широко варьировала в разных исследованиях и клинических наблюдениях. Большинство исследований демонстрировало высокую эффективность ФДТ с полной регрессией образования в 36 - 83% наблюдений и продолжительностью безрецидивного периода до 51 мес. Имелись и отдельные клинические наблюдения, в которых ФДТ оказалась неэффективна. Возможно, описанные результаты были связаны с неправильно подобранными режимами ФДТ или большой площадью поражения. Большинство авторов отмечают хороший косметический эффект ФДТ и полное отсутствие рубцов после проведенного лечения. Таким образом, ФДТ является эффективным и перспективным методом лечения эритроплазии Кейра, однако, требующим тщательной отработки режимов применения и более глубокого изучения противоопухолевого и противовирусного компонентов механизма действия.

Ключевые слова: 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты, фотодинамическая терапия, эритроплазия Кейра

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Introduction

Penile cancer is a relatively rare pathology. In Western countries, the disease is rare, its frequency being below 1 case per 100,000 men [1]. In the United States, the proportion of penile cancer is from 0.3% to 0.6% of all cancers in men and 2% in the structure of malignancies of the male genitals [2]. Penile cancer is divided into surface forms (erythroplasia of Queyrat, Bowen's disease), which originate from squamose epithelium, are limited to it and do not penetrate the underlying dermis, and invasive tumors (all T categories). Invasive forms are represented by squamous cell carcinoma, which accounts for more than 95% of all cases of penile cancer [2].

Erythroplasia of Queyrat, as a specific clinical process, was first described by L. Queyrat in 1911. In 1912, J.T. Bowen described two cases of precancerous dermatosis, which was later called Bowen's disease. Both terms have been used interchangeably in dermatology and urology for a long time, but currently these are clinically different diseases [3].

Erythroplasia of Queyrat refers to carcinoma in situ (CIS) of the penis characterized by the appearance of a slowly growing shiny bright red plaque with clear borders on the balanus or the inner leaf of the foreskin; the disease is mainly found in senior men. Between 10% and 33% of penile CIS cases progress to invasive squamous cell carcinoma [4].

The connection between erythroplasia of Queyrat and HPV

Many studies state a close correlation between penile CIS and human papillomavirus (HPV) infection. According to the literature, the prevalence of HPV in penile cancer varies from 15% to 71%, depending on the type of tumor and the sensitivity of the virus detection method. HPV is associated with 80 to 100% of cases of basaloid and warty penile cancer, and 33 to 35% of keratinizing and verrucous forms of the disease [5, 6].

The main topic of discussion is the relationship of HPV infection with the risk of progression of erythroplasia of Queyrat to squamous cell carcinoma and the risk of relapse after antitumor treatment if HPV infection remains. The number of studies is limited, which makes it impossible for us to draw reliable conclusions about the presence and the strength of this relationship. However, the connection between primary erythroplasia of Queyrat and HPV infection has been confirmed in many studies [6, 7].

U. Wieland et al. [8], who studied the correlation between erythroplasia of Queyrat and other forms of penile cancer and HPV infection, obtained results that clearly confirm the relationship. The authors found HPV DNA in all patients with erythroplasia of Queyrat and none in the control group of patients with inflammatory penile lesions. HPV type 8 was detected in all tissue samples of patients with erythroplasia of Queyrat, and type 16 was found in 88% of the samples. Half of the surveyed individuals were found to have genital HPV of type 39 and/or 51, with a high carcinogenic risk. It should be noted that all the HPV type 8 DNA nucleotide sequences found in erythroplasia of Queyrat showed some polymorphism among themselves and differed in the specificity of the nucleotide sequence from the reference HPV type 8 sequence. Determination of viral load in patients with erythroplasia of Queyrat by PCR showed that the level of HPV type 16 in biopsies from the pathological focus was 1 to 5 orders of magnitude higher than the level of HPV type 8. In Bowen's disease, HPV type 8 was not detected in the biopsy material.

The study of J. B. Wang et al. also included results confirming the link between HPV infection and penile CIS [9]. The authors found type 16 HPV DNA in 56.9% of cases of squamous cell carcinoma of the external sex organs *in situ*. The test for HPV type 16 DNA was positive in 33.3% of cases of erythroplasia of Queyrat.

The methods of treatment of erythroplasia of Queyrat

For a long time, the leading method of treatment of the disease was surgical. In most cases, penectomy was performed, which is a crippling operation and a strong psycho-traumatic factor for patients, in some cases leading to depression. With this in mind, organ-preserving treatment options were studied in order to improve functional results without reducing patient survival rate. Local application of 5-fluorouracil alone or in combination with other methods can be effective for non-invasive lesions of non-hairy skin areas [10], since there are some reports of clinical observations of secondary progression of the tumor process from hair follicles after treatment [11]. Effective treatment methods also include local simple excision, circumcision for lesions limited to the foreskin, and Mohs micrographic surgery [2, 12, 13]. Laser surgery with carbon dioxide or Nd:YAG [14, 15], cryotherapy [16], and radiotherapy [17] are also used to treat erythroplasia of Queyrat. Recently, 5% Imiquimod cream has been successfully used [18, 19].

Erythroplasia of Queyrat is characterized by high rates of relapse after the use of all the described therapies, which may be associated with participation of HPV in the pathogenes of the disease [3]. Thus, one of the goals of therapy is to target the HPV. Currently, there is no optimal treatment option for HPV-associated penile CIS, in which it is possible to effectively fight both the underlying disease and the HPV infection. Features of the pathogenesis of the disease indicate the feasibility of developing a treatment method that has both antitumor and antiviral effects, which is why photodynamic therapy (PDT) is of particular interest in the treatment of erythroplasia of Queyrat.

The mechanism of the antiviral effect of PDT

The photodynamic antiviral effect does not depend on specific interaction with receptors. This non-specificity of photodynamic damage is one of its advantages. Given the genetic flexibility of viruses (as well as bacteria), this non-targeted mechanism of action is less likely to initiate the development of resistance in viruses [20]. Since photodynamic effects are usually local, the clinical use of photodynamic inactivation is limited mainly to localized viral lesions, such as herpes lesions or warts [21]. Systemic effects of photodynamic treatment have been identified recently that trigger the body's immune response [22-25]. This makes the use of PDT as an antiviral treatment an even more promising method.

The therapeutic effect of PDT on viruses is implemented at the expense of the formation of reactive oxygen intermediate (mostly singlet oxygen) with the activation of the photosensitizer under the influence of light of a certain wavelength.

The localization of the photosensitizer near sensitive molecular targets is extremely important in the implementation of the photodynamic effect. This is due to the short lifetime of singlet oxygen formed in the biological environment, which is measured by microseconds [26]. The specific time of inactivation depends on the location of the photosensitizer, for example, 0.4 ± 0.2 μs near the membranes in living cells [27] or 1.2 ± 0.3 μs in blood vessels [28]. Longer periods of singlet oxygen existence have also been recorded [29]. The distance of intracellular diffusion of singlet oxygen is small relative to the cell diameter. This means that the effect of singlet oxygen generated inside the cell is spatially limited to its immediate environment. However, singlet oxygen generated near the cell membrane may be able to penetrate the membrane.

The size of viruses usually ranges from 0.02 to 0.3 μm, although some very large viruses up to 1 μm are also known. Viruses contain one type of nucleic acid: DNA or RNA, which is bound to a protein shell called a capsid. In complex viruses, the capsid is surrounded by a lipoprotein envelope, which is a structure derived from the membranes of the virus-infected cell. Taking into account the basic structure of viruses, there are three main molecular targets for reactive oxygen intermediates (ROI) generated during the photodynamic reaction: nucleic acids, viral proteins, and viral lipids, if any (Fig.) [22, 30, 31]. The latter are an additional target for ROI, and, consequently, such viruses with a lipid and/or protein shell are usually more sensitive to photodynamic effects [22].

Review of the findings of clinical studies of PDT of erythroplasia of Queyrat

In PDT performed in patients with erythroplasia of Queyrat, the photosensitizer used is usually 5-aminolevulinic acid (5-ALA) or 5-ALA methyl ether [32]. Both 5-ALA and its methyl ether are used locally, in the form of an ointment, which is applied to the affected area as a layer of 1 - 3 mm. The exposure time of the ointment in different studies was from 3 to 5 hours. Almost all researchers noted pronounced pain syndrome in patients during irradiation; the majority of other adverse reactions reported were dysuria, edema of the irradiated tissues and the development of erythema.

The effectiveness of PDT in erythroplasia of Queyrat varies widely in different studies and clinical observations.

A group of researchers from Sweden published the results of a long-term follow-up of 2 patients with eryth-

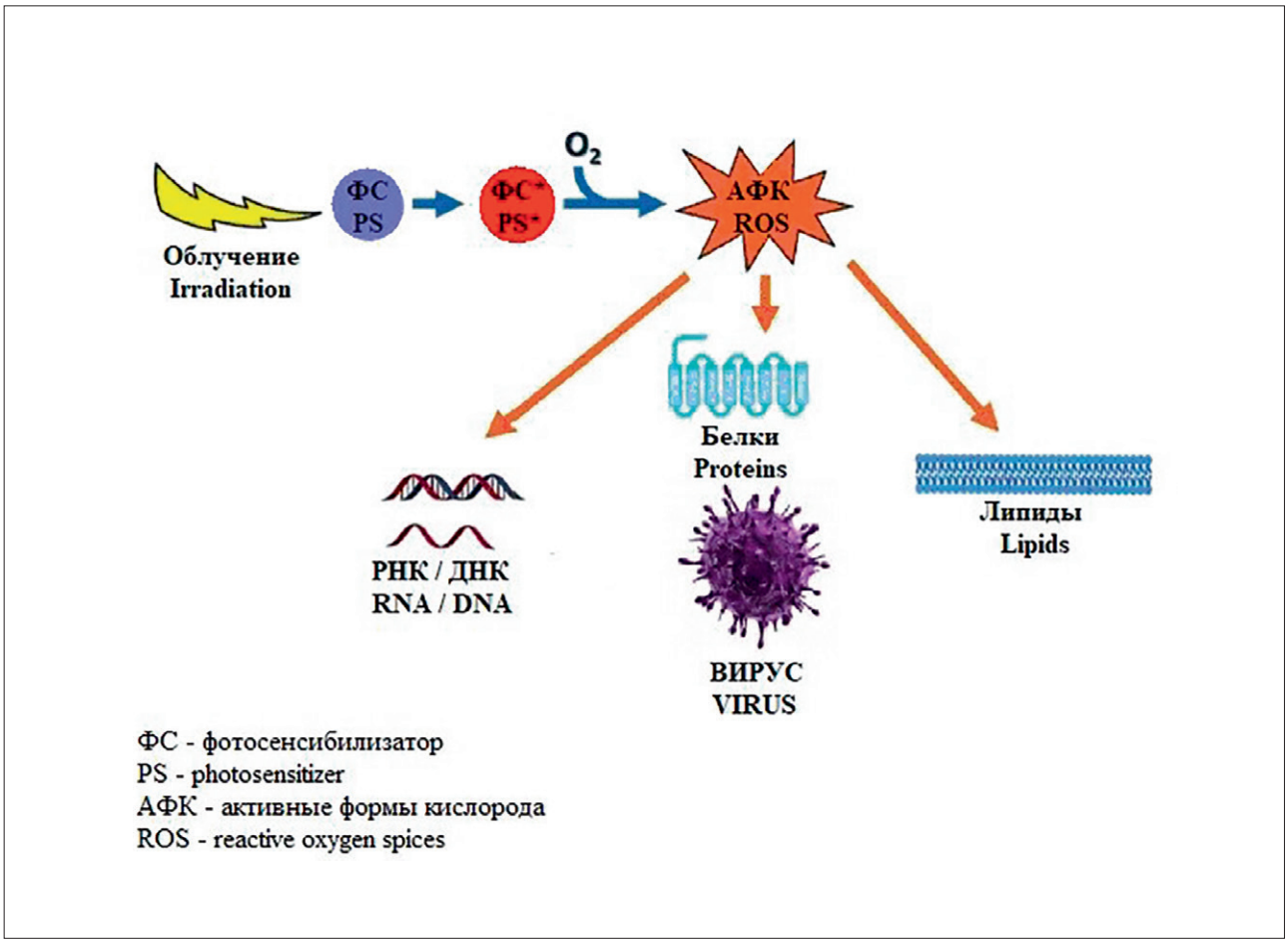

Рис. Мишени фотодинамической инактивации вирусов: нуклеиновые кислоты, белки, липиды
Fig. Targets of photodynamic inactivation of viruses: nucleic acids, proteins, lipids

roplasia of Queyrat after PDT with local application of 20% 5-ALA ointment [33]. One patient was administered 3 courses of PDT, the other, 8 courses. The light dose of each irradiation session was 40-65 J/cm^2, and the power density was 40-65 mW/cm^2. The immediate result of treatment in both patients was evaluated as a complete regression. The follow-up period after treatment was 35 and 40 months. During this time, no recurrence of the disease was registered.

A successful clinical follow-up of a patient with erythroplasia of Queyrat was performed after one course of PDT at P. A. Hertsen Moscow Oncology Research Center [34]. Irradiation was performed once after a 5-hour exposure to the ointment with 5-ALA. The light dose was 150 J/cm^2. The patient was followed up for 1.5 years, with no relapse observed.

Literature provides reports of less successful results of treatment of erythroplasia of Queyrat using PDT with 5-ALA. Researchers from the University Hospital of Wales and the Royal Gwent Hospital (UK) report a clinical follow-up of a patient with erythroplasia of Queyrat after 3 courses of PDT with 20% 5-ALA ointment. The exposure time of the ointment was 4 hours, and the light dose was 105 J/cm^2 [35]. The courses were administered with one month intervals between them. After the third course of PDT, the result was evaluated as a regression of the tumor. However, the researchers noted the occurrence of erythema which remained at the site of irradiation. 4 months after the completion of PDT, on the background of the administration of 5-fluorouracil, a neoplasm was diagnosed at the same place, and a focus of squamous cell cancer was detected during histological examination.

In early 2020 Q.N. Jia et al. reported a clinical follow-up for a patient with erythroplasia of Queyrat who received 2 courses of PDT with 20% 5-ALA ointment. The exposure time to the ointment was 4 hours, the light irradiation dose was 37 J/ cm^2, the irradiation time was 20 minutes [36]. The interval between the courses was 2 weeks. The visit that followed resulted in the discovery of a nodule on the previously treated area of the penis, and the patient was diagnosed with squamous cell cancer based on a histological examination.

There are numerous reports in the literature about the treatment of erythroplasia of Queyrat by PDT with 5-ALA methyl ether.

In 2005, researchers M. R. Lee and W. Ryman [37] described a clinical case of successful use of PDT with 5-ALA methyl ether. Light irradiation was performed after a 3-hour exposure to the cream with 5-ALA methyl ether. The applied layer of cream was 1 mm thick, and 1 g of cream contained 160 mg of the active substance. The radiation wavelength was 630 nm, the light dose was 37 J/cm^2, and the power density was 70 to 100 mW/cm^2. The duration of follow-up was 18 weeks, during which no relapse was detected. Further follow-up was discontinued due to the patient's death unrelated to the principal disease.

P. G. Calzavara-Pinton et al. presented the results of a large-scale retrospective study of the effectiveness of 5-ALA methyl ether in 145 patients with tumor, pre-tumor and infectious diseases treated in 20 dermatological departments and clinics in Italy [38]. In particular, the study evaluated PDT results in 8 patients with erythroplasia of Queyrat. Irradiation was performed after 3-4-hour exposure of the cream with 5-ALA methyl ether (160 mg of the active substance in 1 g of the cream, applied in 1 mm thick layer). The radiation wavelength was 630 nm, and the light dose was 37 J/cm^2. In 5 out of 8 patients, the result of the treatment was evaluated as a complete regression. As the follow-up showed, 2 of these 5 patients later had a relapse.

A group of researchers from Italy presented the results of PDT with 5-ALA methyl ester of erythroplasia of Queyrat in 23 patients [39]. The treatment included 2 courses of PDT with an interval of 1-2 weeks. A cream of 5-ALA methyl ether (160 mg of active substance in 1 g of cream, 1-mm thick layer) was applied to the affected area. The exposure time was 3 hours, after which red light irradiation was performed. The light dose was 37 J/cm^2. Complete regression was obtained in 19 patients, with a follow-up period of 8 to 30 months without relapse (18 months on average). In 3 observations within 3 months after PDT, a relapse of the disease was registered, and 1 patient was found to have fibrosis at the site of irradiation. The cosmetic result in the majority of patients was evaluated as excellent, 4 patients had hyperpigmentation at the PDT site.

Skroza N. et al. report a case of successful PDT treatment with 5-ALA methyl ether in a patient with long-term erythroplasia of Queyrat [40]. A complete clinical response, confirmed by postoperative biopsy, was achieved after 5 weekly courses of treatment. In the course of therapy, moderate edema, erythema and pain were registered within 5 to 7 days after each course of PDT; no problems with urination were observed.

Chinese researchers described the experience of PDT with 5-ALA in 7 patients with erythroplasia of Queyrat [41]. The exposure time of the ointment was from 3 to 5 hours, the light dose: 80-100 J/cm^2, the power density: 60 mW/cm^2. Patients were given from 2 to 7 courses of PDT with an interval of 2 weeks. In 6 out of 7 patients, regression of the pathological process was achieved, while the authors made a special note a good cosmetic effect and complete absence of scars. In 1 case, complete regression could not be achieved due to the initially significant area of the lesion, which spread over 90% of the surface of the penis.

L. Feldmeyer et al. report the results of long-term follow-up of 11 patients with erythroplasia of Queyrat treated with PDT at the University Clinic of Zurich [42]. As a photosensitizer, 5-ALA methyl ether was used in the form of 16% ointment with an exposure time of 3 hours. The light dose for each course of PDT in all patients was 75 J/cm^2. As a result of treatment, 3 out of 11 patients had a complete regression of the tumor, with no relapses during the entire follow-up period of 1.5, 24 and 51 months after the final course of PDT. The number of courses was 19, 7 and 11, respectively, and the interval between them was 1 to 48 weeks.

In 4 patients after 5 to 16 courses of PDT, the immediate effect of treatment was assessed as a partial regression, which persisted for 2 to 45 months with a follow-up period of 4 to 45 months. Later, 2 of these patients were found to have complete regression of the neoplasms after 20 and 45 months of follow-up without any further therapy. In 4 of 11 patients, the progression of the disease was registered after 2 to 4 courses of PDT.

J.Y. Park et al. report the results of clinical observation of a patient with erythroplasia of Queyrat after 10 courses of PDT with 5-ALA methyl ether [43]. The exposure time of the ointment was 3 hours, the light dose was 37 J/cm^2, the power density was 70-100 milliwatt/cm^2. The result of the treatment was estimated as a partial regression. In this connection, treatment with 5% Imiquimod cream was continued. After 4 months, a continued growth of the neoplasm was diagnosed, and a histological examination revealed squamous cell cancer.

A team of Russian authors reports on the experience of successful use of PDT with local application of 5-ALA methyl ether [44]. The patient underwent 2 courses of PDT with an interval of 1 week. The exposure time of the ointment was 3 hours, the light dose, 37 J/cm^2. The result of treatment 3 months after the second course of PDT was evaluated as a complete regression.

Conclusion

Thus, literature describes a significant number of cases of successful treatment of erythroplasia of Queyrat with the use of PDT with 5-ALA and its methyl ester. However, no fundamental studies of the mechanisms of antiviral action against HPV and photocytotoxic action or the assessment of the contribution of these two mechanisms to the overall therapeutic effect in the treatment of this pathology by PDT have been conducted.

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CASE REPORTS

PHOTODYNAMIC THERAPY OF PENILE CANCER

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Abstract

In this article we submit the case report of a patient with cT1N0M0 penile cancer diagnosis. The patient underwent two courses of photodynamic therapy (PDT) using Fotoditazin photosensitizer (PS) and ATKUS-2 diode laser. The PS was administered at a dose of 1 mg/kg of body weight 2 hours prior to the PDT session. The irradiation parameters were: 662 nm laser wavelength, 200 mW/cm^2 power density and 250 J/cm^2 energy density. In the presented clinical observation, we demonstrated that PDT is an effective and safe treatment method in patients with non-invasive penile cancer. The use of photodynamic therapy allowed preserving the physiological urination, sexual function and achieving a good cosmetic effect.

Keywords: penile cancer, photodynamic therapy, fotoditazin.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРИ РАКЕ ПОЛОВОГО ЧЛЕНА

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Резюме

В данной статье представлено клиническое наблюдение за пациентом, имеющим диагноз: рак полового члена cT1N0M0, которому было проведено 2 курса фотодинамической терапии (ФДТ) с использованием фотодитазина и диодного лазера «АТКУС-2». Фотодитазин в дозе 1 мг/кг массы тела вводили пациенту за 2 ч до начала сеанса ФДТ. Параметры облучения: длина волны излучения 662 нм, плотность мощности 200 мВт/см^2, плотность энергии облучения 250 Дж/см^2. В представленном клиническом наблюдении нами продемонстрировано, что ФДТ является эффективным и безопасным методом лечения у пациентов с неинвазивным раком полового члена. Использование ФДТ позволило сохранить физиологическое мочеиспускание, половую функцию и достичь хорошего косметического эффекта.

Ключевые слова: рак полового члена, фотодинамическая терапия, фотодитазин.

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Penile cancer is a rare but aggressive malignancy. In 2017, penile cancer was diagnosed in 667 cases in Russia, which was only 0.24% of all newly diagnosed malignancies in men. However, over the past decade, the incidence of penile cancer has increased by more than 50%, especially in the over 55 age group. In the absence of specific treatment, the 5-year survival rate for this disease is 2.6% [1, 2].

In 95% of cases, penile cancer is a squamous cell carcinoma [3]. The main predisposing factors of penile cancer

are the presence of phimosis with chronic inflammation (up to 60% of cases) and human papillomavirus types 16 and 18 (up to 50% of cases) [4-6].

With adequate treatment, the 5-year survival rate of patients is up to 100% in stage I of the disease and up to 88% in stage II [7]. At these stages, it is possible to use organ-preserving operations that allow patients to maintain their sexual function and have natural urination.

Currently, the question of the most preferred method of treatment for penile cancer has not been solved due to the low prevalence of this disease. There are conflicting data in the literature on relapse-free 5-year survival in patients after organ-preserving and organ-resecting surgery in penile cancer, but the analysis of the results of most studies indicates a probability of local relapse in 50-55% of cases when the penis was preserved [8-10]. However, organ-preserving operations are the most preferable, since penectomy is associated with physical and psychological discomfort for the patient. It should be noted that the occurrence of relapses, subject to their timely diagnosis and treatment, does not have a negative impact on the survival of patients [10, 11].

According to current clinical recommendations, the choice of treatment tactics for malignant diseases is based on the localization, size and type of growth of the primary tumor, categories T, N, M, and degree of anaplasia G [1].

Photodynamic therapy (PDT) is one of the most promising methods of treating a range of oncological and non-oncological diseases. PDT is a technology based on a photochemical reaction that develops as a result of the interaction of laser radiation and a photosensitizer accumulated in pathological tissues.

Currently, PDT is effectively used for the treatment of urological diseases such as penile cancer, bladder cancer, benign prostatic hyperplasia, etc. PDT is also used in the complex treatment of purulent wounds of the scrotum and virus-associated diseases of the penis [12].

Experimental data indicate that the main factors of tumor destruction in PDT are the following components: damage and death of tumor cells, destruction of the microcirculatory bed of the tumor, inflammatory response and immune response of the body [13].

In April 2019, patient K., aged 42, was hospitalized to the Central Clinical Hospital No. 2 named after N. A. Semashko with a referral diagnosis of penile cancer.

For several years before that, the patient had noted the presence of a slight scarring of the foreskin. In February 2018, he first noticed the appearance of redness of the balanus, and visited a urologist at his place of residence, where he was diagnosed with balanoposthitis and prescribed conservative therapy. The patient underwent the prescribed treatment, but it was not effective.

In early 2019, the patient noted progression of the disease which appeared as a space-occupying lesion on the balanus and the foreskin. The patient was repeatedly consulted by the urologist. With a referral diagnosis of penile cancer, he was hospitalized to the Central Clinical Hospital No. 2 named after N. A. Semashko.

Upon admission, his local status included scarring of the foreskin, on the balanus, closer to the coronal sulcus; two lesions, up to 15 mm in diameter of bright red color with an exophytic component up to 5 mm, with a partial transition to the inner leaf of the foreskin, were observed; no infiltration of the spongy body was observed, the urethra was intact, and the inguinal lymph nodes were not changed (Fig. 1).

A biopsy of the neoplasm was performed, which was described as a result of histological examination as a fragment of mucosa with the growth of a moderately differentiated squamous cell cancer with a tendency to keratinization. In a comprehensive examination, which included MRI of the pelvic organs, CT of the abdominal cavity and chest, no data for the damage of regional lymph nodes or the presence of distant metastases were found in the patient.

Taking into account the stage of the disease and the absence of tumor dissemination signs, the oncological council decided to resort to a combined organ-preserving treatment: PDT of the penis with subsequent circumcision.

The patient underwent PDT with the use of Photoditazine (OOO "VETA-GRAND", Russia, registration certificate No. ЛС 001246 dated 18.05.2012) and an "ATKUS-2" diode laser (AO "Poluprovodnikovyie Pribory", Russia). 2 hours before irradiation, the patient was administered Photoditazine, at a dose of 1 mg/kg of body weight. During the manipulation, the focus was affected by laser radiation with a wavelength of 662 nm, a power density of 200 mW/cm^2, and an irradiation energy density of 250 J/cm^2.

Due to the presence of two lesions, the session was conducted with the use of a polypositional method. At the second stage of combined treatment, the patient underwent circumcision. The surgical material was sent for morphological examination. According to the histological conclusion, the tissue featured a growth of moderately differentiated squamous cell cancer with a tendency to keratinization, with an invasion into the subepithelial base of up to 1 mm, and a negative surgical margin.

The immediate effect of this technique was observed after PDT: a demarcation line began to form, and hemorrhagic necrosis of the affected tissues appeared (Fig. 2).

On the day after the surgery, the demarcation line was clearly visualized. A skin slough formed on the right half of the balanus (Fig. 3).

The post-surgery period proceeded smoothly. At the control examination after 1 month, the patient

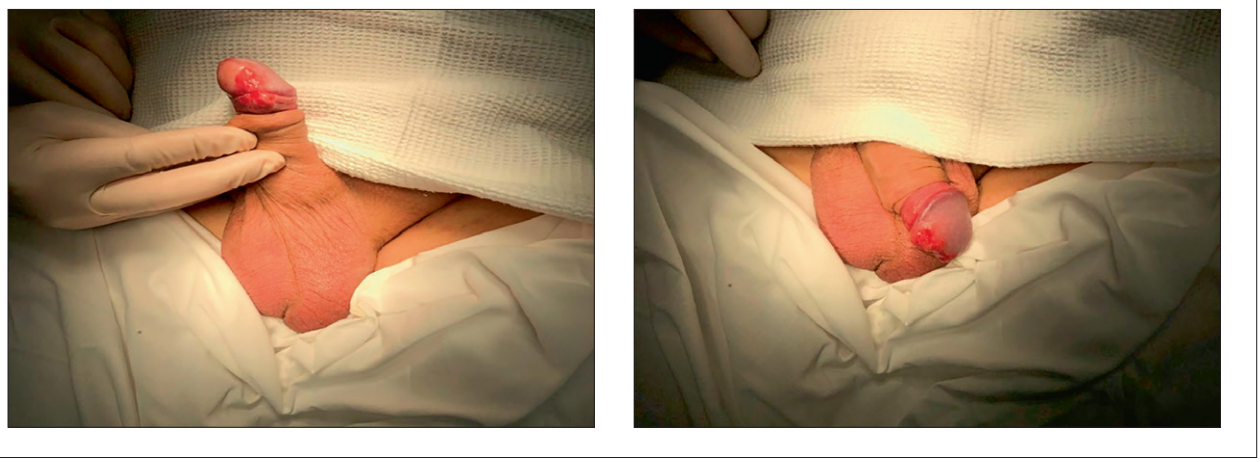

Рис. 1. Клиническая картина до операции
Fig. 1. Clinical picture before the operation

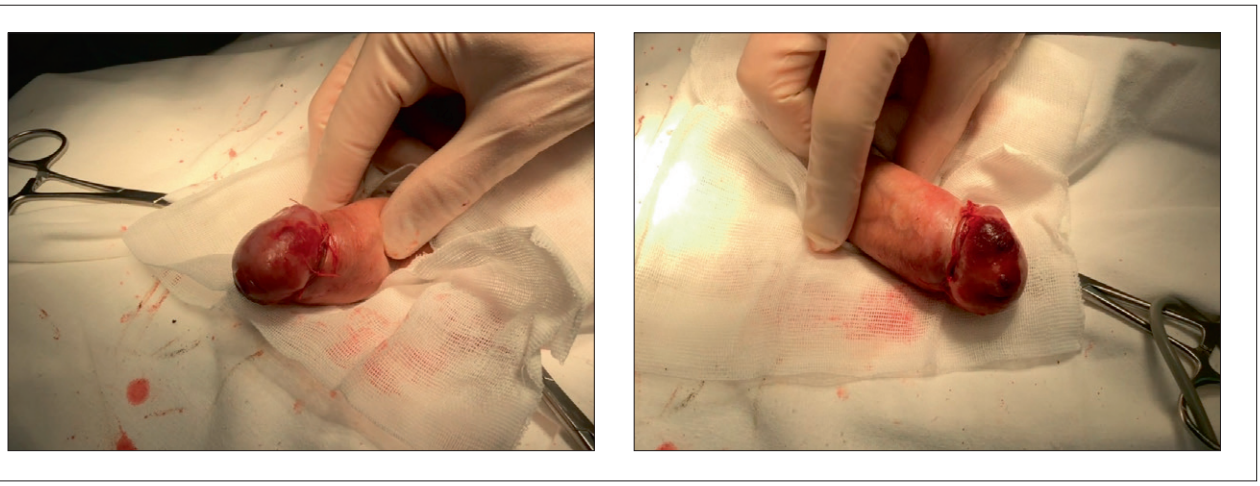

Рис. 2. Клиническая картина после операции
Fig. 3. Clinical picture after the operation

Рис. 3. Клиническая картина, 1-е сутки после операции
Fig. 3. Clinical picture, 1 day after the operation

Рис. 4. Клиническая картина, 25-е сутки после операции
Fig. 4. Clinical picture, 25 days after the operation

Рис. 5. Клиническая картина, контроль через 2 мес
Fig. 5. Clinical picture, control after 2 months

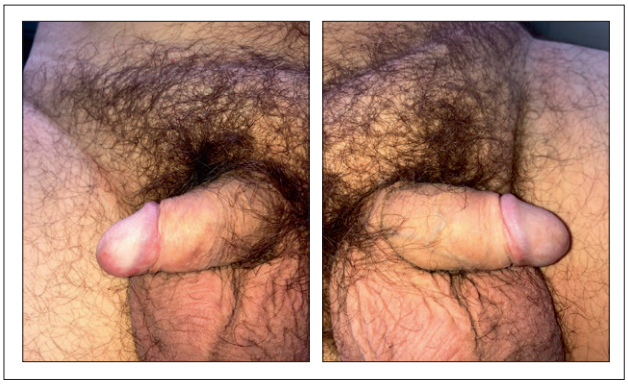

Рис. 6. Клиническая картина, контроль через 1 мес после 2-го курса ФДТ
Fig. 6. Clinical picture, control 1 month after the second PDT course

showed good healing of the postoperative defect on the right (Fig. 4). A control cytological study was performed from the zone of the worst healing. Conclusion: cells of the squamous epithelium with signs of inflammation.

During the control examination after 2 months, the patient showed complete healing of the surgery area, without visible cosmetic defects. However, on the left side of the balanus, a modified area measuring 5 mm in diameter was observed (Fig. 5). To exclude the continued growth of the tumor, a cytological study was performed. No data were obtained for the presence of tumor cells. The clinical situation was discussed at the oncological council. Taking into account the clinical picture and high aggressiveness of the penile cancer, it was decided to administer a second course of PDT.

The patient underwent a repeated course of PDT with the use of the method described above. During a control examination 1 month after the second course, a complete regression of the neoplasm was confirmed, and no cosmetic defects were observed (Fig. 6).

In our account of the clinical observation, we have demonstrated that PDT is an effective and safe method of treatment in patients with non-invasive penile cancer. This method does not involve any serious operational risks.

The use of PDT allowed for the preservation of physiological urination and sexual function, and it also produced a good cosmetic effect.

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Текст статьи набирается в текстовом редакторе (Microsoft Word) кеглем 12 пунктов через 1,5 интервала, желательно шрифтом Times New Roman Cyr, перенос слов не делается. Размеры полей: верхнее и нижнее – 20 мм, левое – 30 мм, правое – 20 мм. Абзацный отступ – 10 мм.

Рекомендуемый объем статьи, включая таблицы и литературу – в пределах 12–15 страниц формата А4. Все страницы должны быть пронумерованы (нумерация страниц начинается с титульной).

Оригинальные статьи согласно общепринятым международным правилам должны содержать следующие разделы: титульная страница, вступление, материалы и методы (можно по отдельности), результаты, обсуждение, заключение, литература.

Титульная страница должна содержать:

- название статьи (выравнивание по центру, заглавные буквы);
- инициалы и фамилию каждого автора (выравнивание по центру);
- названия организаций, в которых работают авторы (если автор работает и выполнял исследования в нескольких организациях, желательно указывать названия всех организаций), города и страны (выравнивание по центру, названия организаций должны быть даны в соответствии с данными портала e-library, в случае нескольких организаций перед названием каждой указывается порядковый номер в формате верхнего индекса и после фамилии каждого автора также верхним индексом обозначается его принадлежность к определенной организации или организациям);
- резюме статьи в неструктурированном виде (без выделения отдельных разделов) объемом 150–200 слов;
- ключевые слова (5–10 слов);
- контактную информацию для общения читателей с ответственным автором для публикации в свободном доступе (e-mail);
- ссылку на статью для цитирования.

На английском языке необходимо продублировать: фамилию и инициалы автора(ов), название статьи, аннотацию, ключевые слова.

В тексте следует использовать только общепринятые сокращения (аббревиатуры). Не следует применять сокращения в названии статьи. Полный термин, вместо которого вводится сокращение, следует расшифровывать при первом упоминании его в тексте (не требуют расшифровки стандартные единицы измерения и символы).

При представлении результатов статистического анализа данных обязательным является указание использованного программного пакета и его версии, названий использованных статистических методов, приведение описательной статистики и точных уровней значимости при проверке статистических гипотез. Для основных результатов исследования рекомендуется рассчитывать доверительные интервалы.

Единицы измерения физических величин, гематологические, биохимические и другие показатели величин, применяемые в медицине, должны представляться в единицах метрической системы (Международной системы единиц – СИ). При названии различных соединений необходимо использовать терминологию ИЮПАК.

Таблицы, рисунки и текст должны дополнять друг друга, а не дублировать.

Используемый в статье иллюстративный материал (фотографии, рисунки, чертежи, диаграммы) должен быть контрастным, рисунки – четкими. На микрофо-

тографиях необходимо указать метод окраски, увеличение. Все подписи, используемые в схемах, графиках и т.д., а также названия рисунков должны быть продублированы на английском языке через "/".

Таблицы и рисунки нумеруются в соответствии с порядком их цитирования в тексте. Каждая таблица должна иметь краткое название и иметь ссылки в тексте. Заголовки граф должны точно соответствовать их содержанию. Использованные в таблице сокращения подлежат расшифровке в конце таблицы.

Библиография должна быть приведена в конце статьи и оформлена в соответствии с ГОСТ Р 7.0.5–2008, в самом же тексте следует указывать только номер ссылки в квадратных скобках цифрами. Ссылки нумеруются в порядке цитирования. В список литературы не включают неопубликованные работы. Не допускаются ссылки на диссертации, тезисы, сборники конференций и авторефераты диссертаций.

За точность библиографии несет ответственность Автор.

Пример оформления списка литературы:

1. Миронов А.Ф. Фотодинамическая терапия – новый эффективный метод диагностики и лечения злокачественных опухолей // Соросовский образовательный журнал. – 1996. – № 8. – С. 32–40.
2. Кармакова Т.А., Филоненко Е.В., Феофанов А.В. и соавт. Динамика накопления и распределение АЛК-индуцированного протопорфирина IX в ткани базальноклеточного рака // Российский биотерапевтический журнал. – 2006. – Т. 5, № 1. – С. 26.
3. Фут К. Свободные радикалы в биологии // пер. с англ. – М.: Мир, 1979. – Т. 2. – С. 96 – 150.
4. Castano A.P. et al. Mechanisms in photodynamic therapy: part one – photosensitizers, photochemistry and cellular localization // Photodiag. Photodynam. Ther. – 2004. – Vol. 1. – P. 279–293.

Все статьи, поступающие в редакцию, проходят многоступенчатое рецензирование, замечания рецензентов направляются Автору без указания имен рецензентов. После получения рецензий и ответов Автора редколлегия принимает решение о публикации (или отклонении) статьи.

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