SONODYNAMIC AND SONO-PHOTODYNAMIC THERAPY IN ONCOLOGY

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Abstract

In the present publication, authors have analyzed the results of using sonodynamic and sono-photodynamic therapy with photosensitizing agents of various classes (hematoporphyrin, 5-aminolevulinic acid, chlorin derivatives, etc.) in experimental oncology. In a number of *in vitro* and *in vivo* studies, the high antitumor efficacy of the above treatment methods has been proven. Ultrasonic treatment with a pulse frequency of 1–3 MHz and an intensity of 0.7 to 5 W/cm^2, independently and in combination with photo-irradiation of experimental tumors, can significantly improve the cytotoxic properties of photosensitizers. This became the basis for testing the methods in patients with malignant neoplasms of various localizations. Scientists from South-East Asia presented the preliminary results of the use of sonodynamic and sono-photodynamic therapy with photosensitizers in the treatment of malignant pathology of the mammary gland, stomach, esophagus, prostate, lung and brain. Analysis of the obtained data indicates the absence of serious adverse events and an increase in the antitumor efficacy of treatment, which included these treatment methods with chlorin-type photosensitizers.

Key words: sonodynamic therapy, sono-photodynamic therapy, photosensitizers, malignant tumors.

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СОНОДИНАМИЧЕСКАЯ И СОНО-ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В ОНКОЛОГИИ

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Резюме

В представляемой публикации авторами произведен анализ результатов применения сонодинамической и соно-фотодинамической терапии с фотосенсибилизирующими агентами различных классов (гематопорфирин, 5-аминолевулиновая кислота, производные хлорина и др.) в экспериментальных исследованиях и клинической онкологии. В ряде *in vitro* и *in vivo* исследований доказана высокая противоопухолевая эффективность указанных выше методов лечения. Ультразвуковое воздействие с частотой импульсов 1–3 МГц и интенсивностью от 0,7 до 5 Вт/см^2 в отдельности и в комбинации с фотооблучением экспериментальных опухолей, позволяет существенно повысить эффективность лечения. Это стало основой для апробации методов у пациентов со злокачественными новообразованиями различных локализаций. Учеными из стран Юго-Восточной Азии представлены предварительные результаты применения сонодинамической и соно-фотодинамической терапии с фотосенсибилизаторами в лечении злокачественной патологии молочной железы, желудка, пищевода, предстательной железы, легкого и головного мозга. Анализ полученных данных свидетельствует об отсутствии серьезных нежелательных явлений и повышении противоопухолевой эффективности лечения, в которое были включены данные методы лечения с фотосенсибилизаторами хлоринового ряда.

Ключевые слова: сонодинамическая терапия, соно-фотодинамическая терапия, фотосенсибилизаторы, злокачественные новообразования.

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Introduction

Currently, the possibility to use ultrasonic radiation (US) as an antitumor agent is studied extensively. The study of biological effects of ultrasonics with various frequencies, intensities and durations of action showed that US has a corresponding activity [1, 2].

According to some authors, US with a pulse rate of 0.5–3 MHz and an intensity of 0.5–5 W/cm^2 can increase cytotoxicity of various chemotherapeutic agents associated with an increase in permeability of the cell membranes and action of effects such as cavitation, hyperthermia and sono-induced free-radical oxidation of the tumor cell biological structures [3–5]. The new specialty has been called "sonodynamic therapy" (SDT), and such agents are commonly called sonosensitizers (SS). Radiosensitizers (dimexide, metronidazole) and a number of chemotherapeutic agents (bleomycin, adriamycin, cisplatin, etoposide, 5-fluorouracil, etc.) belong to the SS class in the first place [6, 7].

However, in the early 1990s, a research group from Tokyo guided by T. Yumita [8] published the early results confirming the high efficiency of SDT with a photosensitizer (PS) hematoporphyrin.

In recent years, results of in vitro and in vivo studies have been published showing great antitumor effects of the proposed method in the treatment of various specific forms of malignant tumors (breast cancer, lung cancer, liver cancer, colorectal cancer, pancreatic cancer, soft tissue sarcoma, skin melanoma, osteosarcoma, ascitic forms of ovarian neoplasms, leukemias, gliomas [4, 9]). The key findings of these studies are listed in Tables 1 and 2.

In a number of publications, authors provided data on synergistic enhancement of the cytotoxicity of photosensitizers on combined exposure of several physical factors (ultrasonic and laser radiation) to a sensitized tumor cell [1, 4, 32–34]. This specialty was called sono-photodynamic therapy (SPDT). The results of main studies using SPDT with sonodynamic exposure are shown in Table 3.

The main mechanisms of SPDT

The antitumor sono-photodynamic effect is based on reactions that develop:

1. during photodymamic therapy: – direct cytotoxic effects due to free-radical oxidation of biological structures (Fig. 1) [43, 44];

– disturbance in the blood supply to the tumor tissue due to damage to the endothelium of blood vessels feeding the tumor (Fig. 1) [43-45];

– activation of components of the immune system (Fig. 1) [43-45].

2. during sonodynamic therapy:

– physical processes (Fig. 2) [1, 2, 46];

– physicochemical processes (Fig. 2) [1, 2, 46];

– biological reactions (Fig. 2) [1, 2, 46].

The results of all the above reactions proceeding in a tumor cell on combined exposure of photosensitizing agents, ultrasonic and laser radiation are apoptosis, necrosis and autophagy [1, 2, 43–46].

Apoptosis develops due to the action of sonodynamic and photodynamic effects at a low radiation intensity, while necrosis develops when high-intensity radiation is used. In the former case, the triggering mechanism is disruption of lysosomal and mitochondrial membranes leading to the rapid release of mitochondrial cytochrome C into cytosol followed by the apoptosome and procaspase-3 activation [1,2, 43–46]. In the latter case (specific to photodynamic effects), the triggering mechanism is damage to components of the tumor microvasculature with the development of vascular stasis, thrombosis and congestion. According to most authors, the key factor triggering the necrosis process is the formation of an increased concentration of Ca2+ ions in cytoplasm due to disruption of mitochondrial membranes and endoplasmic reticulum. The above mentioned ions activate cysteine proteinases – calpains – leading to the destruction of lysosomes and the release of lysosomal enzymes (cathepsins) followed by the start of calpain-cathepsin necrosis pathway driving tumor cell death [43, 44].

Clinical testing of SPDT in patients with malignant tumors

A few authoring teams make the first attempts to use SDT and SPDT in a clinical setting. Preliminary results have been obtained showing the efficiency and safety of the proposed method in the treatment of metastatic breast cancer, head and neck tumors, colorectal cancer, lung tumors, esophageal cancer, prostate tumors [33, 47-49].

T. Inui et al. reported on the successful follow-up of a patient with terminal breast cancer with skin invasion after previous surgical treatment (October 2011) treated with Gc protein-derived macrophage-activating factor (GcMAF; intramuscularly; 0.5 ml 2 times a week, 21 administrations), hormonotherapy with the aromatase inhibitor Exemestane (Aromasin, 25 mg/day, orally) and 19 sessions of SDT with chlorine e6 (25 mg/kg, intravenously) and 5-aminolevulinic acid (10 mg/kg, orally) photosensitizers.

In January 2013, the progression of the disease was detected in the patient on the basis of suction biopsy data with the development of corresponding clinical picture (cough, pain, swelling right arm). The results of PET/CT (June 2013) showed the presence of a metastatic tumor of soft tissues in the axillary region, permeation along the spinal cord, an intrapleural nodular tumor component and metastatic pleurisy on the right side. After the conservative treatment, the regimen of which is indicated above, the PET/CT examination data (September 2013) showed a significant decrease in the size of tumors in axillary and intrapleural regions. Signs of metastatic pleurisy were not detected. No serious adverse events were observed [48].

X. Wang et al. reported on the outcomes of treatment of 3 patients with metastatic breast cancer treated using

Таблица 1
Применение сонодинамической терапии в эксперименте *in vitro*
Table 1
Application of sonodynamic therapy in an *in vitro* experiment

Авторы Authors	Штамм опухоли Tumor strain	ФС, доза (мг/кг) PS, dose (mg/kg)	Параметры ультразвука Ultrasound parameters	Эффективность Efficacy
Xiong W. et al., 2015 [10]	Саркома 180 Sarcoma 180	Синопорфирин натрия, 0,05 мкг/мл Synoporphyrin sodium, 0.05 mkg/ml	1,1 МГц 2 Вт 0,5; 1 и 1,5 мин 1,1 MHz 2 W 0.5; 1 and 1.5 minutes	Количество жизнеспособных клеток: ФС + УЗ (0,5 мин) – 63,54%; ФС + УЗ (1 мин) – 48,79%; ФС + УЗ (1,5 мин) – 19,55% (p<0,05). Количествоапоптотических клеток: контроль – 4,1%; ФС + УЗ (0,5 мин) – 44,2%; ФС + УЗ (1 мин) – 49,15%; ФС + УЗ (1,5 мин) – 79,5% (p<0,05). Amount of viable cells: PS + US (0.5 minute) – 63.54%; PS + US (1 minute) – 48.79%; PS + US (1.5 minute) – 19.55% (p<0.05) Amount of apoptotic cells: PS + US (0.5 minute) – 44.2%; PS + US (1 minute) – 49.15%; PS + US (1.5 minute) – 79.5% (p<0.05)
Sun H.et al., 2015 [11]	Адено-карцинома эндометрия Ishikawa, HEC-1α Endometrial adeno-carcinoma, Ishikawa, HEC-1α	Гемато-порфирин, 15 и 50 мкг/мл Hematoporphyrin, 15 and 50 mkg/ml	1 МГц, 1 Вт/см^2; 1 мин – Ishikawa; 1 МГц, 2 Вт/см^2, 4 мин – HEC-1α 1 MHz, 1 W/cm^2, 1 minute – Ishikawa; 1 MHz, 2 W/cm^2; 4 minutes – HEC-1α	Количество жизнеспособных клеток: Ishikawa: контроль – 100%; ФС– 85%; УЗ – 45%; ФС + УЗ – 25% (p<0,01). HEC-1α: контроль – 100%; ФС– 50%; УЗ – 80%; ФС + УЗ – 15% (p<0,01). Количество апоптотических клеток: Ishikawa: контроль – 0%; ФС – 10%; УЗ – 90%; ФС + УЗ – 95% (p<0,05). HEC-1α: контроль – 10%; ФС– 45%; УЗ – 20%; ФС + УЗ – 70% (p<0,01). Amount of viable cells: Ishikawa: control – 100%, PS – 85%, US – 45%, PS +US – 25% (p<0.01) HEC-1α: control – 100%, PS – 50%, US – 80%, PS + US – 15% (p<0,01). Amount of apoptotic cells: Ishikawa: control – 0%, PS – 10%, US – 90%, PS +US – 95% (p<0.05) HEC-1α: control – 10%, PS – 45%, US – 20%, PS + US – 70% (p<0,01).

Li Y.N. et al., 2015 [12]	Остеосаркома UMR106 Osteosarcoma UMR106	5-аминолевулиновая кислота(5-АЛК), 2 мкг/мл 5-aminolevulinic acid (5-ALA), 2 mkg/ml	1 МГц, 2 Вт/см^2, 7 мин 1 MHz, 2 W/cm^2, 7 minutes	Количество апоптотических клеток в группе ФС + УЗ – 27,2±3,4% (p<0,05); Активные формы O_2 – 32,6±2,2% (p<0,05) по сравнению с контролем, УЗ, ФС. Amount of apoptotic cells: in PS + US group – 27.2±3.4% (p<0.05) Reactive oxygen species – 32.6±2.2% (p<0.05) in comparison with control, US and PS.
Hu Z. et al., 2015 [13]	Меланома Melanoma	5-АЛК, 2 мкг/мл 5-ALA, 2 mkg/ml	1 МГц, 1,5 Вт/см^2 1 MHz, 1.5 W/cm^2	В группе ФС + УЗ: количество апоптотических клеток, % генерации активных форм O_2достоверно выше (p<0,05). Отмечена сверхэкспрессия гена miR-34a (в 16 раз выше, чем в группах сравнения). Снижение уровня антиапоптотических факторов (BCL2, CCND1, CDK6, SIRT1). In PS + US group: amount of apoptotic cells, % of reactive oxygen species generation is significantly higher (p<0.05). Marked overexpression of the miR-34a gene (16 times higher than in comparison groups). Reduced anti-apoptotic factors (BCL2, CCND1, CDK6, SIRT1).
Liu X. et al., 2015 [14]	Остеосаркома MG-63 Osteosarcoma MG-63	Гемато-порфирин, 20 мкг/мл Hemato-porphyrin, 20 mkg/ml	1 Вт/см^2, 0,5 мин 1 W/cm^2, 0.5 minutes	В группе ФС + УЗ отмечено достоверное увеличение интенсивности апоптоза (прокаспаза-3, каспаза 3 и 9). In the PS + US group, a significant increase in the intensity of apoptosis was noted (pro-caspase-3, caspase 3 and 9).
Wang X. et al., 2015 [15]	Гепато-целлюлярная карциномаHepG2 Hepatocellular carcinoma HepG2	Гипокреллин В, 2,5 мкг/мл Hypocrellin B, 2.5 mkg/ml	0,46 Вт/см^2, 8 с 0.46 W/cm^2 8 seconds	В группе ФС + УЗ выявлено более интенсивное повреждение митохондрий, лизосом, комплекса Гольджи, эндоплазматического ретикулума. In the PS + US group, more intense damage to mitochondria, lysosomes, the Golgi complex, and the endoplasmic reticulum was detected.
Xiang J.et al., 2014 [16]	Карцинома яичников человека НО-8910 Human ovarian carcinoma HO-8910	Метиленовый синий, 100 мкг/мл Methylene blue, 100 mkg/ml	1,7 МГц, 0,46 Вт/см^2, 5 с 1.7 MHz, 0.46 W/cm^2, 5 seconds	Количество колоний НО-8910 в группах: ФС + УЗ – 4 (p<0,05); ФС – 30; УЗ – 25. The number of HO-8910 colonies in groups: PS + US – 4, PS – 30, US – 25 (p<0.05).

Dai S. et al.2014 [17]	Глиома С6 Glioma C6	Гемато-порфирин, 20 мкг/мл Hemato-porphyrin, 20 mkg/ml	0,6; 0,8 и 1 МГц, 1 Вт/см^2, 1 мин 0.6, 0.8 and 1 MHz, 1 W/cm^2. 1 minute	Количество жизнеспособных клеток: при УЗ (0,6 МГц) – 43,2±3,2% при УЗ (0,8 МГц) – 57,1±3,7% при УЗ 1 МГц – 60,2±2,6%. Количество апоптотических клеток: контроль – 4,2±0,5% УЗ – 16±0,8%; ФС+УЗ – 49,4±2,6% (p<0,05). Amount of viable cells: US (0.6 MHz) – 43.2±3.2% US (0.8 MHz) – 57.1±3.7% US (1 MHz) – 60.2±2.6% Amount of apoptotic cells: control – 4.2±0.5% US – 16±0.8%; PS + US – 49.4±2.6% (p<0.05)
Li Y.J. et al. 2014 [18]	Рак поджелудочной железы Capan-1 Pancreas carcinoma Capan-1	5-АЛК, 5 мкг/мл 5-ALA, 5 mkg/ml	1 МГц, 2 Вт/см^2, 5 мин 1 MHz, 2 W/cm^2, 5 minutes	Количество жизнеспособных клеток: контроль – 100%; УЗ – 85±5,2%; ФС + УЗ – 59,2±7,9% (p<0,05). Количество апоптотических клеток: контроль – 9,1±1,2%; ФС – 9,5±1,2% (p=0,078); УЗ – 13,1±1,5%; ФС + УЗ – 34,6±5,6% (p<0,001). Amount of viable cells: control – 100%, US – 85±5.2%, PS + US – 59.2±7.9% (p<0.05) Amount of apoptotic cells: control – 9.1±1.2%, PS – 9.5±1.2% (p=0.078), US – 13.1±1.5%, PS + US – 34.6±5.6% (p<0.001).
Su X. et al. 2014 [19]	Миелогенная лейкемия человека К562 Human myelogenous leukemia K562	Протопорфирин, 5 мкг/мл Protoporphyrin, 5 mkg/ml	1,1 МГц, 1 Вт/см^2, 1 мин 1.1 MHz, 1 W/cm^2, 1 minute	Количество жизнеспособных клеток: контроль – 100%; ФС – 91,1% (p>0,05); УЗ – 85,9% (p>0,05); ФС + УЗ – 39% (p<0,01). Активные формы O_2: ФС – 10,13% (p>0,05); УЗ – 5,47% (p>0,05); ФС + УЗ – 23,87% (p<0,01). Amount of viable cells: control – 100%, PS – 91.1% (p>0.05), US – 85.9% (p>0.05), PS + US – 39% (p<0.01) Reactive oxygen species: PS – 10.13% (p>0.05), US – 5.47% (p>0.05), PS + US – 23.87% (p<0.01).

Chen B. et al. 2013 [20]	Аденокарцинома легких человека SPCA-1 Human lung adenocarcinoma SPCA-1	Хлорин e_6, 0,2 мг/мл Chlorin e_6, 0,2 mg/ml	1 МГц, 1 Вт/см^2, 1 мин 1 MHz, 1 W/cm^2, 1 minute	Количество некротических клеток: ФС – 3,73±0,34%; УЗ – 17,62±1,1%; ФС + УЗ – 74,23±1,02% (p<0,05). Amount of necrotic cells: PS – 3.73±0.34%, US – 17.62±1.1%, PS + US – 74.23±1.02% (p<0.05).
Su X. et al. 2013 [21]	Миелоидная лейкемия человека U937 Myelogenous leukemia human U937	Гемато-порфирин, 5 мкг/мл Hemato-porphyrin, 5 mkg/ml	1,1 МГц, 1 Вт/см^2, 1 мин 1.1 MHz, 1 W/cm^2, 1 minute	Количество жизнеспособных клеток контроль – 100%; ФС – 95,1%; УЗ – 82,99%, ФС+УЗ – 45,4% (p<0,05). Количество апоптотических клеток: ФС – 4%; УЗ – 15,8%; ФС + УЗ – 35,6% (p<0,05). Amount of viable cells: control – 100%, PS – 95.1%, US – 82.99%, PS+US – 45,4% (p<0.05). Amount apoptotic cells: PS – 4%, US – 15.8%, PS + US – 35.6% (p<0.05).

Таблица 2
Применение сонодинамической терапии в эксперименте *in vivo*

Table 2
Application of sonodynamic therapy in *in vivo* experiments

Авторы Authors	Штамм опухоли, животные Tumor strain,animals	ФС,доза (мг/кг) PS,dose (mg/kg)	Параметры ультразвука Ultrasound parameters	Эффективность Efficacy
Xiong W. et al., 2015 [10]	Саркома 180 мыши BALB/c Sarcoma 180 Mice BALB/c	Синопорфирин натрия, 2 мг/кг Sinoporphyrin sodium, 2 mg/kg	1,9 МГц, 4 Вт/см^2 1.9 MHz, 4 W/cm^2	Коэффициент торможения роста опухоли: ФС – 19,71%;УЗ – 32,56%; ФС + УЗ – 89,92% (p<0,01) The rate of tumor growth inhibition: PS – 19.71%, US – 32.56%, PS + US – 89.92% (p<0.01)
Foglietta F. et al., 2015 [22]	Аденокарцинома молочной железы Mat B III Крысы Wistar Mammary adenocarcinoma Mat B III Wistar rats	5-АЛК, 375 мг/кг 5-ALA, 375 mg/kg	Импульсный режим: 0,88 мДж/мм^2, 500 импульсов, 4 импульса/с Pulse mode 0.88 mJ/mm^2, 500 pulses, 4 pulses per second	7 Т МРТ через 72 ч после лечения: объем опухоли (см^3): контроль – 2,08±0,2; УЗ – 1,64±0,28; ФС – 1,56±0,74; ФС + УЗ – 0,79±0,39 (p<0,05) 7 T MRI 72 hours after treatment:tumor volume (cm^3): control – 2.08±0.2, US – 1.64±0.28, PS – 1.56±0.74, PS + US – 0.79±0.39 cm^3 (p<0.05)

Li Y. et al., 2015 [23]	Остеосаркома UMR106 Крысы Wistar Osteosarcoma UMR106 Wistar rats	5-АЛК, 250 мг/кг 5-ALA, 250 mg/kg	1 МГц, 2,5 Вт/см^2, 7 мин 1 MHz, 2.5 W/cm^2, 7 minutes	Объем опухолей на 10-е сутки после лечения – в группе ФС + УЗ – 400 (мм^3), что достоверно больше, чем в контроле ($p<0,01$), ФС и УЗ ($p<0,05$) The volume of tumors on 10th day after treatment: in the PS + US group – 400 mm^3, which was significantly higher than in the control ($p<0.01$), PS and US groups ($p<0.05$)
Alomol-hoda M. et al., 2015 [24]	Спонтанная адено-карцинома молочной железы Мыши BALB/c Spontaneous mammary adeno-carcinoma Mice BALB/c	Гемато-порфирин, 10 мг/кг Hemato-porphyrin, 10 mg/kg	0,15 МГц, 0,2 Вт/см^2 + 1 МГц, 2 Вт/см^2, 30 мин Фракции УЗ на 1,6,12,18 сут 0.15 MHz, 0.2 W/cm^2 + 1 MHz, 2 W/cm^2, 30 minutes Sonication on the 1st, 6th, 12th and 18th day	Коэффициент торможения роста опухоли в группе ФС + УЗ (4 фракции) был на 50% выше, чем в других группах ($p<0,05$) The rate of tumor growth inhibition in the PS + US group (4 fractions) was 50% higher, than in other groups ($p<0.05$)
Hu Z. et al., 2015 [25]	Меланома Мыши BALB/c Melanoma BALB/c mice	5-АЛК, 250 мг/кг 5-ALA, 250 mg/kg	1 МГц, 2 Вт/см^2, 5 мин 1 MHz, 2 W/cm^2, 5 minutes	Коэффициент торможения роста опухоли был достоверно выше в группе ФС + УЗ ($p<0,05$) The rate of tumor growth inhibition was reliably higher in the PS + US group ($p<0.05$)
Song D. et al., 2014 [26]	Глиома с6 Крысы Wistar Glioma c6 Wistar rats	Гемато-Порфирин, 10 мг/кг Hemato-porphyrin, 10 mg/kg	1 МГц, 0,5 Вт/см^2, 2 мин 1 MHz, 0.5 W/cm^2, 2 minutes	Объем опухоли на 14-е сутки после лечения: ФС – 125 мм^3; УЗ – 100 мм^3; ФС + УЗ – 60 мм^3 ($p<0,05$) Tumor volume on the 14th day after treatment: PS – 125 mm^3, US – 100 mm^3, PS + US – 60 mm^3 ($p<0.05$).
Li C. et al., 2014 [27]	Саркома S180 Мыши BALB/c Sarcoma S180 BALB/c mice	DVDMS, 1,2 и 4 мг/кг DVDMS, 1.2 and 4 mg/kg	1,9 МГц, 3 мин 1.9 MHz, 3 minutes	Коэффициент торможения роста опухоли на 14-е сутки: ФС – 22,81%; УЗ – 25,67%; ФС + УЗ – 56,27% ($p<0,05$). The rate of tumor growth inhibition on the 14th day: PS – 22.81%, US – 25.67%, PS + US – 56.27% ($p<0.05$).

Wang S. et al. 2014 [28]	Murine melanoma B16F10 Мыши BALB/c и nude Murine melanoma B16F10 BALB/c and Nude mice	5-АЛК, 250 мг/кг 5-ALA, 250 mg/kg	1,1 МГц, 2 Вт/см^2, 5 мин 1.1 MHz, 2 W/cm^2, 5 minutes	Коэффициент торможения роста опухоли на 11-е сутки: УЗ (BALB/c) – 35,95%; УЗ (nude) –31,36% ФС + УЗ (BALB/c) – 60,94%; ФС + УЗ (nude) – 59,89% (p<0,05). The rate of tumor growth inhibition on 11th day: US (BALB/c) – 35.95%, US (nude) – 31.36%, PS + US (BALB/c) – 60.94%, PS + US (nude) – 59.89% (p<0.05).
Gao G. et al., 2013 [29]	SAS Мыши BALB/c SAS Mice BALB/c	5-АЛК, 250 мг/кг 5-ALA, 250 mg/kg	1,1 МГц, 2 Вт/см^2, 5 мин 1.1 MHz, 2 W/cm^2, 5 minutes	Коэффициент торможения роста опухоли на 14-е сутки: УЗ – 22,38%; ФС + УЗ – 43,77% (p<0,05). The rate of tumor growth inhibition on 14h day: US – 22.38%, PS + US – 43.77% (p<0.05).
Chen B. et al. 2013 [30]	Адено-карцинома легких человека SPCA-1, Мыши Kunming Human lung adenocarcinoma SPCA-1 Kunming mice	Хлорин e_6, 10; 20; 40 мг/кг Chlorin e_6, 10; 20 and 40 mg/kg	0,4; 0,8; 1,6 МГц, 1,6 Вт/см^2 0.4, 0.8 and 1.6 MHz, 1.6 W/cm^2	Максимальный противоопухолевый эффект: ФС 40 мг/кг + УЗ 1,6 Вт/см^2 Maximum antitumor efficacy: PS 40 mg/kg + US 1.6 MHz
Yamaguchi F. et al., 2013 [31]	Глиобластома человека U87MG Мыши BALB/c Human glioblastoma U87MG BALB/c mice	5-АЛК, 100 мг/кг 5-ALA, 100 mg/kg	25 кГц, 4 Вт/см^2, 4 мин 25 KHz, 4 W/cm^2, 4 minutes	Средний объем опухоли на21-е сутки: контроль – 6,89±1,19 мм^3; ФС – 4,85±1,59 мм^3; УЗ – 5,08±2,77 мм^3; ФС + УЗ – 0,08±0,08 мм^3 (p<0,05). Mean tumor volume on 21st day: control – 6.89±1.19 mm^3, PS – 4.85±1.59 mm^3, US – 5.08±2.77 mm^3, PS + US – 0.08±0.08 mm^3 (p<0.05).

Таблица 3
Применение соно-фотодинамической терапии в экспериментах *in vitro* и *in vivo*

Table 3
Application of sono-photodynamic therapy in *in vitro* and *in vivo* experiments

Авторы Authors	Штамм опухоли, животные Tumor strain, animals	ФС, доза (мг/кг) PS, dose (mg/kg)	Параметры: ультразвук/ фотооблучение (ФО) Parameters: ultrasound/ photo- irradiation (PI)	Эффективность Efficacy
	In vitro			
Bakh-shizadeh M., et al., 2017 [35]	Карцинома кишечника CT26 CT26 colon tumor	Липосомальная форма фталоцианина цинка Liposomal zinc phthalo-cyanine	1,1 МГц, 1 Вт/см^2, 10 мин; 300 Дж/см^2, 160 мВт/см^2, λ=670±20 нм 1.1 MHz, 1 W/cm^2, 10 minutes; 300 J/cm^2, 160 mW/cm^2, λ=670±20 nm	В группах животных, получавших лечение методом СФДТ, отмечено статистически значимое торможение роста опухолей (p<0,01) и улучшение показателей выживаемости (p<0,05) Statistically significant inhibition of tumor growth (p<0.01) and improvement in survival rates (p<0.05) were observed in groups of animals treated with the SPDT method.
Wang P. et al., 2015 [36]	Адено-карцинома молочной железы 4T1 Адено-карцинома молочной железы человека MDA-MB-231 Адено-карцинома молочной железы человека MCF-7 Murine 4T1 mammary cancer Human breast cancer MDA-MB-231 Human breast cancer MCF-7	Хлорин e_6, 1 мкг/мл Chlorin e_6, 1 mkg/ml	1 МГц, 0,36 Вт/см^2, 1 мин; 1,2 Дж/см^2, λ=650 нм 1 MHz, 0.36 W/cm^2 1 minute; 1.2 J/cm^2 λ=650 nm	Коэффициент торможения роста опухоли на 22-е сутки: ФС + ФО – 24,22%; ФС + УЗ – 25,87%; ФС + ФО + УЗ – 47,48%; ФС + УЗ + ФО – 52,2% (p<0,01 – контроль; p<0,05). Среднее число метастазов в группах: контроль – 63,43; ФС + ФО – 39,14; ФС + УЗ – 38,43; ФС + ФО + УЗ – 16,43; ФС + УЗ + ФО – 24,43. The rate of tumor growth inhibition on the 22nd day after treatment: PS + PI – 24,22%; PS + US – 25,87%; PS + PI + US – 47.48%; PS + US + PI – 52.2% (p<0.01). Mean amount of metastasis in groups: control – 63.43; PS + PI – 39.14; PS + US – 38.43; PS + PI + US – 16.43; PS + US + PI – 24.43.

Tomankova K. et al., 2014 [37]	Карцинома шейки матки HeLa Cervical carcinoma HeLa	Дисульфонат фталоцианина хлоралюминия ClAlPcS2, 0,5; 5; 50 мкг/мл Chloroaluminium pthalocyanine disulfonate, 0.5, 5 and 50 mkg/ml	1 МГц, 2 Вт/см^2, 10 мин; 7,2 Дж/см^2, λ=660 нм 1 MHz, 2 W/cm^2, 10 minutes; 7.2 J/cm^2, λ=660 nm	Авторами отмечено статистически значимое увеличение количества апоптотических и некротических клеток в группе ФС + УЗ + ФО по сравнению с ФС + УЗ и ФС + ФО (p<0,001). The authors noted a statistically significant increase in the number of apoptotic and necrotic cells in the PS + US + PI group compared with PS + US and PS + PI (p<0.001).
Li Q. et al., 2014 [38]	Рак молочной железы мышей 4T1 Murine 4T1 mammary cancer	Хлорин e$_6$, 1 мкг/мл Chlorin e$_6$, 1 mkg/ml	1 МГц, 0,36 Вт/см^2, 1 мин; 1,2 Дж/см^2, λ=650 нм 1 MHz, 0.36 W/cm^2, 1 minute; 1.2 J/cm^2, λ=650 nm	Количество жизнеспособныхклеток: ФС – 101,52%;УЗ – 99,41%; ФО – 101,84%;УЗ + ФО – 100,77%. ФС + УЗ – 85,6%, ФС + ФО – 69,11%, ФС + УЗ + ФО – 47,8% (p<0,01). Активные формы O$_2$:контроль – 5,87%; ФС + УЗ – 7,77%;ФС + ФО – 62,93%; ФС + УЗ + ФО – 83,83%. Amount of viable cells: PS – 101.52%,US – 99.41%, PI – 101.84%, US + PI – 100.77%, PS + US – 85.6%, PS + PI – 69.11%, PS + US + PI – 47.8% (p<0.01) Reactive oxygen species: control – 5.87%, PS + US – 7.77%, PS + PI – 62.93%, PS + US + PI – 83.83%.
Wang H. et al., 2013 [39]	Адено-карцинома молочной железы человека MDA-MB-231 Human breast cancer MDA-MB-231	Хлорин e$_6$, 1 мкг/мл Chlorin e$_6$, 1 mkg/ml	1 МГц, 0,36 Вт/см^2, 1 мин; 1,2 Дж/см^2, λ=650 нм 1 MHz, 0.36 W/cm^2, 1 minute; 1.2 J/cm^2, λ=650 nm	Количество жизнеспособныхклеток: ФС – 100,35%; УЗ – 99,41%; ФО – 102,08%; УЗ + ФО – 103,83%. ФС + УЗ – 90,21% (p>0,05); ФС + ФО – 74,4% (p<0,05); ФС + УЗ + ФО – 45,08%; ФС + ФО + УЗ – 51,2%. Amount of viable cells: PS – 100.35%, US – 99.41%, PI – 102.08%, US + PI – 103.83%, PS + PI – 74.4% (p>0.05), PS + US + PI – 45.08%, PS + PI + US – 51.2% (p<0.05).

Li J.H. et al. 2013 [40]	Глиома С6 Glioma C6	Гемато-порфирин, 10 мкг/мл Hematoporphyrin, 10 mkg/ml	1 МГц, 0,5 Вт/см^2, 1,5 мин; 20–240 Дж/см^2, λ=630 нм 1 MHz, 0.5 W/cm^2, 1.5 minutes; 20–240 J/cm^2, λ=630 nm	Авторами отмечено статистически значимое увеличение количества апоптотических и некротических клеток, активных форм O_2 в группе ФС + УЗ + ФО по сравнению с ФС + УЗ и ФС + ФО (p<0,001). Максимальная инициация апоптоза отмечена при комбинации УЗ и ФО в дозе 80 Дж/см^2. The authors noted a statistically significant increase in the number of apoptotic and necrotic cells, reactive oxygen species in the PS+US+PI group compared with PS + US and PS + PI (p<0.001). The maximum initiation of apoptosis was observed with a combination of US and PI at an exposure dose of 80 J/cm^2.
			In vivo	
Wang P. et al., 2015 [36]	Адено-карцинома молочной железы мышей 4T1 Мыши BALB/c Murine 4T1 mammary cancer, BALB/c mice	Хлорин e_6, 20 мг/кг Chlorin e_6, 20 mg/kg	1,9 МГц, 1,6 Вт/см^2, 3 мин; 120 Дж/см^2, λ=660 нм 1.9 MHz, 1.6 W/cm^2, 3 minutes; 120 J/cm^2, λ=660 nm	Количество жизнеспособных клеток через 24 ч после лечения: контроль и ФС + УЗ – без эффекта; ФС + ФО – 30,89%; ФС + УЗ + ФО – 52,17%; ФС + ФО + УЗ – 55,71% (p<0,05). Amount of viable cells 24 hours after treatment: control and PS + US – without effect: PS + PI – 30.89%, PS + US + PI – 52.17%, PS + PI + US – 55.71% (p<0.05).
Церковс-кий Д.А. и др., 2015 [41, 42]	Глиома С6 Крысы Glioma C6 Rats	Фотолон, 2,5 мг/кг Photolon, 2.5 mg/kg	0,88 МГц, 0,7 Вт/см^2, 10 мин; 50 Дж/5 мм^2, λ=660±5 нм 0.88 MHz, 0.7 W/cm^2, 10 minutes; 50 J/5 mm^2, λ=660±5 nm	Увеличение продолжительности жизни животных по отношению к контролю для групп: операция + ФС + УЗ – 88,1%; операция + ФС + ФО – 122,4%; операция + ФС + УЗ + ФО – 194,1% (p<0,05). Increase of life expectancy for animals compared to the control for groups: surgery + PS + US – 88.1%, surgery + PS + PI – 122.4%, surgery + PS + US + PI – 194.1% (p<0.05).

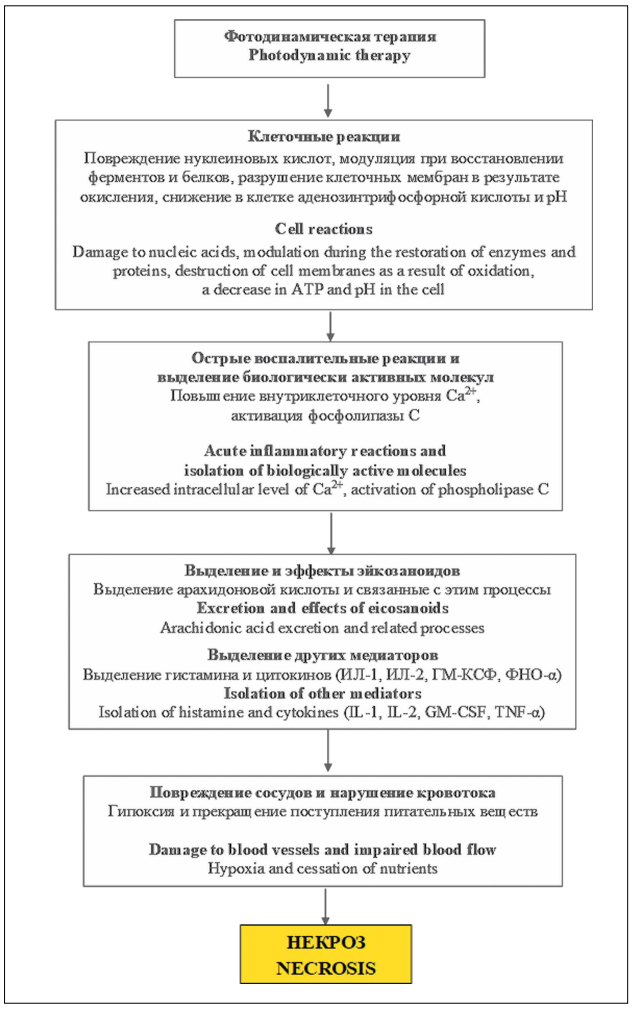

Рис. 1. Механизм некроза при ФДТ (Goldman M.P., 2010)
Fig. 1. PDT-induced necrosis (Goldman M.P., 2010)

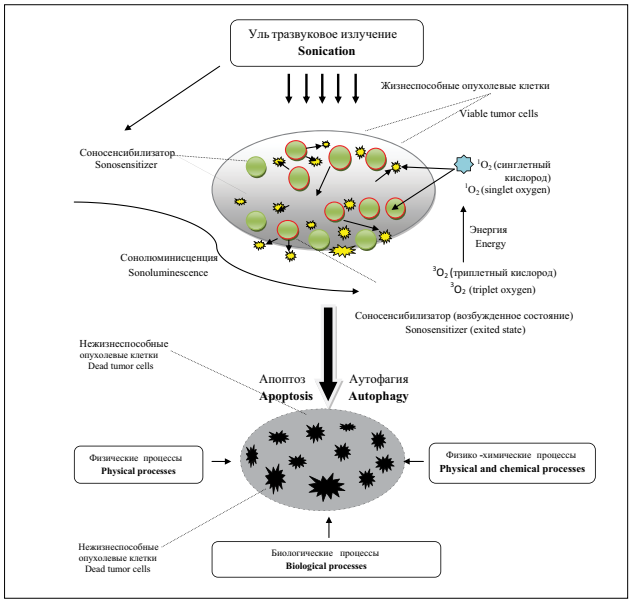

Рис. 2. Механизмы, лежащие в основе сонодинамической терапии
Fig. 2. Mechanisms of sonodynamic therapy

the SPDT method with the Sonoflora 1 PS (chlorophyll derivative, 30–60 mg, subglossally, 2–3 days). Photoradiation was carried out in a low-intensity mode using laser equipment with a radiation wavelength of 630 nm (light dose was 36 J/cm^2; power density was 20 mW/cm^2; duration was 30 min), ultrasonic treatment was conducted with a frequency of 1 MHz and an intensity of 2 W/cm^2 for 20 minutes. The therapy began 3–4 days after the PS administration and lasted 3 days. The treatment was repeated every 1–2 weeks.

Patient 1 had the progressive breast carcinoma after surgical treatment, chemoradiation therapy, Herceptin, Zometa courses, etc. After 3 SDT sessions, the relief of clinical symptomatology and the partial response were detected (according to the data from PET/CT). Patients 2 and 3 had the progressive breast carcinoma with metastatic lesions appearing in internal organs. After 2 SDT sessions, the partial response were reported (according to the data from PET/CT). 28 months after the treatment, distant metastases were not detected [50, 51].

L. Q. Li et al. presented the first case of using SPDT with the Sonoflora PS (subglossally, on the 1st and 2nd day) in 7 patients with esophageal and gastric adenocarcinomas at the ASCO Annual Meeting in 2014. From the 4th to the 6th day, both the tumor growth zone and the patient's entire body were exposed to the photoradiation and ultrasound. In 2 patients, no adverse reactions were noticed. In 5 patients, there were adverse events of the 1st and the 2nd grade (moderate pain, burns), which were easily relieved. The complete regression rate was 42.8% (n=3), the partial regression rate was 42.8% (n=3), and no effect was in 1 patient. The objective therapeutic effect was 85% [49].

D. Murphy et al. from the Skills Laboratory RACS (Melbourne, Australia) presented the results of the phase one clinical trial using SPDT with the Radochlorin, Sonnelux and Photosoft photosensitizers in the treatment of 66 patients with prostate cancer after the curative surgical treatment. The photosensitizers were administered subglossally or orally 16–24 hours before the treatment. Photoradiation parameters: the maximum power was 2 W, the absorbed dose of light was 4000-5000 J. Ultrasound parameters: 1 W. The treatment was conducted through transrectal, transurethral and percutaneous approaches. The maximum session duration was 25 minutes. The course of treatment included 3 procedures per week and was repeated twice for 12 months. The morbidity was 1.5% (n=1 is an urethral stricture). The authors noted the relief of clinical symptoms of the disease, the stabilisation or reduction of PSA after 6 months, the decrease in prostate volume and the absence of erectile dysfunction [52].

In 2009, J. N. Kenyon from The Dove Clinic (Hampshire, England) published the outcomes of treatment of 115 patients with malignant tumors (n=31, breast cancer; n=14, inoperable lung cancer; n=13, colon cancer; n=8,

prostate cancer; n=6, ovarian cancer; n=6, lymphoma; n=4, head and neck tumors; n=4, esophageal cancer; n=3, cervical cancer, n=3, gliomas, etc.) using SPDT with the Sonnelux-1 metallo-chlorine agent as a PS. The sublingual administration of the PS was slow and lasted for 2–5 hours. Photoradiation was performed using lasers with radiation wavelengths of 660 nm and 940±30 nm, ultrasonic treatment was conducted with a pulse intensity of 1 W/cm^2. The course of treatment included 3 sessions. The authors noted the high tolerability of the method and the absence of serious adverse events. The detailed description of findings upon survival criteria can be found in the publication [33].

Zhang W. et al. published the results of the pilot study involving the use of SPDT combined with chemotherapy in the treatment of 12 patients with metastatic (brain, internal organs, bones) breast cancer. SF1, SFa and UF chlorophyll derivatives were used as photosensitizing agents. Ultrasonic treatment was conducted both in continuous and pulsed modes with a pulse intensity of 1±10% MHz and an intensity of 2 W/cm^2 for 20–40 minutes daily 4–6 days after the sublingual administration of the PS and immersion of patients into a special water bath. The radiation was supplied to both nidi and the patient's entire body from 125 specially designed ultrasonic applicators. Photoradiation was carried out using laser equipment in a low-intensity mode (λ=554 nm, 45 mW/cm^2) for 30 minutes daily. 9 of 12 patients received additional chemotherapy treatment (according to standards of treatment accepted in the research centre). The number of SPDT courses was 1–4: 3 courses of SPDT in the mono mode, 9 courses of SPDT + chemotherapy. The median follow-up time was 34 months (9–68). Detected adverse events corresponded to grades 1-3 (CTCAE, version 3.0): weakness, pain in the nidus area, etc.). The therapeutic response was observed in 75% of cases, the complete regression rate was 16.7%, the partial regression rate was 58.3%, and the stabilisation was observed in 25% of cases. The authors concluded that the inclusion of SPDT in the comprehensive treatment regimen for patients with metastatic breast cancer can improve the outcomes of treatment of this severe disease and expand the range of therapeutic options [53].

During the study in our clinic, we tested the method of intraoperative SPDT with the chlorine based PS in 15 patients with recurrent glioblastoma. Methodology: the photolon solution was administered to patients via IV infusion at a dose of 2–2.5 mg/kg 30 minutes before the end of the surgery in the form of total or near-total resection of the recurrent tumor. After the infusion, the tumor bed was filled with 0.9% saline solution, then local ultrasonic treatment was conducted with a pulse rate of 1 MHz and a radiation intensity of 1 W/cm^2 for 10 minutes (Phyaction USTH 91, GymnaUniphy N.V., Bilzen). At the second stage after meticulous hemostasis, photoradiation of the tumor bed and walls was performed at light doses of 50–100 J/cm^2 using a laser apparatus generating radiation with a wavelength of 660±5 nm (UPL-FDT, Imaf Axicon, Belarus). The adverse reaction rate was 20% (n=2, convulsive disorder; n=1, cerebral edema with the development of hemiparesis and paresthesias). All adverse events corresponded to grades 1-2 of the CTCAE criteria (Version 4.0), were easily relieved and were not directly related to the sono-photodynamic therapy. The median overall survival of deceased patients was 23.1 months; the median survival after SPDT was 8.2 months [54].

Conclusion

As indicated by results of the experimental studies in cell culture and laboratory tumor-bearing animals presented in the literature, SPDT is an efficient option for antitumor treatment of various specific forms of malignant tumors [35-42]. Currently, several research teams are taking the first steps in testing the method in a clinical setting. The scientists from the South-East Asia presented preliminary results of using SPDT with photosensitizing agents in the treatment of malignant lesions of the breast, stomach, esophagus, prostate, lung and brain. The analysis of the obtained data indicates the absence of serious adverse events and increase in antitumor effects of the treatment regimens that have included SPDT with chlorine based photosensitizers [48–54].

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