ORIGINAL ARTICLES

PHOTODYNAMIC THERAPY OF CANCER OF LARGE DUODENAL PAPILLA AND EXTRAHEPATIC BILE DUCTS

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Abstract

The problem of treating patients with malignant neoplasms of the extrahepatic bile ducts and the large duodenal papilla remains relevant due to the growing incidence, high mortality, and a pronounced decrease in the quality of life of patients, despite the radical surgery. The purpose of this study was to evaluate the effectiveness of photodynamic therapy (PDT) in inoperable patients with malignant tumors of these localizations.
The study is based on the treatment of 79 patients with adenocarcinoma of large duodenal papilla and extrahepatic bile ducts. 29 patients received palliative bile drainage operations with PDT. 50 patients in the control group only had palliative bile drainage operations. Patients in the study group received from 1 to 3 PDT courses in a year. In total, 29 patients received 52 PDT courses. The tolerance to the method and the life expectancy of patients were evaluated.
The median survival of patients who underwent PDT was 18 months (11–60 months); in the control group – 11.5 months.
PDT, in combination with bile drainage operation, is an effective method for the treatment of inoperable patients with malignant neoplasms of the extrahepatic bile ducts and the large duodenal papilla in the absence of severe complications and with easy tolerance to therapy by patients. For the treatment and prolongation of life of patients whose radical surgical treatment is associated with a high risk of death, PDT seems to be the best treatment option. Results of PDT treatment for cancer of this localization are comparable with the results of radical surgeries and exceed those for palliative surgeries.

Keywords: cancer of large duodenal papilla, cancer of extrahepatic bile ducts, photodynamic therapy, photosensitizer, laser.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ РАКА БОЛЬШОГО ДУОДЕНАЛЬНОГО СОСОЧКА И ВНЕПЕЧЁНОЧНЫХ ЖЕЛЧНЫХ ПРОТОКОВ

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Резюме

Проблема лечения пациентов с злокачественными новообразованиями (ЗНО) внепечёночных желчных протоков (ВЖП) и большого дуоденального сосочка (БДС) остается актуальной в связи с растущей заболеваемостью, высокой летальностью и выраженным снижением качества жизни пациентов, несмотря на проведение радикальной операции. Цель данного исследования заключалась в оценке эффективности применения фотодинамической терапии (ФДТ) у неоперабельных больных с злокачественной опухолью данной локализации.
В исследование вошли 79 больных аденокарциномой БДС и ВЖП. Для лечения 29 больных применяли паллиативные желчеотводящие операции и ФДТ, 50 больным, составившим группу контроля, выполняли только желчеотводящие операции. Количество курсов ФДТ в основной группе составило от 1 до 3 в течение года. В общей сложности 29 больным проведено 52 курса ФДТ. Оценивали переносимость метода и продолжительность жизни больных.
Медиана выживаемости больных, которым выполнялась ФДТ, составила 18 мес (11–60 мес), в группе контроля – 11,5 мес.
ФДТ в комбинации с желчеотводящими операциями является эффективным методом лечения неоперабельных больных с ЗНО БДС и ВЖП при отсутствии тяжелых осложнений и с легкой переносимостью терапии пациентами. Для лечения и продления жизни больных,

радикальное хирургическое лечение которых сопряжено с высоким риском развития летального исхода, ФДТ представляется оптимальным вариантом терапии. Результаты ФДТ по продолжительности жизни сравнимы с радикальными операциями и превышают таковые для паллиативных операций.

Ключевые слова: рак большого дуоденального сосочка, рак внепеченочных желчных протоков, фотодинамическая терапия, фотосенсибилизатор, лазер.

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Introduction

The use of photodynamic therapy (PDT) for the treatment of patients with malignant neoplasms over the past 20 years has become so wide-spread that it is now used for tumors that are the most aggressive and difficult to access with other treatment methods [1-5]. One of these localizations is malignant tumors of the biliary tract. A group of malignant tumors that develop from the epithelium of the bile ducts is referred to by a general term of cholangiocarcinoma (ChC), which includes intrahepatic, portal, and distal forms. 80% of ChCs are extrahepatic: portal vein ChC and distal ChC [6-10]. The latter includes duodenal papilla carcinoma (DPC). ChC develops against the background of long-term chronic inflammation of the bile ducts and is very pernicious. It is radical surgery that gives hope to the patients. However, in 80-90% of patients, ChC is diagnosed only upon the observation of the first clinical sign of the disease, which is mechanical jaundice, and at that stage surgery is impossible due to the extent of the process. By the time when mechanical jaundice develops, the tumor often invades the large vessels of the hepatoduodenal ligament, the portal vein, or passes to the head of the pancreas, which reduces the possibility of performing radical surgery to 23-50% [11-15]. Performing this extensive and traumatic operation is accompanied by high rates of postoperative mortality (up to 40%), and 50-75% of patients have relapses of the disease [11, 16, 17]. Chemotherapy and radiation therapy are less than effective, and adjuvant chemotherapy does not reduce the frequency of postoperative relapses [8, 13-15]. The average life expectancy of these patients is 3 to 6 months after the diagnosis [8-10]. As early diagnosis remains difficult, and treatment options for ChC are limited, the prognosis of 5-year survival of the patients remains low and is on average 5-15% [9-11, 17].

Being a less invasive and relatively safe method of treatment, local excision of the tumor is used, but it is accompanied by a high frequency of relapses. As for radical surgery in connection with malignant tumors of the bile ducts, the authors of publications most often refer to a high frequency of relapses, reaching 80% of cases [18, 19]. The average life expectancy after radical surgery in the form of gastropancreatoduodenal resection (GPDR) is 1.5-2 years, and 5-year survival rate does not exceed 10-20% [4, 5, 11].

Patients with obturation jaundice and contraindications to GPDR usually undergo palliative interventions: draining endoscopic procedures with the introduction of endoprostheses or the creation of bypass anastomoses. However, the tumor quickly grows into an endoprosthesis, which is accompanied by restenosis and jaundice. The average life expectancy after palliative surgery is 4 to 12 months.

Radiation therapy of the malignant tumors of this zone, both external and endoluminal irradiation (brachytherapy), is technically difficult to perform, ineffective, and, therefore, rarely used. For the treatment of this pathology, chemotherapy is also ineffective.

This situation makes us look for less traumatic and, at the same time, more effective methods of treating patients with malignant tumors of duodenal papilla and extrahepatic bile ducts. A method that meets these requirements is photodynamic therapy (PDT).

PDT is a well-known method of treating various diseases and, above all, malignant tumors, in which a photosensitizer (FS), which selectively accumulates in tissues with increased metabolism, is activated by local irradiation of pathologically altered tissues with light ath a wavelength corresponding to the peak of absorption of the PS. The photodynamic reaction that occurs in the presence of oxygen causes the generation of singlet and other reactive oxygen intermediates that have a detrimental effect on tumor tissues, which subsequently leads to tumor resorption [5, 20]. The action of reactive oxygen intermediates is manifested either by direct cytotoxic damage to the tumor [5, 16], or by the destruction of the blood vessels feeding the tumor [20, 21]. At the same time, depending on the photosensitizer used, the vascular mechanism accounts for up to 60% of the antitumor effect of PDT, while the direct cytotoxic effect

is about 30%. Along with that, PDT stimulates the immune responses of the body both due to the direct inflow of lymphocytes, neutrophils, and macrophages into the PDT-exposed tumor tissues (which in itself leads to a slowdown in tumor growth due to the release of tumor necrosis factor by macrophages), and due to the action of cytokines (interleukin 6 and interleukin 10) responsible for the antitumor effect of PDT [17, 22-28].

PDT opens up wide opportunities for various therapeutic effects of radical and palliative nature when other methods of treatment have already been exhausted or are not applicable at all.

The first publication on the use of PDT for inoperable common bile duct cancer in a female patient who had 7 PDT courses for 4 years appeared in 1991 [29, 30]. It was only much later that publications appeared on the few series of clinical observations on the use of PDT for bile duct cancer [21, 31, 32].

The analysis of literature sources on the use of various methods of elimination of obturation jaundice in ChC, i. e., surgical, combined and complex methods of ChC treatment, including literature reviews covering more than 2,200 patients undergoing percutaneous transhepatic biliary drainage and 8,100 patients undergoing endoscopic biliary drainage [27], indicates the unanimous opinion of researchers that the use of PDT for the treatment of DPC and extrahepatic bile duct cancer is possible in the cases when surgical intervention involves significant risk, in patients with severe comorbidities, in the presence of a disseminated, technically non-removable tumor (palliative PDT intended to relieve the bothersome symptom of mechanical jaundice due to the biliary tract obturation by a tumor), the presence of locoregional and remote metastases in patients (palliative PDT), and the patients' refusal of surgical treatment.

Materials and methods

The work performs a comparative analysis of the treatment effectiveness of two groups of patients with biliary tract cancer who had counterindications for radical surgical treatment.

We observed 79 patients with cancer of the major duodenal papilla and extrahepatic bile duct cancer. The main group included 29 patients who underwent percutaneous transhepatic drainage, endoscopic stent placement, or T-shaped drainage device installation during trial laparotomy in 2001-2015; at the second stage, after elimination or reduction of jaundice, PDT was applied. The control group included 50 patients who had only surgery to evacuate bile in the period from 1991 to 2001. Histological verification of the diagnosis confirmed that all patients had adenocarcinoma of various degrees of differentiation. In the main group, the tumor focus was localized in the porta hepatic in 2 (6.9%), in the choledochus, in 3 (10.3%), in the gall bladder and cystic duct, in 4 (13.8%), and in duodenal papilla, in 20 (69.0%) patients. In the control group, liver cancer was diagnosed in 21 (42.0%), choledochal cancer in 9 (18.0%), gallbladder and cystic duct cancer in 6 (12.0%), and duodenal papilla cancer in 14 (28.0%) patients.

The main reason for refusal to perform radical surgical treatment in the main group was the presence of severe somatic pathology and, therefore, a high anesthetic risk.

The clinical picture of patients was dominated by mechanical jaundice phenomena, and in this connection, the majority of patients underwent various palliative surgical interventions, depending on the location of the tumor. In the main group of 3 patients with DPC, the phenomena of mechanical jaundice were eliminated by conservative therapy and PDT, which resulted in recanalization of tumor stenosis, leading to an improvement in the outflow of bile to the duodenum. Later, those patients had stents installed in the duodenal papilla duct and terminal choledochus 6, 9, and 11 months after PDT due to the renewed growth of the tumor. On average, the jaundice-free period after PDT in mono mode was 7.8 months.

Depending on the dissemination of the tumor process and the conditions created by previous medical interventions, we used various methods of light delivery to the therapy site:

- endoscopic surface irradiation of the DPC from the side of the duodenal lumen with a light guide equipped with a straight diffuser;
- endoscopic endoluminal irradiation of the duodenal papilla duct and the terminal part of the common bile duct with a light guide with a 2 - 4 cm long cylindrical diffuser inserted through the mouth of the duodenal papilla or papillosphincterotomic opening;
- irradiation of the tumor with a light guide with a cylindrical diffuser delivered to the tumor side through the lumen;
- transfistulous endoluminal irradiation of the common bile duct, cystic and hepatic ducts with light guides with a 2-5 cm long cylindrical diffuser with radiopaque metal markers in the presence of a bile fistula created earlier for biliary tract decompression;
- combined methods of light guidance using surface irradiation of duodenal papilla from the duodenal lumen and the terminal choledochus, with the introduction of a light guide with a cylindrical diffuser from the duodenum or terminal choledochus with the introduction of a light guide through a drainage catheter or through a transhepatic drainage.

In the case of endoscopic irradiation with a light guide with a cylindrical diffuser, the latter was introduced through the endoscope's biopsy channel under visual

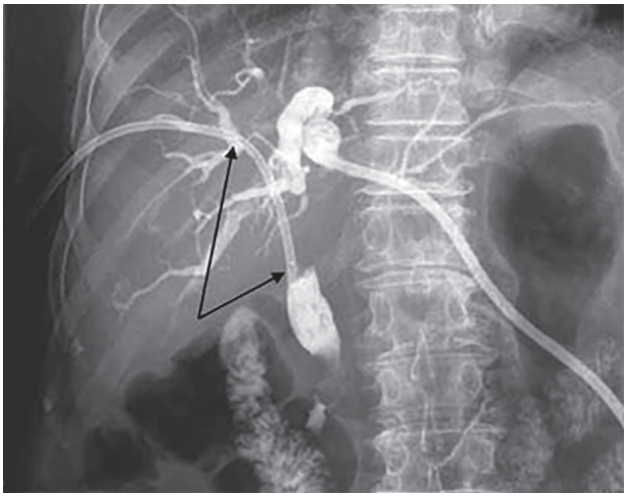

Рис. 1. Вариант чрезфистульного облучения у больной раком ворот печени Bismuth-IV с метастазами в печени и легких (продолжительность жизни 23 мес) после раздельного транспеченочного дренирования. Рентгеноконтрастные метки указаны стрелками
Fig. 1. Variation of transfistular irradiation in a patient with cancer of liver port Bismuth-IV with metastases in liver and lungs (survival time 23 months) after transherpatic draining. Radiopaque marks are indicated by arrows

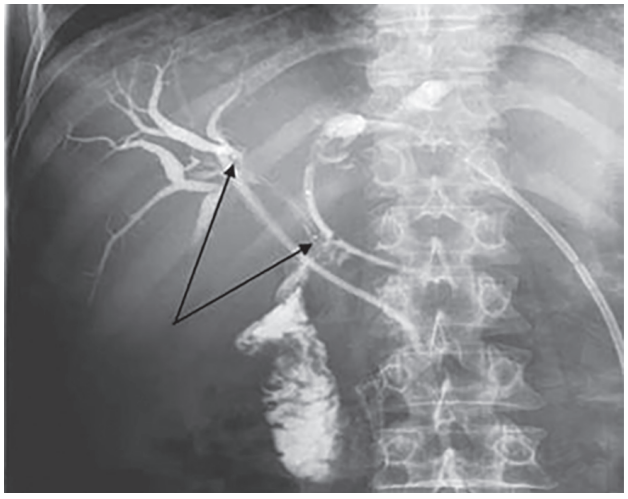

Рис. 2. Вариант чрезфистульного облучения у больной раком ворот печени Bismuth-IV после раздельной чрескожной холангиостомии. Рентгеноконтрастные метки указаны стрелками
Fig. 2. Variation of transfistular irradiation in a patient with cancer of liver port Bismuth-IV after transcutaneous cholangiostomy. Radiopaque marks are indicated by arrows

control into the choledochal lumen through the duodenal papilla mouth or papillosphincterotomic opening.

When using a light guide with a polished flat end or with a microlens at the end, the latter was also introduced through the endoscope biopsy channel, and the light irradiation was performed on the duodenal papilla tumor under visual control.

Transfistulous irradiation was performed in patients who had previously undergone surgical interventions in the form of external drainage of the bile ducts in order to address the issue of mechanical jaundice. Fistulography was performed, in which the extent of the tumor stricture and the adequacy of drainage standing were evaluated. Then a light guide with a cylindrical diffuser and radiopaque marks located on the borders of the diffuser was introduced through the drainage tube. The X-ray contrast markers being used for orientation, the diffuser was placed inside the stenosed bile duct with an overlap of the stenosis zone by 0.5 - 1 cm at each edge of the tumor (Fig. 1, 2). The length of the diffuser on the light guide was selected on the basis of the size of the tumor as determined by the length of the tumor stenosis.

After the placement of the light guide in the appropriate position, the drainage tube was pulled out, in part of in full, in order to avoid partial absorption of laser radiation by the walls of the drainage tube. With a stenosis length of more than 4-5 cm, light exposure was performed from several positions of the diffuser, moving the light guide under X-ray TV control. After the completion of the PDT procedure, the light guide was removed and the drainage tube was installed in the same position under x-ray control.

Transfistulous radiation was performed on 13 (46.4%) patients. In 4 of them, it was found impossible to re-install drainage in its initial position. The passage of bile is provided due to the expansion of the tumor-stenosed section of the bile duct as a result of PDT exposure.

The duration of the light exposure session in the PDT process was calculated based on the size of the tumor, the length of the diffuser of the light guide used, and the required specified energy density of the supplied laser radiation. This procedure was performed in an endoscopic or X-ray room, depending on the chosen method of laser radiation delivery. No pain relief was required during the procedure.

In case of the endoscopic method of irradiation, protease inhibitors and spasmolytics were prescribed in normal dosages in order to prevent the possible development of acute pancreatitis. Prevention measures were taken, depending on the situation, within 2 to 3 days after PDT.

Despite the satisfactory tolerability of the procedure by all patients, in the postoperative period 25 patients (89.3%) had a fever reaction and pain syndrome of varying severity, depending on the intensity of the photodynamic reaction of the tumor. Pain appeared, as a rule, 3 to 5 hours after the PDT session due to developing tissue edema, localized in the right hypochondrium and epigastric region, and completely stopped in 2 to 4 days. In 6 patients, it was necessary to administer narcotic an-

algesics to relieve the pain syndrome. Fever response, as an inflammatory component of PDT, was observed in 22 patients (75.8%). Body temperature normalized in 3 to 4 days after a PDT session. The remaining 4 patients had no adverse reactions associated with PDT.

The PS used was Photosens, sulfated aluminum phthalocyanin (FSUE «SSC NIOPIK», Russia, registration certificate PN000199/02 dated 04.03.2010) and Photoditazine, a derivative of e6 chlorin (OOO "VETA-GRAND", Russia, registration certificate no. ЛС 001246 dated 18.05.2012). Photosens accumulates in the tumor in a concentration that is 1.5 - 2 times higher than that in healthy tissues. Photoditazine is characterized by rapid accumulation in the tumor in maximum concentration after 2 to 3 hours, followed by a gradual decrease in concentration after 4 to 5 hours. After 24 hours, only trace quantities of the drug are detected in the blood, which makes it possible to avoid the long-term skin photosensitivity typical for first-generation PS products. Photoditazine has a high tropism to tumor tissues. According to various authors [35], the maximum contrast ratio varies from 5 to 20. Fotosens was administered in doses of 0.8-1.0 mg per kilo of body weight, Photoditazine was most often administered in doses of 0.6-0.7 mg per kilo of body weight, less often in 0.8-0.9 mg per kilo of body weight.

The PDT session was performed after a certain period of time corresponding to the achievement of maximum PS accumulation in the tumor. With Photosense used as PS, laser light exposure was performed after 24 hours from the moment of the drug administration, and with Photoditazine, after 2.5-3 hours.

The sources of laser radiation used were "Latus" semiconductor device (OOO "Atcus", Russia) with a maximum output optical power of 2 W and a wavelength of 662 nm, and LFT-02-Biospec laser system for photodynamic therapy (OOO "Biospec", Russia) with an output optical power of up to 2.5 W and a wavelength of 672 nm.

Laser irradiation was performed using flexible quartz monofilament light guides with a cylindrical diffuser and X-ray contrast markers, with an end diffuser or a microlens at the end (ZAO "Poluprovodnikovyie Pribory", OOO "Polironik", OOO "Elomed", Russia).

The output power at light exposure was 0.5 and 1.0 W, the power density was 200-500 mW/cm^2 or 200-500 mW/cm of the diffuser length. The energy density for endoluminal irradiation using light guides with a cylindrical diffuser ranged from 50 to 100 J/cm of the length of the diffuser to 250-300 J/cm.

Results

We managed to track the life expectancy of all patients in the main and control groups. The direct results of PDT application were evaluated based on clinical and instrumental data (X-ray computed tomography, magnetic resonance imaging and cholangiopancreatography, ultrasound, duodenoscopy with biopsy for duodenal papilla tumors). The number of PDT courses varied from 1 to 3 in a year. Follow-up examination of patients was performed in 3, 6, and 12 months after the treatment.

Despite the relatively satisfactory tolerability of the procedure by patients, after 12 (23%) PDT courses out of the 52 conducted, adverse reactions and complications were observed. The greatest number of complications was observed in patients with duodenal papilla carcinoma who had laser radiation brought to the affected area with the endoscopic method. The nature of adverse reactions and complications is shown in Table

The greatest number of adverse reactions and complications observed were in the form of cholangitis, which occurred 12-24 hours after the PDT session and was manifested as fever, the yellowing of the skin and sclera, increased blood bilirubin levels due to the direct fraction. Cholangitis was stopped with conservative treatment in 3 to 4 days. We do not consider the cholangitis symptoms as a specific complication of PDT. Cholangitis can occur as a result of any X-ray examination with contrast enhancement or an endoscopic intervention on the extrahepatic bile duct. Despite the preventive measures taken for all patients, one patient had pancreatitis sympthoms. They were also stopped by conservative measures in 3 days. Photosensitivity phenomena in the form of erythema of open skin areas were recorded in 1 patient, and are associated with prolonged excretion of Photosens and the patient's failure to observe the light regime.

The most severe complication was fibroulcerative duodenitis, which occurred in 3 cases, one of them with partial duodenal obstruction, which required longer-term conservative therapy. The phenomena of fibrinous-ulcerative duodenitis were observed in cases when Photosens was used, and are associated, in our opinion, with its lower tropicity to the tumor tissues compared to the preparations of the chlorin group.

The total number of complications was also higher when Photosens was used (58.3%) as PS, compared to Photoditazine (41.7%). There were no lethal outcomes.

The median survival time of patients who underwent PDT was 18 months (the minimum time being 12.5 months and the maximum 60 months). In the group where only palliative surgery was performed, the median survival was 11.5 months (minimum time: 4 months, maximum time: 14 months), $p < 0.0001$ (Fig. 3).

Discussion

In 1978, T. Dogherty published the first paper on the successful clinical use of PDT at the US National Cancer Institute. This article triggered the use of PDT for the treatment of cancer of superficial localizations and some visceral ones. After 7 years, J. S. McCaughan used PDT for a bile duct cancer patient [29]. It was a remarkable

Таблица
Побочные реакции и осложнения при ФДТ рака большого дуоденального сосочка и внепеченочных желчных протоков в зависимости от использованного фотосенсибилизатора, абс. ч.
Table
Adverse reactions and complications in PDT of cancer of the large duodenal papilla and extrahepatic bile ducts, depending on the photosensitizer used

Характер осложнения Type of complication	Фотосенс Photosens	Фотодитазин Fotoditazin	Всего Total
Панкреатит Pancreatitis	1		1
Холангит Cholangitis	1	5	6
Фибринозно-язвенный дуоденит Fibrinous-ulcerative duodenitis	3		3
Фибринозно-язвенный дуоденит с явлениями стеноза двенадцатиперстной кишки Fibrinous-ulcerative duodenitis with duodenal stenosis	1		1
Эритема кожи Skin erythema	1		1
Всего (%) Total (%)	7 (58,3%)	5 (41,7%)	12 (100%)

story of a persistent struggle for the life of a seemingly doomed person.

In 1985, a 50-year-old woman was diagnosed with a common bile duct adenocarcinoma during a cholecystectomy. A T-shaped drainage was left in place, and after 2 months, the first course of PDT with a hematoporphyrin derivative at a dose of 2 mg per kilo of body weight was performed during laparotomy. A light guide with a cylindrical diffuser was introduced with the use of a choledochoscope. After PDT, a U-shaped tube was left in the bile duct to prevent the development of jaundice. In the following 4 years, 6 more PDT courses were administered to the patient. The choledochoscope was inserted through a U-shaped drain tube. 2 years after the start of treatment for common bile duct cancer, the patient was diagnosed with endometrial cancer, for which she underwent surgery and radiation therapy. The patient died 4.5 years later [29].

In Russia, PDT was successfully used for the first time in 1998, for stage I duodenal papilla cancer (T1N0M0) in a 67-year-old patient who was admitted with mechanical jaundice and who had counterindications against surgical treatment because of a high degree of surgical and anesthetic risk due to severe concomitant diseases: coronary heart disease, bilateral nephrolithiasis, and pyelonephritis with partial renal failure. On 14.02.98, the pa-

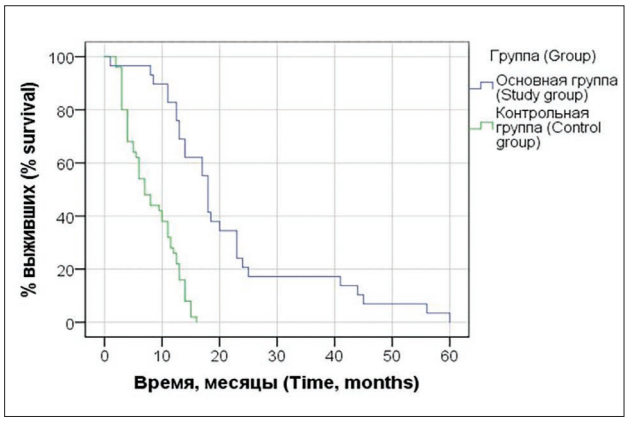

Рис. 3. Общая выживаемость пациентов основной и контрольной групп (по Каплан-Мейеру)
Fig. 3. Overal survival of patients of the study and control groups (Kaplan–Meier estimator)

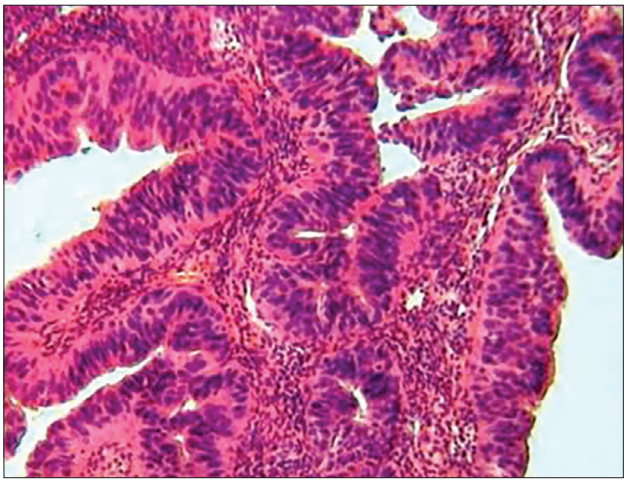

Рис. 4. Гистология. Высокодифференцированная темноклеточная сосочковая аденокарцинома. Окраска гематоксилин-эозином. Ув. х20. [25]
Fig. 4. Histology. Highly differentiated dark cell papillary adenocarcinoma (staining with hematoxylin-eosin, x20). [25]

tient underwent endoscopic papillosphincterotomy in Moscow City Clinical Hospital No. 1 (by Yu. V. Vasilenko). Histological examination revealed a tumor in the biopsy material that had the structure of a highly differentiated dark-cell papillary adenocarcinoma. Expressed cellular polymorphism with violation of the rows and polarity of tumor cells, with the presence of atypical mitoses in them. Tumor cells form glandular and glandular-like structures (Fig. 4) [25].

On 21.04.98, the patient had an intravenous injection of Photosens, a second-generation PS produced in Russia (FSUE «SSC NIOPIK», Russia, registration certificate PN000199/02 dated 04.03.2010) the dose being 0.8 mg per kilo of body weight, and after 24 hours a session of endoluminal laser irradiation was performed using a light guide with a 2 cm long cylindrical diffuser, and then, in addition, the duodenal papilla was superficially irradiated from the side of the duodenum lumen with a light guide with a polished end that creates direct exposure of the surface to the light beam. Irradiation was performed with ALT PDT-670/500 "Alpha-Photosens", a medical device manufactured by NPO "Polyus" based on a laser on yttrium aluminate with neodymium, generating light with a wavelength of 670 nm. Control gastroduodenoscopy performed 3 weeks after the course of PDT, revealed residual phenomena in the form of edema of the descending duodenum mucosa and the smoothness of the relief. The papilla tissues are edematous, whitish in color, dense. An influx of transparent bile from the choledochoduodenal anastomosis is observed, there are no signs of the violation of the patency of the terminal department of the choledoch. Histological conclusion on a biopsy from the papilla and the surrounding mucosa: there are signs of malignancy in the form of occasional glands, which have the epithelium characterized by polymorphism, hyperchromic nuclei, and single atypical mitoses. The surrounding tissues are observed to have the phenomena of sclerosis, edema, moderate inflammatory infiltration, dystrophic changes, which should be considered as manifestations of therapeutic pathomorphosis of the tumor [25] (Fig. 5).

The patient's condition was quite satisfactory, and the biochemical parameters normalized. Dynamic follow-up in 1, 5, 10, 16, 22, 24 and 30 months after PDT with a set of diagnostic tests (gastroduodenoscopy with multiple biopsies, computed tomography, ultrasound of the abdominal cavity) did not reveal a recurrence of the duodenal papilla tumor or its metastases. The results of a control histological examination 22 months after PDT: the mucous membrane with the phenomena of stroma edema, hyperplasia of part of the glands, and moderate signs of inflammatory changes. In some areas, the phenomena of fibrosis, uneven edema of the stroma with inflammatory infiltration consisting mainly of lymphocytes, are observed. No signs of malignant cells were found [25] (Fig. 6). The patient's body mass increased by 7 kg. The patient was observed for 3.5 years after the PDT course and died of concomitant pathology without signs of major duodenal papilla cancer recurrence [27].

Similar descriptions on the use of PDT of inoperable ChC can be found in the literature starting from the mid-1990s. [21, 31, 32]. For instance, M. Ortner et al. reported the effective use of PDT of unresectable ChC in 9 patients who earlier had had ineffective bile duct drainage by stenting [31].

Patients were intravenously administered Photophrin at a dose of 2 mg per kilo of body weight, and after 2 days, a session of endoluminal light exposure was performed with cholangioscope that had wavelength of 630 nm and energy density of 180 J/cm^2. Patients had a decrease in serum bilirubin for at least 2 months, and an improvement in the quality of life when assessed on the Karnofsky Scale from 32% before treatment to 70% after PDT. Over the 30-day period, there were no lethal outcomes.

At the 8th International Photodynamic Association World Congress (Vancouver, Canada, 2001), 2 reports were made on the use of PDT in ChC. A group of authors from Germany reported on PDT to 9 patients with ChC. 48 hours after intravenous administration of Photophrin at a dose of 2 mg per kilo of body weight, a PDT session was performed with a light source wavelength of 630 nm, light guides with a 3-7 cm long cylindrical diffuser, the effective fields overlapping the proximal and distal edges of the tumor stenosis. The luminous density was 180 J/cm^2 of the diffuser length. The light guide was introduced by retrograde cholangiopancreatography

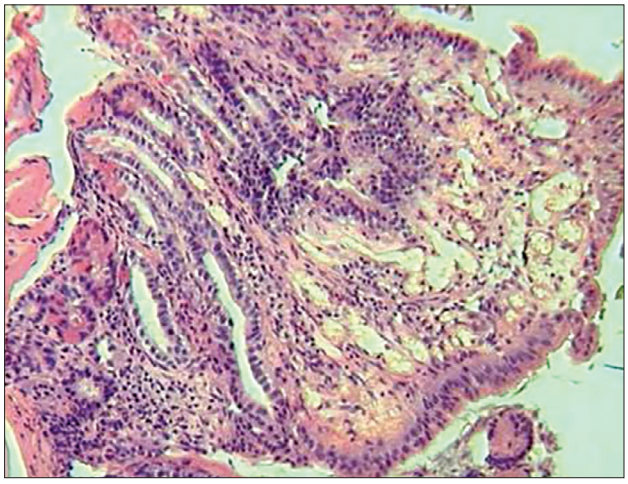

Рис. 5. Гистология. Аденокарцинома большого сосочка двенадцатиперстной кишки. Проявления терапевтического патоморфоза опухоли через 3 недели после фотодинамической терапии. Окраска гематоксилин-эозином. Ув. х20. [25]
Fig. 5. Histology. Adenocarcinoma of the major duodenal papilla. Manifestation of therapeutic pathomorphosis 3 weeks after PDT (staining with hematoxylin-eosin, x20). [25]

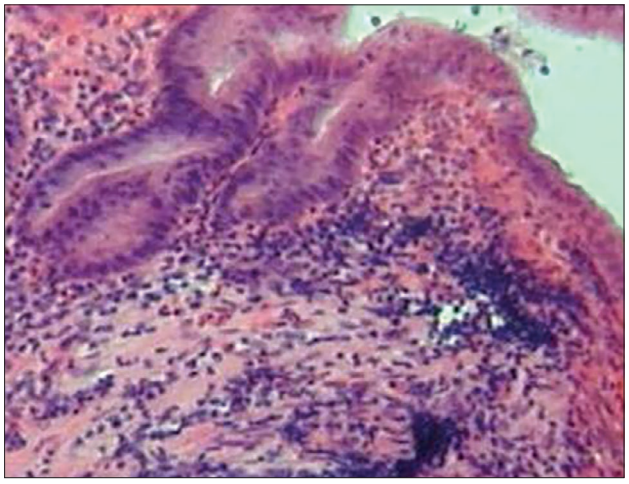

Рис. 6. Гистология. Большой дуоденальный сосочек. слизистая оболочка с явлениями отека стромы, гиперплазии части желез и умеренными признаками воспалительных изменений без признаков злокачественного роста. Окраска гематоксилин-эозином. Ув. х20. [25]
Fig. 6. Histology. Large duodenal papilla, mucosa with signs of edema, hyperplasia of some glands and moderate signs of inflammatory changes but no malignant growth (staining with hematoxylin-eosin, x20). [25]

method or through percutaneous drainage. For 3 patients who had only partial effect or none at all, PDT was repeated in 3 months. At the end of the PDT session, all patients were fitted with 1 or 2 plastic stents or had a percutaneous biliary drainage. Of the 9 patients, 3 were alive in the period from 51 to 225 days.

The median survival was 78 days, with variations from 12 to 371 days. The survival rate of patients depended on the localization of the tumor in the bile ducts according to the Bismuth classification. With multiple foci and lesions of the right and left hepatic ducts (Bismuth IV), the 90-day mortality rate was 80%. In all cases, the death was caused by the dissemination of the process. The authors conclude that PDT of disseminated ChC is a new promising local method of treatment without severe complications that increases the life expectancy of this category of patients [28].

Another report from the California Pancreatic and Biliary Diseases Institute (Los Angeles, USA) discusses the effectiveness of a combination of treatment methods, including endoscopic metal stent placement, high-dose brachytherapy, and PDT, in 13 patients with disseminated inoperable ChC Bismuth type III and IV. Stents were placed in the right and left hepatic ducts. Brachytherapy was performed in 3 patients at a dose of 30 Gy, coarsely fractionated, while 10 patients received 60 Gy in 2 separate courses.

PDT was performed 2 days after intravenous administration of hematoporphyrin at a dose of 2 mg per kilo of body weight by endoscopic intraluminal irradiation. As a result, the bilirubin level in the patients' blood serum decreased, and the quality of life and survival increased. The average life expectancy (17 months) was slightly different from that after brachytherapy administered as a single therapy. However, it significantly exceeded the quality of life and life expectancy of patients who were treated only with drainage and chemotherapy [33].

In the Russian Federation, only a few works on the use of PDT in the treatment of ChC were published [1-3]. A group of authors from the St. Petersburg I. I. Mechnikov State Medical Academy reported the use of PDT in 6 patients with common hepatic duct cancer. At the first stage, drainage of the bile ducts was performed, which was followed, after the elimination of the cholestasis phenomena, by a course of PDT with Radachlorine, with the light energy density of 200 J/cm^2. The average life expectancy was 360 days. All patients had progressive tumor growth along the duct. The authors consider PDT as a method of choice for palliative therapy in inoperable hepaticocholedochus tumors.

Analytical reviews of the literature on the issue published in the last 10 years confirm that PDT is useful in the treatment of inoperable ChC [5, 9, 11, 12, 16, 27].

Our data on the analysis of PDT effectiveness for duodenal papilla and extrahepatic bile duct cancer in inoperable patients in comparison with the results of drainage and other palliative operations are comparable with the results obtained by other authors.

Conclusion

Our research has shown that PDT in combination with bile-evacuating surgery is an effective method of treating inoperable patients with DPC and extrahepatic bile duct cancer; it is not accompanied by severe complications and is easily tolerated by patients. PDT is the optimal method for treating and prolonging the life of patients with somatically burdened history who have counterindications to radical surgical treatment, or in cases when such treatment involves a high risk of lethal outcome.

The methods developed for bringing laser radiation to the site of exposure (endoscopic surface, endoscopic intraluminal, transfistulous intraluminal) provide adequate access to all departments of the extrahepatic bile ducts for PDT.

Fotoditazine and Photosens used for PDT have comparable clinical effectiveness, but the use of Fotoditazine is preferable due to fewer adverse reactions and complications.

The results of PDT in terms of life expectancy are quite comparable to radical surgery and exceed those for palliative surgery.

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