

PREDICTION OF THE EFFECT OF THE PHOTODYNAMIC THERAPY ON SURVIVAL IN PATIENTS WITH STAGE IV OF PANCREATIC CANCER

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Abstract

The article presents the results of a study of survival after complex palliative treatment of patients with malignant tumors of the pancreas stage IV in two comparable groups of patients. The aim of the study is to determine the prognostic factors affecting survival in patients with stage IV pancreatic cancer who received local and systemic photodynamic therapy. In the main group, which consisted of 19 patients with histologically verified stage IV pancreatic malignant tumor, palliative treatment was performed using photodynamic therapy. In the comparison group, consisting of 28 patients with histologically verified malignant tumor of the pancreas stage IV, palliative treatment was performed without the use of photodynamic therapy. On the background of the use of local and systemic photodynamic therapy in the main group it was observed a statistically significant increase in life expectancy compared with the comparison group. The three-month survival of patients who received local and systemic photodynamic therapy is affected by the level of fibrinogen before treatment. The level of fibrinogen above 3.40 g/l makes it possible to predict a decrease in the probability of three-month survival after photodynamic therapy. Thus, complex treatment with the use of photodynamic therapy for stage IV malignant tumors of the pancreas can increase the survival rate of patients.

Key words: malignant tumors of the pancreas, photodynamic therapy, forecasting, survival, prognostic factors.

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ПРОГНОЗИРОВАНИЕ ВЛИЯНИЯ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ НА ВЫЖИВАЕМОСТЬ У ПАЦИЕНТОВ С IV СТАДИЕЙ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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Резюме

В работе представлены результаты исследования выживаемости в двух сопоставимых группах больных после комплексного паллиативного лечения больных со злокачественными новообразованиями поджелудочной железы IV стадии. Целью исследования было определить прогностические факторы, влияющие на выживаемость у больных IV стадией злокачественного новообразования поджелудочной железы, которым планируется проведение локальной и системной фотодинамической терапии. В основной группе, включавшей 19 пациентов с гистологически верифицированным злокачественным новообразованием поджелудочной железы IV стадии, проводили паллиативное лечение с применением фотодинамической терапии. В группе сравнения, включавшей 28 пациентов с гистологически верифицированным злокачественным новообразованием поджелудочной железы IV стадии, проводили паллиативное лечение без применения фотодинамической терапии. На фоне применения локальной и системной фотодинамической терапии

в основной группе наблюдали статистически значимое увеличение продолжительности жизни по сравнению с группой сравнения. Исследования показали, что на трехмесячную выживаемость пациентов, которым планируется проведение локальной и системной фотодинамической терапии, влияет уровень фибриногена до лечения. Уровень фибриногена выше 3,40 г/л позволяет прогнозировать снижение вероятности трехмесячной выживаемости после проведения фотодинамической терапии. Таким образом, комплексное лечение с применением фотодинамической терапии злокачественных новообразований поджелудочной железы IV стадии позволяет увеличить выживаемость пациентов.

Ключевые слова: злокачественные новообразования поджелудочной железы, фотодинамическая терапия, прогнозирование, выживаемость, прогностические факторы.

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Introduction

Pancreatic cancer is an important problem of modern oncology. Being a relatively rare disease and occupying only 3.3% in the structure of cancer incidence in Russia it ranks fifth in the structure of cancer mortality [1, 2, 3, 4, 5].

The modern standard of treatment for patients with malignant neoplasms of the pancreatobiliary zone is complex treatment, in which the surgical method plays the main role. At the same time, due to a long period of slight symptoms and late treatment of patients at the time of diagnosis, more than half of patients already have advanced stage IV of the underlying disease [1, 2]. Most patients can only receive palliative treatment, while the most important factor in successful treatment is the elimination of life-threatening complications such as obstructive jaundice and cholangitis [6, 7, 8, 9, 10]. Against the background of the development of technologies for decompression of the bile ducts, and the emergence of new regimens and drugs for chemotherapy treatment, the prognostic median survival of these patients has not changed over the years, still amounting to 3.7 months for unresectable tumors, which is one of the lowest median survival among tumors of the gastrointestinal tract [2]. Mortality in the first year of life in patients with malignant neoplasms of the pancreas also remains high and amounts to 68% [1].

At the same time, due to the lack of a significant improvement in the results of palliative treatment despite the development of chemotherapy, there is a search for other methods of palliative treatment for this category of patients.

One such method is photodynamic therapy (PDT). PDT is a technique for influencing tumor cells with the help of special drugs that accumulate in them and, becoming chemically active in the presence of light of a certain wavelength and oxygen, lead these cells to die through apoptosis, necrosis, and autophagy. Conducted in 2002 and 2014 studies of the effect of contact PDT on

the outcomes of complex treatment of pancreatic cancer suggest that PDT in combination with surgical methods is promising in increasing the life expectancy of patients with malignant neoplasms of the pancreatobiliary zone [8, 9].

The aim of this study is to determine the prognostic factors affecting survival in patients with stage IV pancreatic malignancy who are scheduled for local and systemic PDT.

Materials and Methods

An open non-randomized comparative survivorship study included 47 patients with histologically verified stage IV pancreatic malignancy who underwent complex treatment at the regional hepatological center of the Barnaul City Hospital No. (Barnaul, Russia) from 2017 to 2020. The patients were divided into two groups. The inclusion criteria for the study were age from 18 to 95 years, histologically verified diagnosis of stage IV pancreatic malignancy, and signed informed consent for surgical treatment during hospitalization. The exclusion criteria were mortality in less than 24 hours, HIV infection and infection with viral hepatitis B, C, and D, acute myocardial infarction with cardiogenic shock, and blood cancer. The main group included 19 patients who underwent complex palliative treatment with PDT. The comparison group included 28 patients who underwent complex palliative treatment without PDT. The distribution of patients into groups was carried out without randomization: patients who signed a consent to PDT due to the presence of contraindications to the use of alternative methods of treatment were included in the main group. Patients who refused PDT were included in the comparison group. The design of the study was approved by the Local Ethics Committee of the "Altai State Medical University" of the Ministry of Health of the Russian Federation (extract from protocol No. 11, November 27, 2017). Comparative characteristics of groups by

sex and age are presented in Table 1. No statistically significant differences were found.

Comparative characteristics of groups according to the histological type of neoplasm are presented in Table 2. No statistically significant differences were found.

Palliative surgical treatment included surgical treatment of life-threatening complications, primarily obstructive jaundice: percutaneous transhepatic mono- and bilobar drainage of the bile ducts, stenting of the bile

ducts under ultrasound and X-ray control, and bypass biliodigestive anastomoses. Symptomatic conservative treatment included infusion, detoxification, analgesic, hepatoprotective, and antibacterial therapies [5].

All patients of the main group underwent palliative local and systemic PDT using an intravenous photosensitizer photoditazine (LLC "VETA-GRAND", Russia). Photoditazine was injected intravenously, after dissolution in 0.9% natural saline solution, at a dose of 1-1.4

Таблица 1

Сравнительная характеристика больных по возрасту и полу

Table 1

Comparative characteristics of patients by age and sex

Показатель Index	Основная группа Main group		Группа сравнения Comparison group		p
	M±SD		M±SD		
Возраст Age	62.53±10.74		60.79±9.27		0.568
	абс./ abs.	%	абс./ abs.	%	p
Женский пол Female	8	42.11	14	50.00	0.815
Мужской пол Male	11	57.89	14	50.00	0.815

Примечание: p – статистическая значимость различий между основной группой и группой сравнения.
 Note: p – statistical significance of differences between the main group and the comparison group.

Таблица 2

Сравнительная характеристика больных по гистологическому типу новообразования

Table 2

Comparative characteristics of patients by histology of tumor

Гистологический тип/ Histological type	Основная группа/ Main group		Группа сравнения/ Comparison group		p
	абс./ abs.	%	абс./ abs.	%	
Высокодифференцированная аденокарцинома/ High differentiated adenocarcinoma	3	15.79	5	17.86	0.834
Умеренно дифференцированная аденокарцинома/ Moderately differentiated adenocarcinoma	4	21.05	8	28.57	0.811
Низкодифференцированная аденокарцинома/ Low differentiated adenocarcinoma	8	42.11	12	42.86	0.803
Недифференцированная аденокарцинома/ Non-differentiated adenocarcinoma	3	15.79	2	7.14	0.644
Плоскоклеточный рак/ Squamous cell carcinoma	1	5.26	0	0	0.844
Нейроэндокринный рак/ Neuroendocrine cancer	0	0	1	3.57	0.843

Примечание: p – статистическая значимость различий между основной группой и группой сравнения.
 Note: p – statistical significance of differences between the main group and the comparison group.

mg/kg of body weight. In the process of administration, intravenous systemic PDT was performed through peripheral access to the cubital vein using an apparatus for intravenous blood irradiation with a monochromatic light source with a power of 0.7 W at a wavelength of 662-665 nm, an exposure dose of light of 1200-1400 J/cm², and a radiation power density of 0.22 W/cm². After 5 hours from the end of the infusion, local contact PDT was performed by irradiation using a software specialized two-wave laser device with a power of 0.7 W with monochromatic light with a wavelength of 662 nm with an exposure dose of light of 220 J/cm² with a radiation power density of 0.22 W/cm² through percutaneous transhepatic antegrade access and endoscopically with video esophagoduodenoscopy through retrograde access under endo-ultrasound control [13]. The purpose of local PDT was to achieve cell apoptosis at the periphery of the neoplasm in combination with a complex decrease in the concentration of atypical cells in the systemic circulation using systemic PDT.

Complex treatment with the use of local and systemic PDT was performed by the following algorithm: fluorescence diagnostics on a laser electronic spectrum device "Biospec" (New Surgical Technologies, Russia), local and systemic PDT on a software specialized two-wave apparatus "LAMI-Helios" (JSC "New Surgical Technologies", Russia) according to TS 9444-001-53807582-2010.

Complications of surgical treatment were assessed using the Clavien-Dindo scale [14]. In all patients of the main group, the indicators of hemostasis, proteolysis, and systemic inflammation were analyzed. Determination of the concentration of fibrinogen in plasma according to Clauss (1957) was carried out with a set of reagents from the company "Technology-Standard" (Russia).

To determine the concentration of tissue plasminogen activator (t-PA) in blood serum, the TECHNOZYM t-PA Ag EDTA ELISA kit for enzyme immunoassay was used (Cat. No. TC12007, Technoclone Herstellung von Diagnostika und Arzneimitteln GmbH, Austria). The optical density of the solution in wells at a wavelength of 450 nm was measured using an Elx808 automatic microplate photometer (BioTec Instruments, Inc., USA).

To determine the concentration of tissue plasminogen activator inhibitor-1 (PAI-1) in blood serum, the TECHNOZYM PAI-1 Antigen ELISA kit for enzyme immunoassay was used (Cat. No. TC12075, Technoclone Herstellung von Diagnostika und Arzneimitteln GmbH, Austria). The optical density of the solution in wells at a wavelength of 450 nm was measured using an Elx808 automated microplate photometer (BioTec Instruments, Inc., USA).

To determine the concentration of tissue factor (TF) in blood serum, the IMUBIND Tissue Factor ELISA kit for enzyme immunoassay was used (Cat. No. REF845,

BioMedica Diagnostics, USA). The optical density of the solution in the wells at a wavelength of 450 nm was measured using an automatic photometer for microplates Elx808 (BioTec Instruments, Inc., USA).

To determine the concentration of tissue factor pathway inhibitor (TFPI) in blood serum, the Human Tissue Factor Pathway Inhibitor (TFPI) ELISA Kit was used (Cat. No. ET1005-1, Assaypro, USA). The optical density of the solution in the wells at a wavelength of 450 nm was measured using an Elx808 automatic microplate photometer (BioTec Instruments, Inc., USA).

To determine the concentration of tumor necrosis factor-alpha (TNF-α) in blood serum, the Human TNF alpha total Platinum ELISA kit for enzyme immunoassay was used (Cat. No. BMS2034/BMS2034TEN, Bender MedSystems GmbH, Austria). The optical density of the solution in the wells at a wavelength of 450 nm was measured using an Elx808 automatic microplate photometer (BioTec Instruments, Inc., USA).

Statistical analysis was performed using the SigmaPlot 14.0 statistical software package (registration number 775400014). To compare two unrelated groups, the nonparametric Mann-Whitney test was used, since, according to the Shapiro-Wilk test, all the studied parameters, except for gender and age, had a non-normal distribution in the main group and the comparison group. To compare unrelated groups with a normal distribution, Student's parametric test was used, and for relative values – Fisher's z-test. The results for indicators with a non-normal distribution are presented as median (Me), first (Q1) and third (Q3) quartiles, mean (M) and its standard deviation (SD). The results for indicators with a normal distribution are presented as the mean (M) and its standard deviation (SD). The method of Kaplan-Meier curves was used to estimate the overall life expectancy, and a log-rank test was used for a comparative analysis of survival. To determine the predictive ability of indicators, ROC analysis was used to calculate AUC, cut-off points with sensitivity and specificity, likelihood ratio (LR+ and LR-), and predictive value (p). The critical level of significance of the results of the study was taken as $p < 0.05$.

Results and Discussion

There were no postoperative complications after PDT in patients of the main group. One patient of the main group (5.26%) was diagnosed with gallbladder empyema after stenting the bile ducts. In one patient of the comparison group (3.57%), a seroma of the postoperative suture was detected after hepaticojejunostomy, and in one patient of the comparison group (3.57%), a subhepatic hematoma was detected after percutaneous transhepatic multilobar drainage of the bile ducts.

There were no statistically significant differences between the number of postoperative complications

between the main and the comparison groups ($p=0.649$). All the complications were of grade IIIa according to the Clavien-Dindo classification.

When assessing life expectancy in parallel compared groups (Table 3), the median survival in the main group was statistically significantly higher compared to the comparison group ($p = 0.04$) (Fig. 1).

Most studies in the field of PDT of malignant neoplasms of the pancreas were carried out in patients without distant metastatic lesions. In a study by Bown et al. [8], Hugget et al. [9], as well as subsequent studies of various photosensitizers using their methods, described in the review by Karimnia et al. [6], the immediate results

of using local PDT in patients with local progression of pancreatic cancer were primarily investigated and the exclusion criterion was the presence of stage IV of the disease in patients. Median survival in these studies ranged from 9.5 to 11 months in patients with stages II and III of malignancy. At the same time, the issue of the possibility of improving long-term outcomes in patients with distant metastases of a malignant neoplasm of the pancreas, which make up the majority of newly diagnosed patients, as well as factors affecting the effectiveness of not only local application of PDT but also long-term outcomes of treatment, remains relevant.

Таблица 3

Сравнительный анализ выживаемости больных

Table 3

Comparative analysis of survival of patients

Группа Group	Медиана выживания, дни Median survival, days Me (Q ₁ ; Q ₃)	95% доверительный интервал 95% confidence interval	p
Основная Main	148 (287;72)	86.145-209.855	0.04
Сравнения Comparison	68 (188;35)	61.253-74.7477	

Примечание: p – статистическая значимость различий между основной группой и группой сравнения.

Note: p – statistical significance of differences between the main group and the comparison group.

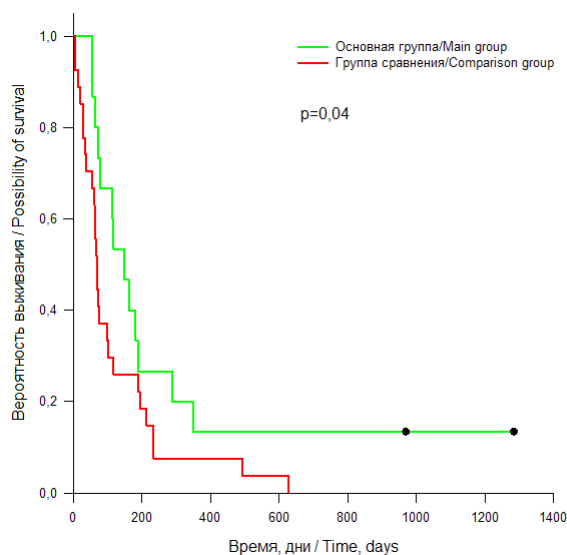


Рис. 1. Сравнительная характеристика выживаемости у пациентов, которым было проведено паллиативное хирургическое лечение злокачественного новообразования поджелудочной железы с применением локальной и системной ФДТ и без ее применения.

Fig. 1. Comparative characteristics of survival in patients who underwent palliative surgical treatment of a malignant pancreatic tumor using local and systemic PDT and without using of it.

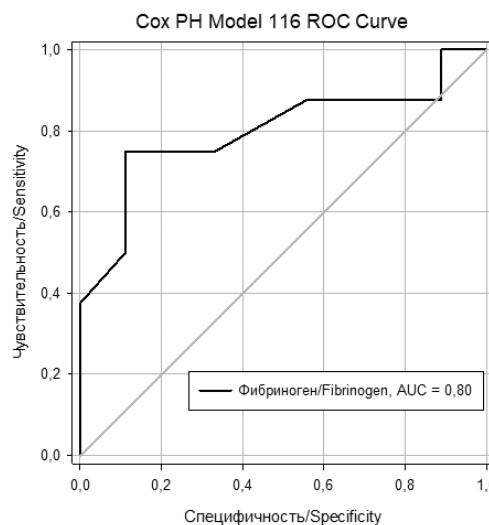


Рис. 2. Результаты ROC-анализа влияния фибриногена на трехмесячную выживаемость у пациентов с раком поджелудочной железы IV стадии.

Fig. 2. Results of ROC analysis of the effect of fibrinogen on three-month survival in patients with stage IV pancreatic cancer.

Таблица 4

Результаты ROC-анализа влияния фибриногена на трехмесячную выживаемость у пациентов с раком поджелудочной железы IV стадии

Table 4

Results of ROC analysis of the effect of fibrinogen on three-month survival in patients with stage IV pancreatic cancer

Показатель Index	AUC (площадь под ROC-кривой) AUC (area under the ROC curve)	Стандартная ошибка (m) Standard error (m)	95% доверительный интервал AUC, (95%CI) 95% confidence interval AUC, (95%CI)	Уровень значимости (p) Significance level (p)
Фибриноген, г/л Fibrinogen, g/l	0,7986	0,1185	0,5664;1,031	0,039
LR+ = 6,75; LR- = 0,28				
TNF-α	0,571429	0,187718	0,2035;0,9394	0,68
TF	0,261905	0,152083	-0,03618;0,5600	0,15
TFPI	0,452381	0,18798	0,08394;0,8208	0,78
TPA	0,571429	0,197777	0,1838;0,9591	0,67
TPA/PAI	0,6	0,185531	0,2364;0,9636	0,57

A causal relationship was analyzed for several markers of hemostasis, systemic inflammation, and proteolysis, taken before PDT, and three-month survival by ROC analysis (Table 4 and Fig. 2). Statistically significant results of the relationship between the level of fibrinogen and three-month survival during PDT were obtained ($p=0.039$), other indicators had no statistically significant effect ($p>0.1$). The quality of the model was considered good (the area under the ROC curve was 0.7986). The cut-off limit, at which the sensitivity of the predictive model is 75%, and its specificity is 89%, was 3.40 g/l. The data obtained allow us to conclude that the level of fibrinogen above 3.40 g/l allows us to predict a decrease in the probability of three-month survival after PDT.

Changes in the hemostasis system in cancer patients are one of the leading problems of modern oncology, while thrombotic complications are one of the leading causes of death in cancer patients [16]. Fibrinogen is an important indicator of coagulation hemostasis, abnormalities of which play a leading role in thrombotic complications in malignant neoplasms and affect patient survival [16].

It can be concluded that the results obtained confirm the data obtained in previous studies on PDT. PDT is the method of choice in patients with malignant neoplasms of the pancreas who are not indicated

for radical surgical treatment and other methods of palliative treatment due to their high toxicity, which can significantly increase the life expectancy of patients. This is especially true for patients with advanced stage IV of the disease, in whom PDT can significantly increase life expectancy in the absence of side effects from therapy. When choosing a management strategy for such patients, especially those with multimorbidity, the method of prediction of the effectiveness of PDT, which would be available in the routine practice of a surgeon and an oncologist, is important. The method proposed based on the results of the study [17] makes it possible to identify patients with advanced stage IV pancreatic malignancy, in whom PDT will most likely increase life expectancy compared to other methods of palliative treatment.

Conclusion

Thus, complex palliative treatment with the use of PDT of malignant neoplasms of the pancreas allows for increasing the life expectancy of patients without causing side effects on the patient. Based on the foregoing, local and systemic PDT can be recommended as a method of choice in the complex palliative treatment of patients with malignant neoplasms of the pancreas, who are not indicated for radical surgical treatment and other methods of palliative treatment.

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