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Photodynamic therapy in breast cancer treatment

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Abstract
Breast cancer is a serious public problem in modern society. Photodynamic therapy (PDT) is increasingly used in modern medicine. Currently, PDT is an innovative method of treating breast cancer. Irreversible damage to neoplastic tissues is associated with the use of physicochemical processes. Generating cytotoxic reactive oxygen species [singlet oxygen ($^1O_2$)] is leading to tumor cell death. At the same time, valuable information can be extracted from breast cancer cells. Photogenerated $^1O_2$ is the major factor responsible for cell necrosis during PDT. $^1O_2$ can react rapidly intracellularly with all organic substances. The use of photodynamic therapy on tissues *in vitro* creates conditions for testing various types of solutions and implementing them in *in vivo* treatment. This article is a review of recent advances in PDT for treatment of breast cancer. PDT is a novel cancer diagnostic and cancer treatment therapy. Therefore, an understanding of the possibility to generate a toxic form of $^1O_2$ is necessary. The knowledge gained from the basics of PDT *in vitro* can be useful in biomedical applications *in vivo*. The current literature mentions PDT in the treatment of cancers located very deep within the human body. Therefore, the development of agents used to deliver $^1O_2$ to the deep cancerous tissue is a new challenge which can have an efficient impact on this discipline. This review covers the literature between 2000–2022.

Keywords: Breast cancer tissues; Intracellular; Photodynamic therapy; Reactive oxygen species; Treatment

Highlights:
- Photodynamic therapy is selective therapeutic and improves the effectiveness of drug targeting to tumor tissue *in vivo*.
- The drug used in photodynamic therapy can end up in the neoplastic tissue, where it is activated with oxygen and light.
- Photodynamic therapy allows for characterization of the physical and chemical parameters of healthy and neoplastic tissue.
- Photodynamic therapy allows us to learn about the differences in chemical composition by measuring relaxation times. MRI can help us improve the histopathological assessment of breast cancer.

Introduction

Breast cancer is the most common type of cancer in women in Poland. According to Central Statistical Office of Poland, breast cancer was the cause of death in 24% of women in 2011. Each year the number of breast cancer cases are increasing. Table 1 shows the most common causes of breast cancer in women.

Due to the large number of causes of breast cancer, preventive measures are necessary to increase awareness of risk factors and early detection (Ghoncheh et al., 2016). Duct hyperproliferation is one of the first steps in initiating the formation of breast tumors. Under the influence of constant stimulation with various factors, they may develop into benign or metastatic neoplastic forms (Sun et al., 2017).

In 50% of cases, a breast tumor is detected in the upper-outer quadrant. Almost 20% of the nodules are located in the nipple and areola, 15% in the upper-inner quadrant, in 11% of the lower-outer quadrant. Fig. 1 shows the most common location of tumors in the breast.

The size of the tumor depends on the clinical and pathological features. Diagnostic tools are a helpful tool in locating the tumor. In a situation where the tumor is in an area that is difficult to access, it may be difficult to accurately determine its size (Adesoye and Lucci, 2021). The diagnostic and therapeutic scope of breast cancer is very wide, but it remains one of the most lethal neoplasms (Ernst and Anderson, 2015). Surgery, radiotherapy, chemotherapy, immunotherapy, and hormone therapy are the key methods of cancer treatment. These techniques apply to the treatment of both early and advanced stages of the tumor (Moo et al., 2018). Despite the many tools available, new technologies are still needed to treat all stages of breast cancer. A relatively new therapeutic method that may turn out to be the gold standard in the treatment of neoplastic changes compared to conventional methods is photodynamic therapy (PDT) (Banerjee et al., 2020).

Photodynamic therapy is a relatively young but rapidly developing healing method created in the last century (Daniell and Hill, 1991; Kato, 1996). Currently, it is used to treat – among others – cancers within the head and neck mucosa,

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Table 1. The most common causes of breast cancer (Ghoncheh et al., 2016; Libson and Lippman, 2014; Sun et al., 2017; Winters et al., 2017)

Cause	Characteristic
Age	The incidence of breast cancer increases with age
Age at menarche	Early menstruation can increase your risk of getting sick
Age at first full-term pregnancy	Late first pregnancy can increase risk of breast cancer
Age at menopause	Late-age menopause
Genetic factors	Breast cancer in close relatives, family mutation of the BRCA gene or coexistence of another cancer
Race	The white population has the highest incidence rate
Oral contraceptives	These agents increase risk of breast cancer
Central obesity	May be a predisposing factor for breast cancer
Alcohol	Alcohol increases the risk of breast cancer
Radiation exposure (at a young age)	This cause increases the risk

tumors of the brain, lungs, pancreas, colon, breast, prostate, bladder, cervix and skin (Bozzini et al., 2012; Civantos et al., 2018; de Freitas et al., 2017; Dolmans et al., 2003; Fan and Andrén-Sandberg, 2007; Kawczyk-Krupka et al., 2016; Kostron, 2010; Lam, 1994; Meulemans et al., 2019; Nelke et al., 2014; Nseyo et al., 1998). Since ancient times, light has been used to treat various diseases, e.g., psoriasis, vitiligo, or skin cancers (Kato, 1996). PDT is a method that involves the use of a photosensitizer and light of the appropriate wavelength that will cause selective damage to cancer cells in the body. The effectiveness of this therapy depends on many factors: the type of cancer cells, the type of photosensitizer, the wavelength of light (Agostinis et al., 2011; Dolmans et al., 2003; Kwiatkowski et al., 2018). The mechanism of PDT is based on the oxidation of biomolecules under the influence of light of the appropriate wavelength due to prior administration to the irradiated place of the so-called photosensitizer. This process can take place in two mechanisms (Bacellar et al., 2015; Baptista et al., 2017; Kwiatkowski et al., 2018).

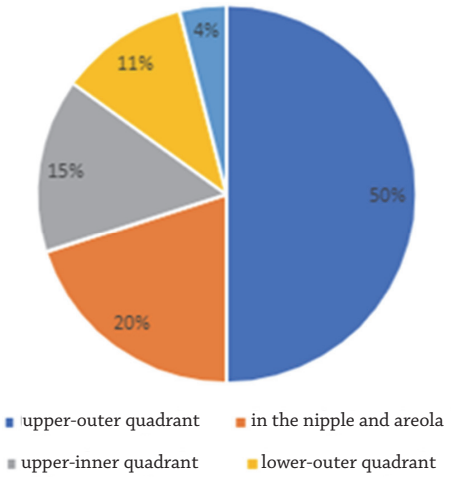

Fig. 1. The most common location of tumors in the breast

Type I – light energy is transferred from excited molecules to biomolecules by means of elehtron/hydrogen transfer in direct contact, where it accumulates and causes specific damage to biomolecules.

Type II – light energy is transferred to molecular oxygen, which then produces singlet oxygen. It is extremely reactive and can damage both cellular proteins and DNA (Agostinis et al., 2011; Kwiatkowski et al., 2018; Postiglione et al., 2011; Spring et al., 2015; van Straten et al., 2017):

1. Possibility of killing cells by direct harmful effects of reactive molecules resulting from the stimulation of photosensitizer. The direct phototoxic effect of PDT is based on irreversible damage to the cell membranes or organelles that are the target of the photosensitizer.
2. Damage to the vascularization of the tumor cuts off the supply of oxygen and nutrients to the cancer cells.
3. Stimulating the host's immune system by triggering an inflammatory response within the tumor and a response to "foreign" cancer cells.

The extent of the damage and the mechanism of action primarily depends on the type of photosensitizer used, but also on the type of cancer, the concentration of the photosensitizer itself, and the wavelength of the light used. To date, the effectiveness of PDT has been proven and introduced to the clinic in the treatment of lesions (located superficially) on mucous membranes or skin (Civantos et al., 2018; de Albuquerque et al., 2019; Lamberti et al., 2014; Meulemans et al., 2019; Nelke et al., 2014). However, there was a problem in the case of deeper lesions, where the challenge is the precise placement of the photosensitizer and the limited ability to penetrate the light wave. Due to the development of technology, fiberoscopes can reach hard-to-reach places and directly apply light with the required wavelength (Mallidi et al., 2016; Pogue et al., 2016). The photosensitizers themselves are also constantly being modified by adding various organ-specific carriers. This allows the photosensitizer to be placed in the target organ after intravenous administration. At the same time, it protects other organs against the potential of harmful effects of PDT in healthy tissues (Abrahamse and Hamblin, 2016; Cao et al., 2018; Hodgkinson et al., 2017; Shirasu et al., 2013). There have also been attempts to introduce photosensitizers that bind to receptors on the surface of cancer cells, e.g., estrogen, progesterone or EGFR (Choi et al., 2015; Lamberti et al., 2014; Stuchinskaya et al., 2011; Tsai et al., 2018; Zhao et al., 2018). In the case of breast cancer, most studies are conducted *in vitro* (Fig. 2).

The search for new, more tissue-specific photosensitizers is constantly ongoing. Research is also conducted on the modification of already available photosensitizing substances to minimize their impact on a specific organ and eliminate the potentially harmful effect of photodynamic therapy on healthy tissues.

The effectiveness of PS is proven in superficial lesions, but clinical trials are also conducted in deeper tumors (Brown et al., 2004). The limitation of this method is the depth of light penetration (Lowdell et al., 1993). PDT based on the use of internal light sources (luciferase-substrate bioluminescent systems) has been described by Shramova et al. (2018). In their work, they used the NanoLuc-furimazine bioluminescent system. This may induce phototoxicity of the miniSOG photosensitizer protein in cancer cells via bioluminescent resonance energy transfer (BRET). It is an alternative to external light sources. In deep tumors, it is difficult to deliver the excitation light to the inside of the body without losing its intensity (Mroz et al., 2011; Shramova et al., 2018) – Fig. 3.

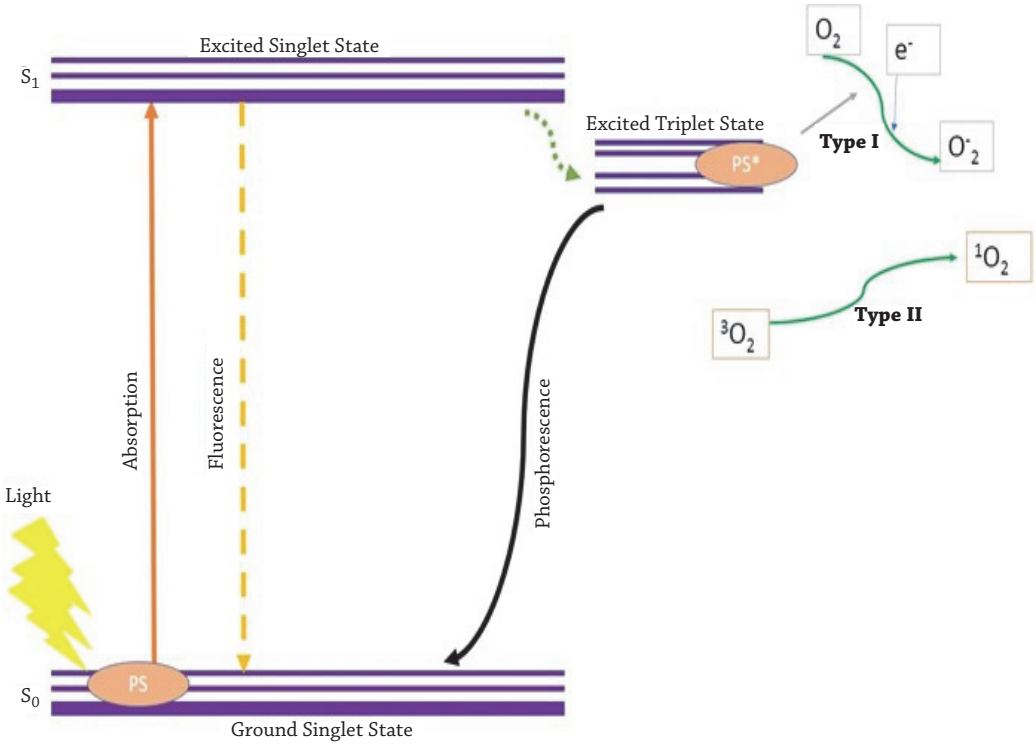

Fig. 2. Diagram of the photodynamic reaction

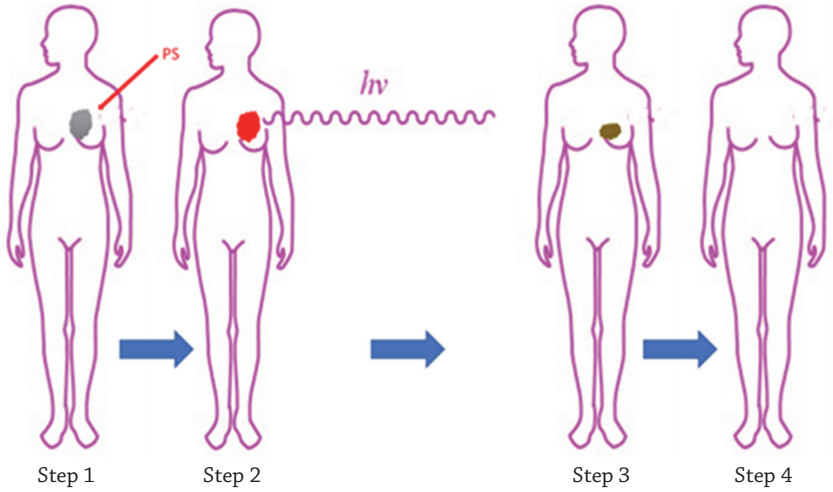

Fig. 3. Four steps during breast cancer PDT. Step 1 – Intravenous administration of PS. Step 2 – Irradiation and activation of PS. Step 3 – Cancer cell destruction. Step 4 – patient after successful PDT. PS – photosensitizer, *hv* – light quantum.

In a study by Banerjee et al. (2020), 12 patients with primary breast cancer without neoadjuvant treatment were given PDT a few days before surgery. In this study, no significant adverse effects were found in patients, except for local pain that was alleviated by painkillers. No skin changes or laboratory changes were observed. There were no complications after the operation that could be associated with PDT. All patients felt well and were discharged with standard recommendations. Histopathological studies revealed standard PDT lesions within tumors such as thrombotic necrosis, apoptosis, chromatin condensation and nucleus pycnosis, vascular lesions, abundant inflammatory infiltrates and stromal edema.

Although the results are promising, there are still many unknowns, e.g., whether the histological type of cancer affects the response to treatment, whether the status of receptors can affect the effects of therapy, and many others. Before PDT is permanently introduced as a treatment method, these doubts will have to be dispelled. For the treatment of breast cancer cells, the following are mostly used: methylene blue (Dos Santos et al., 2020), 5-aminolevulinic acid (5-ALA) (Shinoda et al., 2021), and pyropheophorbide-α methyl ester (Huang et al., 2019).

There is hope associated with the possibility of treating breast cancers that are refractory to standard treatment, e.g., triple breast cancers (Feuerstein et al., 2011; Candido et al., 2018; Chen et al., 2001; Wang et al., 2016). There are hypotheses that PDT can indirectly restore the sensitivity of cancer cells to current treatment methods. Photosensitizers accu-

mulate within cell organelles, contributing to their damage (García Calavia et al., 2018), which entails cell death in a typical mechanism of apoptosis, necrosis, or autophagy. Metal nanoparticles (Ashkbar et al., 2020), photodynamic and photothermal approaches with the aid of curcumin photosensitizer and magnetic nanoparticles (Shang et al., 2021) have already been used.

Materials and methods

The main aim of the experiment was to apply four different photosensitizers to *ex vivo* breast cancer tumor tissue sections and to subject them to photodynamic therapy. All planned tests and measurements required the consent of the Bioethics Committee of the University of Rzeszów (11/11/2018) in accordance with the Helsinki Declaration.

The experiment began in 2019. A group of women diagnosed with breast cancer at an earlier stage of diagnosis qualified for the study. The research group consisted of 30 women diagnosed with breast cancer tumors up to 10 mm in diameter. As a result of the biopsy (carried out at Clinical Hospital No. 1 in Rzeszów), fragments of neoplastic tissue were collected from the patients and properly prepared to obtain histopathological preparations. The procedure of obtaining histopathological preparations was carried out in the Department of Pathomorphology of Clinical Hospital No. 1. Postoperative biological materials were subjected to the natural and standard histopathological procedure. The material was fixed in formalin, alcohol, xylene, and paraffin. The material was stained and secured to glass slides. The research material was divided into four groups. A different photosensitizer was administered to each group (Fig. 4). Table 2 summarizes the type, concentration and length of laser light applied by four research groups.

Being applied to the tissues, the photosensitizers were oxygenated. The appropriate type of photosensitizer was injected into each tissue material in a given group. For this purpose, a syringe with a volume of 10 ml and an injection needle were used. After application of the photosensitizer, the preparations were irradiated with laser light with a wavelength of 532 nm (in the case of groups 1, 2, 3) and with a wavelength of 665 nm (in group 4) for 15 minutes. Fig. 4 shows the method of irradiating tissues with a laser. After the PDT procedure was applied, the histopathological material was analysed under a microscope. The changes that occurred as a result of the PDT procedure used were summarized in the form of micrographs.

Table 2. The concentrations of the prepared photosensitizers and the wavelengths of laser light used in PDT for individual groups

Group number	Photosensitizer	Concentration [mM/L]	Wavelength of light used [nm]
1	Silicon phthalocyanine dichloride	0.0012	532
2	5-Aminolevulinic acid hydrochloride	0.003	532
3	Rose Bengal	0.05	532
4	Protoporphyrin IX disodium salt	3	665

Results

The results of the experiment were visualized and compiled in the form of microscopic images of the analyzed preparations. These are images of neoplastic tissue before PDT (Fig. 5 and 6) and tissue after PDT therapy from a few selected patients. Fig. 7 shows a microscopic image of the tissue before and after the application of the silicon phthalocyanine dichloride photosensitizer and after the exposure of laser light. Fig. 8 shows the microscopic image of the treated tissue fragments before and after the application of photodynamic therapy with 5-aminolevulinic acid. Fig. 9 shows a microscopic image of the tissue before and after the application of the Rose Bengal and after the exposure of laser light. Fig. 10 shows a microscopic image of the tissue before and after the application of the Protoporphyrin IX disodium salt and after the exposure of laser light.

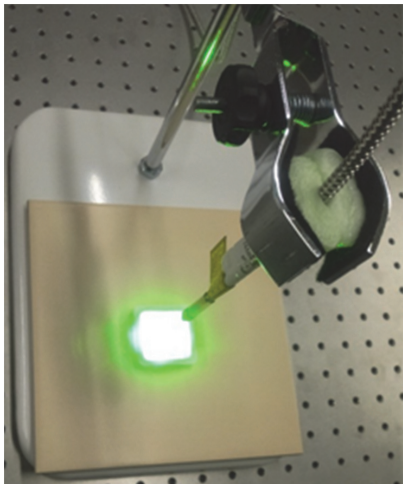

Fig. 4. The method of irradiating tissues with a laser

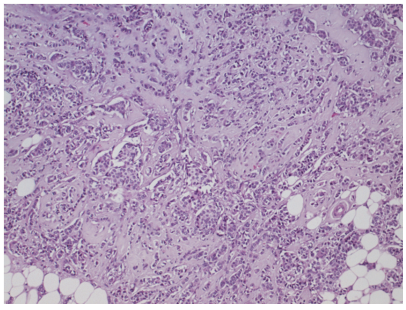

Fig. 5. NOS ductal breast cancer (H + E, x100)

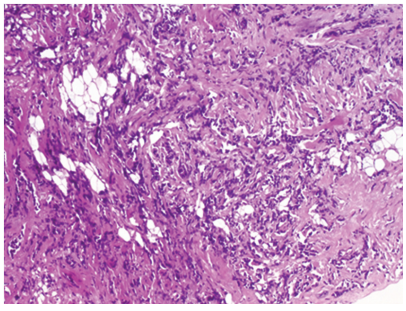

Fig. 6. Ductal breast cancer after using PDT NOS (H + E, x100) – a preparation from the same patient (own photos)

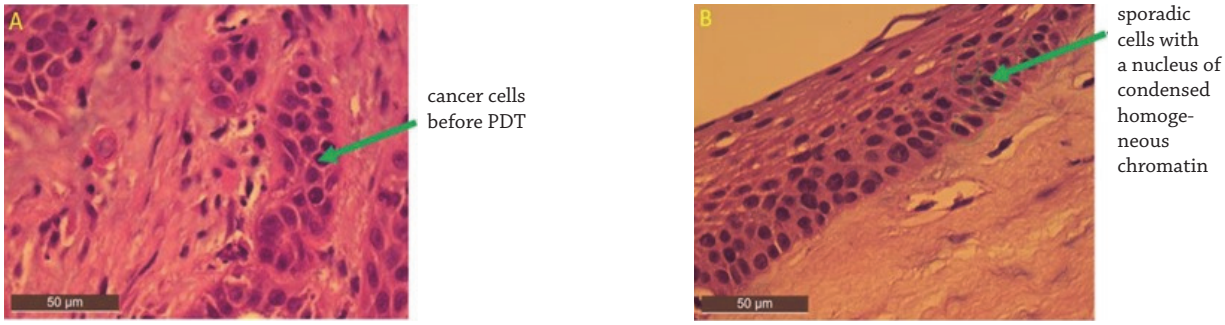

Fig. 7. (**A**) Breast cancer tissue before PDT; (**B**) Breast cancer tissue after PDT with Silicon phthalocyanine dichloride (H&E 25X)

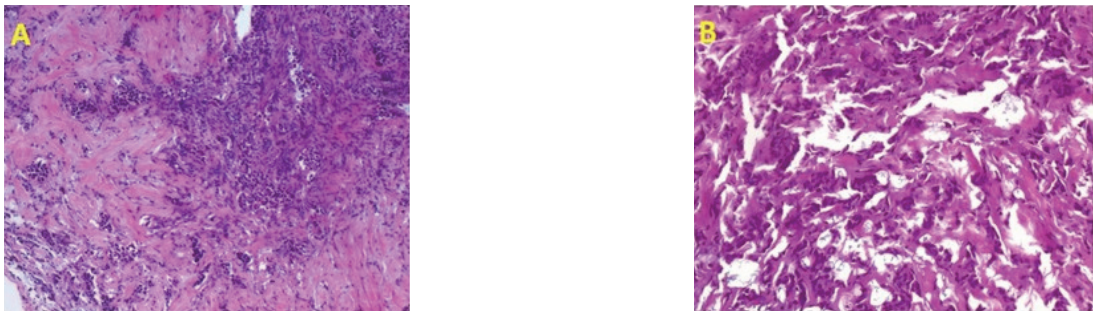

Fig. 8. (**A**) Breast cancer tissue before PDT; (**B**) Breast cancer tissue after PDT with 5-aminolevulinic acid (H&E 25X)

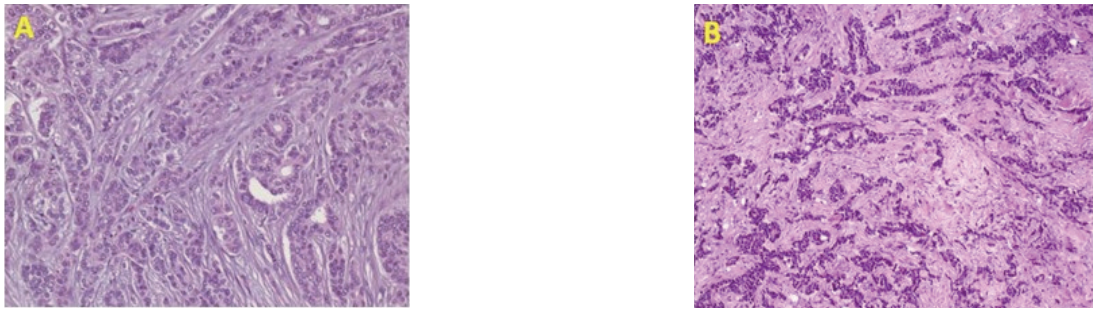

Fig. 9. (**A**) Breast cancer tissue before PDT; (**B**) Breast cancer tissue after PDT with Rose Bengal (H&E 25X)

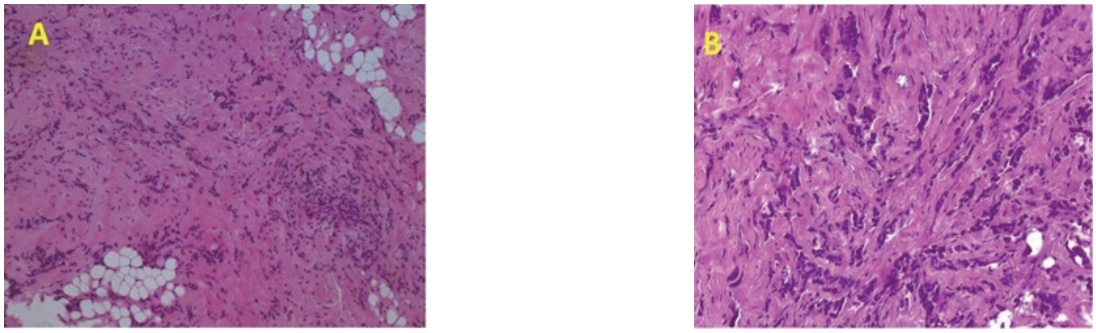

Fig. 10. (**A**) Breast cancer tissue before PDT; (**B**) Breast cancer tissue after PDT with Protoporphyrin IX disodium salt (H&E 25X)

Discussion

As a result of irradiating samples with laser light, the cell activates a cascade of molecular processes that cause cell disintegration, leading to cell apoptosis. Apoptosis, also known as programmed cell death, is an active, structured process that allows the elimination of cells without stimulating the inflammatory process and damaging surrounding tissues. Through apoptosis, infected, damaged, and mutated cells are removed from the body or made redundant, e.g., occurring only at certain stages of development. There are three phases in the process of apoptosis: initiation, executive and degradation. The ability of a cell to respond to a variety of factors through apoptosis is a multi-step process. The course of apoptosis is determined by the physiological state and the activation of biochemical functions in cells. The most common factors that initiate apoptosis are the reactions of ligand recognition and binding to appropriate cell surface death receptors, their activation, and activation of initiating caspases. Cysteine-dependent caspases (specific aspartate proteases) are responsible for the proteolytic breakdown of some components of the cytoskeleton. The external pathway of apoptosis is related to the presence in the plasma membrane – the so-called death receptors – which belong to the TNF family of proteins. As a result of the death receptor binding to a specific ligand, there are conformational changes within the death domain and the formation of a complex.

A process that was observed (after PDT) relatively early on is dehydration of the cell (a decrease in the volume of the cell by 30–50% due to water loss occurs). The specific gravity of the cells increased, which enabled their isolation in a density gradient. One of the most characteristic changes was the condensation of chromatin, which took on a crescent-shape, horseshoe-shape, or sickle-shape (Fig. 7). The cytoplasm was densified, and then the shape and size of the cell changed - the cells became smaller, elongated (Fig. 8). There was a loss of villi and inter-cellular connections. Structure of chromatin became homogeneous and its DNA showed the typical hyperpigmentation (Fig. 9). The nuclear membrane disappeared, and then the entire nucleus was fragmented, the fragments of which, packed and surrounded by fragments of the cytoplasmic membrane, form the so-called apoptotic bodies – excreted from the dying cell and phagocytosed by neighboring cells, both of epithelial and mesenchymal origin, without causing inflammation (Fig. 10). In all cases, the changes induced by PDT are clearly visible in the histopathological changes. The use of different photosensitizers with different concentrations causes similar but not the same changes in the neoplastic tissue.

Conclusions

Today, cancer is a real scourge. The main problem with chemotherapy and radiation therapy is that they not only destroy cancer cells, but also healthy ones. It is harmful to the patient, and to survive such treatment the body must be in good condition. To minimize damage, oncologists and scientists around the world are looking for ways to deliver drugs directly to cancer cells, rather than healthy ones. One such method is photodynamic therapy. The conducted *ex vivo* tests enable the introduction of repeatability in *in vivo* tests. The changes that take place at the cellular level show that the toxic effect of ROS disrupts the physiology of cancer cells, damaging the membranes and other individual elements. *Ex vivo* tests enable the selection of optimal PDT conditions (such as the type of photosensitizer or its concentration). This is an extremely valuable prospect and an opportunity to implement PDT therapy in patients *in vivo*. Hopefully, in the near future, PDT will replace traditional cancer treatment and give many patients the chance to live cancer-free.

Despite the development of medicine and the introduction of new therapeutic methods, breast cancer remains a big problem – both in terms of high incidence and mortality. For this reason, scientists around the world will continue to look for new therapeutic methods. PDT still requires many clinical trials to assess its effectiveness, but so far the results are promising. They show that PDT is an effective, minimally invasive and safe therapeutic method, without significant adverse effects.

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Ethical aspects and conflict of interests
The authors have no conflict of interests to declare.

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