INTRAOPERATIVE FLUORESCENT SPECTROSCOPY AND PHOTODYNAMIC THERAPY OF RECURRENT PELVIS MINOR TUMORS WITH LOCAL RADIATION DAMAGE

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Abstract

This work presents the results of performing intraoperative photodynamic therapy (IOPDT) on 22 patients with recurrent pelvic tumors (cervical cancer – in 18 patients, cancer of the corpus uteri – in 3 patients, cancer of the anal canal – in 1 patient). Prior to the PDT procedure, the patients were injected with photolon photosensitizer (PS) at a dose of 1.0–1.1 mg/kg. After the injection of PS, local fluorescence spectroscopy of tumor lesions was performed to determine the accumulation of drug in various areas of tumors and healthy tissue. Intraoperative laser irradiation was carried out 3–5 hours after the photolon injection with light at 662 nm wavelength using "Latus-2" laser device with a power density of 140 mW/cm^2 and the density of light energy of 40–60 J/cm^2, the number of irradiation fields was 3–5 depending on the anatomical features.

The follow-up period after surgical treatment combined with PDT was from 6 to 24 months. Analyzing the immediate results of the treatment, there were no undesirable events or increase in the number of postoperative complications compared to patients treated without IOPDT. Were registered: transient increase in ALT and AST levels – in 5 patients (13.6%), reduction of oxygenation during anesthesia – in 20 (90.9%), transient fevers in the postoperative period – in 7 (31.8%).

It was noted that IOPDT with photolon drug, while slightly extending the time of the operation, is well tolerated by patients and does not lead to an increase in the number of early postoperative complications or the length of hospitalization.

Key words: evisceration, locally spread tumors of pelvis minor, radiation therapy, radiation damage, tumor recurrence, intraoperative photodynamic therapy, cytoreductive surgery.

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ИНТРАОПЕРАЦИОННАЯ ФЛУОРЕСЦЕНТНАЯ СПЕКТРОСКОПИЯ И ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРИ РЕЦИДИВНЫХ ОПУХОЛЯХ МАЛОГО ТАЗА НА ФОНЕ МЕСТНЫХ ЛУЧЕВЫХ ПОВРЕЖДЕНИЙ

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Резюме

В статье представлены результаты применения интраоперационной фотодинамической терапии (ИОФДТ) у 22 пациентов с рецидивными опухолями органов малого таза (рецидив рака шейки матки – 18 больных, рецидив рака тела матки – 3, рецидив рака анального канала – 1). Для проведения ФДТ пациентам вводили фотосенсибилизатор (ФС) фотолон в дозе 1,0–1,1 мг/кг. После введения ФС выполнялась локальная флуоресцентная спектроскопия опухолевых поражений для определения накопления ФС в различных участках опухоли и в здоровой ткани. Интраоперационное лазерное облучение проводили через 3–5 ч после введения

фотолона светом с длиной волны 662 нм на лазерном аппарате «Латус-2» с плотностью мощности 140 мВт/см^2 и плотностью световой энергии 40–60 Дж/см^2, количество полей облучения составило 3–5 в зависимости от анатомических особенностей.
Период наблюдения за больными после выполнения им хирургического вмешательства в сочетании с ФДТ составил от 6 до 24 мес. При анализе непосредственных результатов лечения не было отмечено нежелательных явлений и увеличения количества послеоперационных осложнений по сравнению с группой больных, которым хирургическое лечение выполнено без ИОФДТ. Зарегистрированы: транзиторное повышение уровня АЛТ и АСТ у 5 пациентов (13,6%), падение оксигенации при введении в наркоз – у 20 (90,9%), транзиторная лихорадка в послеоперационном периоде – у 7 (31,8%).
Отмечено, что исследуемая методика ИОФДТ с препаратом фотолон при незначительном увеличении времени операции хорошо переносится пациентами и не приводит к увеличению количества ранних послеоперационных осложнений и сроков госпитализации.

Ключевые слова: эвисцерация, местно-распространенные опухоли малого таза, лучевая терапия; лучевые повреждения, рецидивы опухолей, интраоперационная фотодинамическая терапия, циторедуктивные операции.

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Introduction

Malignant tumors of the pelvic organs account for more than 25% in the general structure of cancer in the Russian Federation, and the number of patients with this pathology is growing (Fig. 1) [1].

The growth of a pelvic tumor often involves the muscular aponeurotic and bone structures, so radical surgical removal becomes an impossible task and radiation therapy remains the main treatment method. Given this fact, as well as the biological characteristics of malignant neoplasms of this localization, oncologists often have to deal with the relapse of the tumor after radiation exposure. According to some authors, the frequency of such relapses ranges from 14% to 58%, depending on the stage of the disease at the beginning [2, 3]. Radiation therapy is known to affect not only tumor cells, but also neighboring healthy structures. In this connection, such disorders as intra-pelvic radiation fibrosis, radiation-related inflammatory changes, interorgan fistulas, etc. emerge.

The experience gained by oncological institutions in recent years has significantly changed the understanding of the possibilities of surgical treatment for patients with relapses of pelvic tumor after a radical course of radiation therapy. This is due to the fact that in 85–92% of cases relapses after radiotherapy are locally preva-

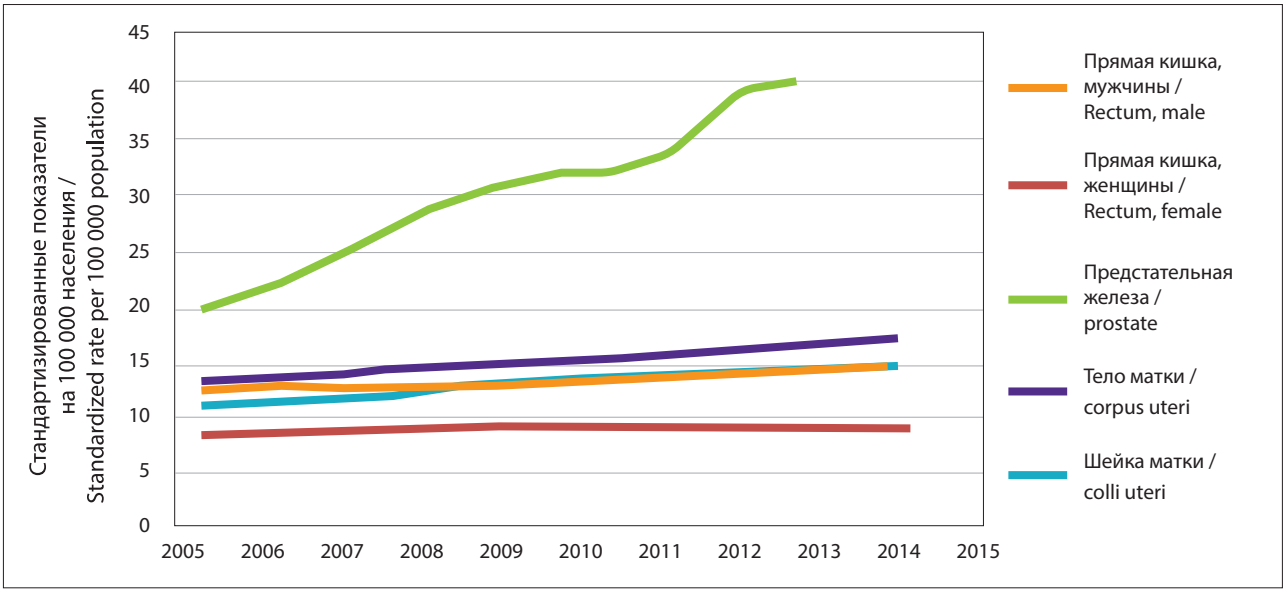


Рис. 1. Ежегодный рост онкологической заболеваемости в Российской Федерации с 2005 по 2015 гг.
Fig. 1. Annual growth of cancer morbidity in Russian Federation from 2005 to 2015

lent, and the main type of care for patients is pelvic evisceration [4]. However, extended and combined surgery, accompanied by extensive intervention on the lymphatic tract and resection of neighboring organs, vascular and nervous structures, does not always lead to a permanent recovery due to the high frequency of progression of the tumor process expressed in subclinical metastases.

To increase the level of ablasticity and reduce the risk of developing repeated local relapse and metastasis in locally advanced pelvic tumors, a search is underway for new methods of specific therapy on the surgical field which can improve oncological treatment results with minimal side effects.

The introduction of intraoperative photodynamic therapy (IOPDT) methods seems to be one of the most promising areas of research in this sphere due to their low invasiveness, low rate of complications and a fairly high degree of reproducibility.

Photodynamic therapy (PDT) is a method of local exposure aimed at a tumor, which is performed in several stages. At the first stage, the patient is administered a photosensitizer (PS). Systemic administration of most photosensitizers leads to the binding of the drug in the blood with lipoproteins (mainly those with low density), globulins and albumins. A longer delay of PS in tumor tissue, compared with healthy tissue, is explained by a large number of lipoprotein receptors in actively proliferating cells, which leads to the selective accumulation of lipoprotein complexes with PS in tumor cells.

At the second stage, the PS molecule is activated by laser radiation. When light is absorbed by a photosensitizer molecule, photochemical reactions start with the formation of singlet oxygen and free radicals, which completely destroy tumor cells over a short period.

It was found that PDT can rapidly induce apoptosis of tumor cells, which allowed a deeper understanding of the nature of their photochemical death and attracted significantly more interest in this method in practical oncology. A specific property of apoptosis after PDT is the high rate of its initiation (less than 30 min) after photodamage. PDT can initiate an apoptotic response directly, bypassing the intermediate transmission pathways of intracellular signals, which may be absent in a number of multidrug-resistant tumors. Studies have shown that lower light doses contribute to the development of apoptosis, while higher ones lead to necrosis. It was determined that the mechanism of triggering apoptosis after PDT is the release of cytochrome C and other mitochondrial factors from the damaged mitochondria into the cytoplasm. Apparently, PDT can initiate other apoptosis development pathways, including modulation of regulatory events of the cell cycle through cyclin-dependent kinases [5–7].

An important feature of the photodynamic effect is the possibility of simultaneous medical and diagnostic procedures, such as fluorescence diagnostics (PD) [8]. FD is based on the ability of tumor cells to accumulate elevated concentrations of endogenous porphyrins and their derivatives, the amount of which increases with the development of pathological processes, as well as other exogenous (administered externally, for example, intravenously) photoactive substances (photosensitizers [9]) and the resulting fluorescence upon irradiation with a certain light wavelengths, and special instruments (spectrum analyzers) determine and record the level of fluorescence at specific points. This method makes it possible to assess the level of PS accumulation in tissues and the prevalence of the tumor process.

Starting from the 1980s, experimental studies were conducted on the effectiveness of peritoneum IOPDT in rabbits [10] and mice [11] with the use of hematoporphyrin derivative as a photosensitizer. In the treatment of CC531 intestinal carcinoma implanted in rat intraperitoneal fatty tissue, in PDT with the use of a photofrin photosensitizer, administered at 5 mg/kg (exposure parameters: wavelength: 628 nm, radiation density: 25–75 J/cm^2), an increase in disease-free survival was observed in all animals of the main group [12].

In parallel, preclinical studies were conducted to determine the indications and potential benefits of IOPDT, assess the toxicity of this type of treatment, and the degree of exposure to PDT on blood flow in the intestinal wall. Research by S. Suzuki et al. did not determine a significant damage to blood vessels or the development of any significant ischemia after IOPDT. In this case, there were no cases of intestinal wall perforation after IOPDT, and no toxicity of the studied method was observed, with the exception of a slight transient decrease in the number of lymphocytes and a moderate increase in the level of transaminases [13].

Several studies examined the effect of IOPDT with various photosensitizers on the inter-intestinal anastomosis, where anastomotic insolvency was not detected [14–17].

Clinical studies have been conducted in the United States to study the distribution of the photosensitizer photofrin, administered at a dose of 2.5 mg/kg, in healthy and tumor tissue and the effectiveness of IOPDT in combination with cytoreductive surgery in patients with disseminated malignant neoplasms of the abdominal cavity, pelvis and retroperitoneal space. Researchers noted significant individual and group variability in the accumulation of the photosensitizer in the tumor and in healthy tissue. Complications that occurred in the early postoperative period, such as a significant amount of discharge by drainage in the early days, as well as cases of thrombocytopenia and pathological values of the liver tests, are described [18–19].

The results of the first phase of clinical studies on the use of IOPDT on the bed of a remote tumor with photofrin (dose: 2.0 mg / kg) in patients with primary or recurring squamous cell carcinoma of the head and neck were published. In the dose range of laser light (30–75 J/cm^2), no dose-limiting toxic effects were observed in patients; the highest used dose of laser light (75 J/cm^2) was considered safe, the follow-up period for patients ranged from 66 to 97 months, while only 6 of them showed progression of the disease [20].

In our country, the use of IOPDT was developed and justified in respect of photosensitizers alasens and photosens in patients with breast cancer [21], photohem and photosens in patients with gastric cancer with peritoneal dissemination, as well as with primary and metastatic lesions of the peritoneum [22, 23]. IOPDT of the peritoneum was tolerated well and did not result in an increase of the frequency, nature and severity of postoperative complications. The use of IOPDT after surgery in patients with conditionally definitive treatment (R0), with less than 15 affected lymph nodes, made it possible to increase the median survival of patients from 29.3 to 43.6 months, and annual survival from 80.0 ± 5.7% to 93.7±4.2%, three-year survival, from 45.5 ± 7.6% to 82.1 ± 7.1% [24].

Thus, literature data indicate a fairly safe use of IOPDT in patients with malignant neoplasms in combination with cytoreductive and palliative treatment. It is advisable to continue the research into the methods of local-regional exposure with the use of IOPDT to improve the results of surgical treatment of pelvic tumors on the background of radiation injuries.

Materials and methods

The aim of this study was to improve the results of treatment of patients with recurrent malignant tumors of the pelvic organs on the background of local radiation injuries by the development and use of IOPDT.

The study group consisted of 22 patients with recurrent tumors of the pelvic organs. The vast majority of patients were women, and the average age was 52.4 years (46.2 ± 16.8 years). The nosological forms of the disease were as follows: cervical cancer, in 18 patients (81.8%), cancer of the uterus, in 3 patients (13.6%), anal cancer, in 1 patient (4.5%).

All patients at the first stage of treatment received radiation therapy according to a radical plan. The progression of the disease after radiation therapy was diagnosed at follow-up within 3 (continued growth) to 60 (recurrence of the disease) months. Relapse distribution with the breakdown by localization was as follows: central relapse was diagnosed in 18 patients (81.8%), and lateral in 4 (18.2%). In this case, the central relapse is the local tumor process that occurred in the primary tumor zone after a radical course of treatment, while the lateral relapse is a regional relapse in the lymph nodes along the main vascular trunk of the pelvis (iliac vessels).

In connection with the treatment of the patients, surgical removal of the tumor was performed in various scopes: anterior evisceration of the pelvis was performed in 6 cases (27.3%), total supralevator evisceration in 8 (36.4%), posterior evisceration in 3 (13.6%), and in 4 patients (18.2%), extended pelvic lymphadenectomy due to lateral recurrence, and in one patient, complete pelvic infralevator evisceration was performed (4.5%). According to pathomorphological data, it was found that R0 resection was performed in 19 cases (86.4%), and R1 in 3 cases (13.6%).

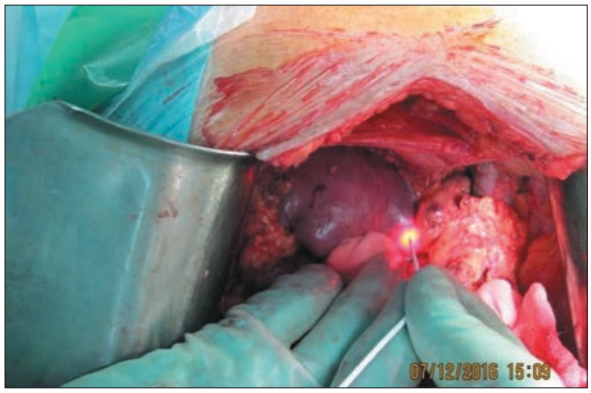
After the resection stage, all patients underwent intraoperative photodynamic exposure of the tumor bed and the regional metastasis pathways. In lateral recurrence, PDT was performed only on the bed of the lateral tumor recurrence.

For IOPDT performed as a part of the combined treatment of recurrent and residual tumors of the small pelvis, patients were first administered PS photolon (a complex of sodium chloride Chlorin e6 and low molecular weight medical polyvinylpyrrolidone developed by RUE Belmedpreparaty, the Republic of Belarus, registration certificate P N015948/01 of 11/30/2012) in a dose of 1.0-1.1 mg/kg, dissolved in 100 ml of 0.9% sodium chloride.

All patients gave informed consent for PDT with intravenous administration of photolon in a hospital setting.

As mentioned earlier, the advantage of PDT is its ability to produce local fluorescence spectroscopy of tumor lesions after administration of photosensitizers. This procedure makes it possible to determine the accumulation of the photosensitizer in various parts of the tumor and healthy tissue in the area of the surgical field. Local fluorescence spectroscopy was performed with the use of LESA-6 complex (ZAO "BIOSPEC", Russia). The radiation of a He-Ne laser with a wavelength of 633 nm was used as a source of radiation exciting the fluorescence of the photosensitizer in biological tissues. The average laser radiation power was 2 mW, and the energy density of local laser radiation on the surface of tissues during one examination was no more than 1 J/cm^2 (Fig. 2).

The spectra of tissues obtained by local measurements were analyzed in terms of the shape, magnitude, and amplitude of the signal. The indicators measured included the area of intensity of the fluorescence (S2) and the area of laser radiation reflected from tissues (S1), as well as their ratio (S2/S1). The ratio of S2/S1 indicators (diagnostic parameter) was used to determine the accumulation of the photosensitizer in the tissues (Fig. 3). Based on the results of each spectral study, a protocol was compiled automatically.



a b

Рис. 2. Проведение интраоперационной флуоресцентной спектроскопии на здоровых и поражённых тканях:
а – опухолевая ткань;
б – здоровый участок кишки
Fig. 2. Intraoperative fluorescence spectroscopy of healthy and diseased tissues:
a – tumor tissue;
b – healthy part of colon

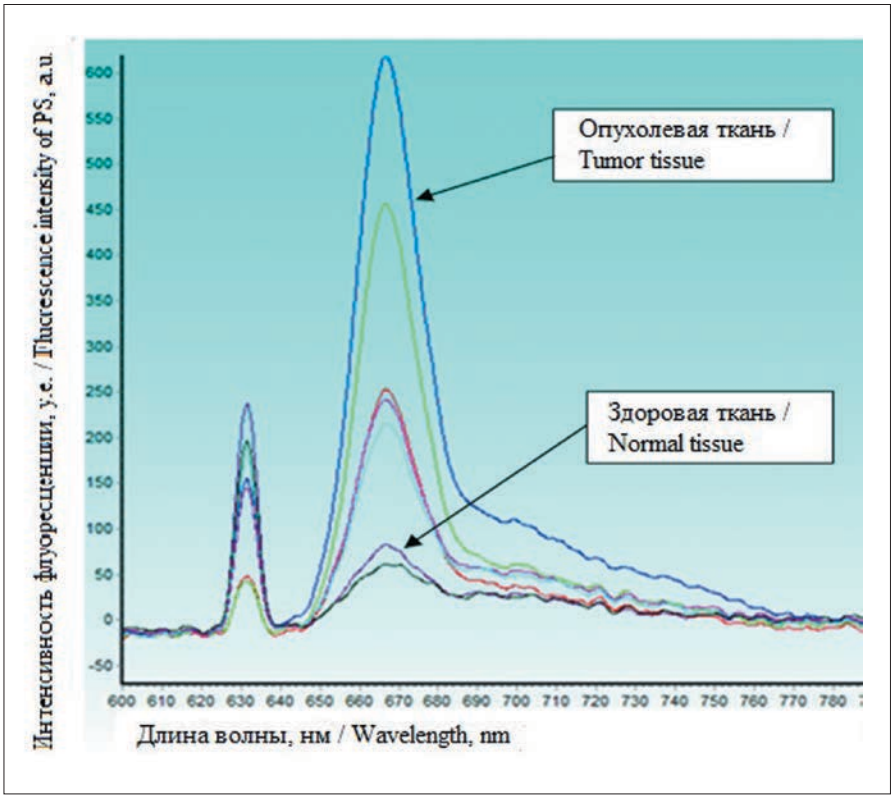


Рис. 3. Спектры флуоресценции, регистрируемые у пациентов
Fig. 3. Fluorescence spectra registered in patients

Intraoperative laser irradiation of the bed of the removed tumor and the area of regional metastasis under conditions of good hemostasis was performed in 3-5 hours after photolon was administered, with light wavelength of 662 nm produced by Latus-2 laser device (ZAO Poluprovodnikovyie Pribory, St. Petersburg, registration

Рис. 4. Сеанс интраоперационной фотодинамической терапии:
а – на ложе удалённой опухоли;
б – на пути регионарного метастазирования
Fig. 4. Intraoperative photodynamic therapy:
a – at the bed of the removed tumor;
b – on the path of regional metastasis

certificate No. FS 022a2006/3307-06 dated 05.16.2006) with a power density of 140 mW/cm^2 and the use of flexible monofilament quartz optical fibers, the light energy density was 40-60 J/cm^2, and the number of irradiation fields was 3–5 depending on the anatomical features (Fig. 4). Additionally, shielding of the loops of the small and large intestine with the sterile material, and, if necessary, other anatomical structures in the operating area, was performed.

The patients were recommended to observe the light regime for 2-3 days after the treatment. No cases of skin phototoxicity have been reported.

Results and discussion

The study found that after the administration of photolon in a dose of 1.0-1.1 mg/kg, an increase in the level of fluorescence in the tumor and unchanged tissues in the area of surgical intervention was recorded in all patients. Fluorescence contrast ranged from 1.4:1–5.0:1 and averaged 2.9 ± 0.4. The data obtained indicate that when using a photosensitizer in the indicated dose, sufficient selectivity of drug accumulation in pathological foci is observed compared to healthy tissues, which can be used for selective intraoperative exposure to PDT with chlorine preparations in order to increase the ablasticity of the operation.

The period of observation of patients after surgical treatment combined with photodynamic therapy ranged from 6 to 24 months. The analyzis of the immediate results of treatment showed no undesirable phenomena and no increase in the number of postoperative complications, with the exception of a transient increase in ALT and AST levels in 5 patients (13.6%), a drop in oxygenation upon introduction to general anesthesia, in 20 (90.9%), transient postoperative fever, in 7 (31.8%). These complications did not require special correction and resolved independently after 10-14 days. The use of the studied IOPDT technique did not lead to an increase in hospitalization, however, in 5 patients (22.7%), inflammation of the laparotomy wound was noted, which required its surgical treatment. However, it is currently not possible to associate this complication with IOPDT due to the small number of patients in the group and the presence of this complication in patients who did not receive IOPDT. Obviously, this zone fell into the field of previous radiation therapy and there were radiation injuries of the anterior abdominal wall, including skin and subcutaneous fat.

To formulate the final conclusions on the benefits of the antitumor effect of PDT, it is planned to recruit a representative group of patients with recurrent pelvic tumors against the background of local radiation injuries, the treatment of which will include IOPDT with photolone, and to further evaluate such criteria as relapse-free survival (in the case of radical surgery, R0), overall survival and quality of life.

Conclusion

According to clinical and experimental studies, PDT can affect tumor cells and, as a result, increase the overall survival of cancer patients.

Intraoperative photodynamic therapy represents a fundamentally new approach in the combined treatment of patients with locally advanced pelvic tumors

after a radical course of radiation therapy. According to preliminary data, IOPDT with chlorine preparations does not increase the number of early postoperative complications and is well tolerated by patients, while the increase to the surgery duration caused by it is insignificant.

The method is promising in terms of further research, and the accumulation of clinical material and the development of exposure modes will make it possible to evaluate its effectiveness and impact on the frequency of tumor relapses in the pelvic organs in the presence of local radiation injuries.

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