In vitro Photodynamic Therapy in the Treatment of Endometrial Cancer

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Abstract

Background Endometrial cancer is the fourth most common type of cancer in the world. Due to the prevalence and high morbidity, it is of key importance to make a quick and accurate diagnosis and effective therapy. The use of photodynamic therapy (PDT) in the treatment of endometrial cancer is a significant challenge in conducting clinical trials. PDT is non-invasive, with few side effects, damaging only neoplastic tissue, leaving healthy adjacent structures intact. Thanks to numerous experiments (also

in vitro), PDT is gaining more and more recognition as a potential tool in endometrium cancer treatment.

Objective The aim of the study was to analyze the effectiveness of photodynamic therapy on endometrial cancer tissue samples in vitro. Additionally, the aim of the experiment was to analyze the effects of PDT on endometrial cancer tissues in histopathological examination.

Methods In the in vitro experiment of PDT, sections of endometrial cancer tissue taken from female patients were subjected to. Rose Bengal was used as a photosensitizer in order to assess the usefulness of the applied PDT and to introduce these solutions into the in vivo test procedure.

Results Changes on the cellular substrate, such as: chromatin condensation, disturbed structure and shape of cell nuclei were observed in all tissues subjected to PDT.

Conclusions The PDT experiment in vitro offers opportunities and hopes for using the chosen procedure also in vivo.

Keywords endometrial cancer; photodynamic therapy; in vitro; treatment; rose bengal

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in industrialized countries [1-2]. Endometrial cancer is the 6th most commonly occurring cancer in women and the 15th most common cancer overall. There were more than 417,000 new cases of endometrial cancer in 2020 [3]. The incidence of endometrial cancer is associated with in-creased mortality [4]. Each year, over 89,000 patients die [5]. In 2020 this number was 97,370 according to World Cancer Research Fund [3]. A large percentage of patients is diagnosed at an earlier stage of the disease [6-8]. Most of the diagnosed patients are in the fifth and sixth decade of life [9-10]. The incidence of endometrial cancer is increasing in young women, and the incidence in childbearing age (under 40) ranges from 3% to 14% [11]. Figure 1 presents the graph showing 10 countries with the highest rates of endometrial cancer in 2020. Age-standardised rates (ASR) per 100,000 scale was applied. These are a summary measure of the rate of disease that a population would have if it had a standard age structure [3].

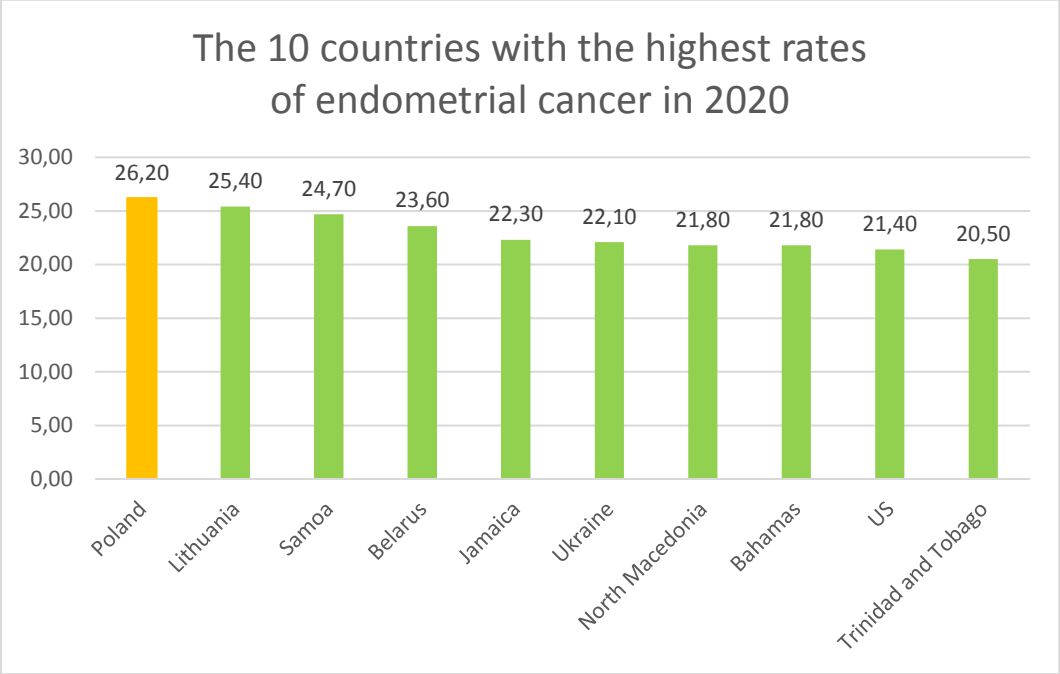

Fig. 1 10 countries with the highest rates of endometrial cancer in 2020

1.1. Endometrial carcinoma types

The incidence of endometrial cancer depends on many factors. These are i.a. genetic factors, the patient's age (early first menstruation, late menopause), infertility, previous or ongoing illnesses, obesity, early and long-term contraception and the country of origin of the patient [1,12-15].

Traditional classification of endometrial cancer may be based on clinical and endocrine features (e.g. type I and II) or histopathological features (e.g. endometrioid, serous, or clear cell adenocarcinoma). The subtypes defined by the different classification systems are somewhat correlated, but there is considerable heterogeneity in biological, pathological, and molecular characteristics in the tumor types from both classification systems [16].

In clinical classification there are two major types of endometrial tumors. Type I endometrial carcinomas are mostly endometrioid adenocarcinomas which appear to develop from abnormal glandular proliferation (i.e. endometrial hyperplasia) driven by hormonal mechanisms [17-18]. The cause of its formation is influenced by several factors. These include obesity, diagnosed polycystic ovary syndrome in patients, anovulatory cycles, irregular menstruation and increased production of estrogen by the ovaries. Its structure is very similar to the endometrium, hence the name. It is classified as a milder type due to its minimal invasiveness and low aggressiveness [19-22].

In contrast, type II endometrial carcinomas often show serous or clear cell histology and arise from atrophic endometrium in a less hormone dependent manner. In addition, the subtypes of these cancers are characterized by characteristic molecular changes, and endometrioid carcinomas are more clearly associated with increased levels of sex-steriod hormones and the expression of hormone receptors [17-18]. The cause of type II cancer is primarily the patient's age. This type of cancer is more common in patients in the sixth and seventh decade of life. Type II carcinomas include serous, clear cell, undifferentiated, mucous, and squamous cell carcinomas [15, 22-23]. The medical classification also includes intermediate types between I and II types of cancer. These include cases in which the cancer exhibits to a greater or lesser extent different clinical, histopathological and molecular features of the two types. Another type of endometrial cancer is lobular carcinoma. It is uncommon and most often metastasizes to the gastrointestinal, gynecological and peritoneal tracts [24].

Endometrial tumors are divided into five histological subtypes: endometrioid, serous, mixed (combination of endometrioid and serous), clear cell, and malignant mixed Mullerian tumor. Rare subtypes that occur are classified as "other". Almost 75% of endometrial cancers are of the endometrioid type [16, 25]. Although the endometrioid subtype may be of low or high grade, other tumor types (i.e. serous and clear cell types) are high grade [26, 27].

1.2. Endometrial carcinoma cell histotypes

The cells that line the glands in endometrial cancer are compact, columnar, with multiple layers and features of atypia [29]. Atypia as a group of abnormal malignancies in the structure of cells is characterized by a number of neoplastic changes. Features of atypia include: cell enlargement, an increase in the volume of the nucleus relative to the cytoplasm, anisocytosis (change in the shape and size of cells), irregular outline of the cell nuclei, hyperchromatosis (increase in the amount of DNA in cells), heterochromasia (uneven staining), irregular thickening of the cell membrane and uncontrolled mitotic processes [30]. Endometrioid cancer also takes the form of squamous cell carcinoma. Serum cancer differs from endometrioid cancer by pronounced nuclear pleomorphism, visible nucleoli, and sparse cytoplasm. It has a characteristic papillary structure, solid or microcystic. Tumors do tubulocytic growth, papillary or solid growth and polygonal or conical cells with pronounced pleomorphism of the nucleus, visible nucleoli and pure cytoplasm [30-31].

1.3. Endometrial cancer treatment

Endometrial cancer is the most common gynecological malignancy and its incidence is increasing. The diagnosis of endometrial cancer in young women of reproductive age is rare. Indeed, only 4% of endometrial cancer patients are under the age of 40. It is usually diagnosed in postmenopausal women. The purpose of endometrial cancer diagnosis is to identify women with early-stage endometrial cancer who require only total hysterectomy and bilateral oophorectomy. Women with a family history of hereditary colorectal cancer unrelated to polyposis are more likely to develop endometrial cancer

[5,26]. Surgery is the most common form of treatment for endometrial cancer. It involves the complete bilateral removal of the ovaries and fallopian tubes [28].

Photodynamic therapy is a modern method that uses light to heal. PDT is based on photochemical reaction between light, a non-toxic photosensitizer and oxygen. Production of singlet oxygen by excitation of a photosensitizer is the main output of this process, thanks to which the target tumor cells can be destroyed by local necrosis of the neoplastic cells [32, 33]. Endoscopic access to the uterus puts PDT in the spotlight in the treatment of endometrial diseases. PDT has the potential to be an effective conservative treatment for benign and malignant endometrial lesions [34].

2. Materials and Methods

2.1.Endometrial cancer tissues

18 cases of endometrial cancer after chemotherapy were included in the study. Patients diagnosed with endometrial cancer were 30-50 years of age. The biopsy material was collected from patients diagnosed with endometrial cancer. The interference in the tissues was minimized by using a sharp scalpel, avoiding crushing the material. The material was collected under sterile conditions using a core needle biopsy with a diameter of 1.2 mm. Following a biopsy of the neoplastic tissues, it was decided to experimentally undergo PDT to test and test this form of cancer treatment and to implement it in future in vivo studies. The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by the Ethics Committee of 10/11/2018.

2.2.Histopathology

As a result of the surgery (biopsy) from patients with endometrial cancer, the material in the form of tissue sections was collected and fixed in 10% buffered formalin solution (4%) for a period of 24 hours.

The fragments are embedded in substances that penetrate into the tissues, which give them adequate hardness. This makes it possible to prepare suitably thin sections. After fixation, the sections were placed in cassettes. The tissue material from the cassettes was rinsed, dehydrated, passed in intermediate fluids and embedded in paraffin. Thus, block preparations were obtained. This step is called infiltration and was carried out at 52ºC

Sections were cut from the paraffin blocks using a microtome (MICROTOM LEICA RM 2245). The paraffin block was placed in a microtome stand and quadrilateral sections were punched. In order to minimize the undesirable effects occurring during this stage (rolling up and sticking the sections together), the temperature was sufficiently low and the preparations were properly dehydrated. The most important standard technique for histological imaging is hematoxylin and eosin staining. This is called viewing staining, which allows you to evaluate the entire structure of the tissue by contrasting the staining of the cytoplasm and cell nuclei. At this stage, the Multistainer (LEICA ST 5020) was used - as a universal device for staining histopathological preparations. The final step was to cover the stained fragments with a coverslip. Prior to cover, the space between the slide and coverslip was filled with histofluid. Figure 2 shows the laboratory accessories used during the histopathological procedure.

After the histopathological procedure, the tissues were analyzed and assessed under a microscope (LEICA DM 1000 LED).

Fig.2 Laboratory accessories (a-d) used during the histopathological procedure

2.3.Photodynamic Therapy and histopathology

Histopathological material was subjected to photodynamic therapy. A solution of rose bengal (photosensitizer) in a volume of 1 ml was applied to the tissues. Rose Bengal (RB) (95%), oxygen gas (99%) was purchased from STP & DIN Chemicals, Bielsko-Biała, Poland. The water for the preparation of the appropriate RB concentration was purified using the AquaB Duo reverse osmosis system from Fresenius Medical Care, Singapore Pte. Ltd. The photosensitizer solution was gassed with pure oxygen for 2 minutes. The therapy uses a laser with a wavelength of 532 nm and a power of 350 mW. The irradiation treatment was performed from a distance of 10 cm in order not to heat the tissues. The temperature on the surface of the tissue after 15 minutes of exposure did not exceed 30°C. A solid-state laser (pumped green semiconductor LD laser, MGL-III-532 nm / 300 mW) was used in the experiment. The emitted light covered the entire surface of the tumor and was evenly distributed throughout the tissue. Figure 3. shows the rose bengal vial and the process of irradiating endometrial cancer tissue with a laser.

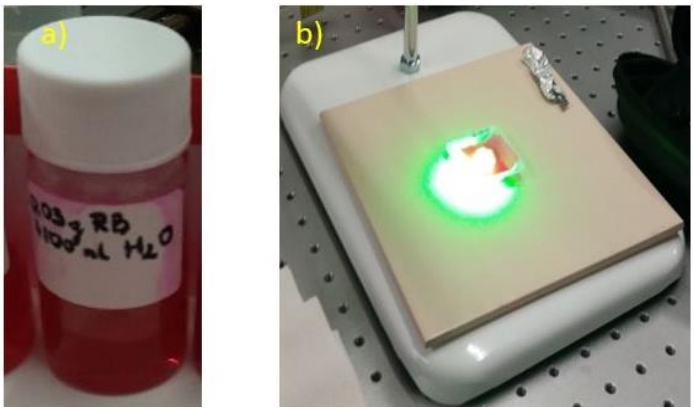

Fig.3 a) rose bengal vial, b) the process of irradiating endometrial cancer tissue with a laser

Histopathological evaluation of microscopic images of tissues after PDT was performed at the Department of Pathomorphology at the Clinical Hospital No. 1 in Rzeszów using a LEICA DM1000 LED microscope (LEICA Microsystems, Wetzlar, Germany). The damage to cancer cells due to the photosensitizer used and exposure to laser light was assessed mainly on the basis of the glandular and testicular architecture, the degree of chromatin condensation, the presence or absence of distinct nucleoli, and the severity of tissue stromal swelling.

3. Results

PDT therapy with the use of an aqueous solution of rose bengal resulted in a reduction in the number of neoplastic cells. As a result of PDT therapy, the size of cells and their physiology changed (they became incomplete and fragmented). Post-PDT neoplastic cells were characterized by the lack of uniform nuclear chromatin, no visible nucleoli and no other elements of the nucleus. The nuclear structure and cytoplasm of the cell have disappeared. Figures 4-6 show microscopic pictures of three endometrial cancer tissues before and after the application of photodynamic therapy.

Figure 4a) shows the image of endometrial carcinoma of tissue no. 1 before the PDT procedure. Whereas in figure 4b) the image of endometrial cancer tissue after PDT is presented.

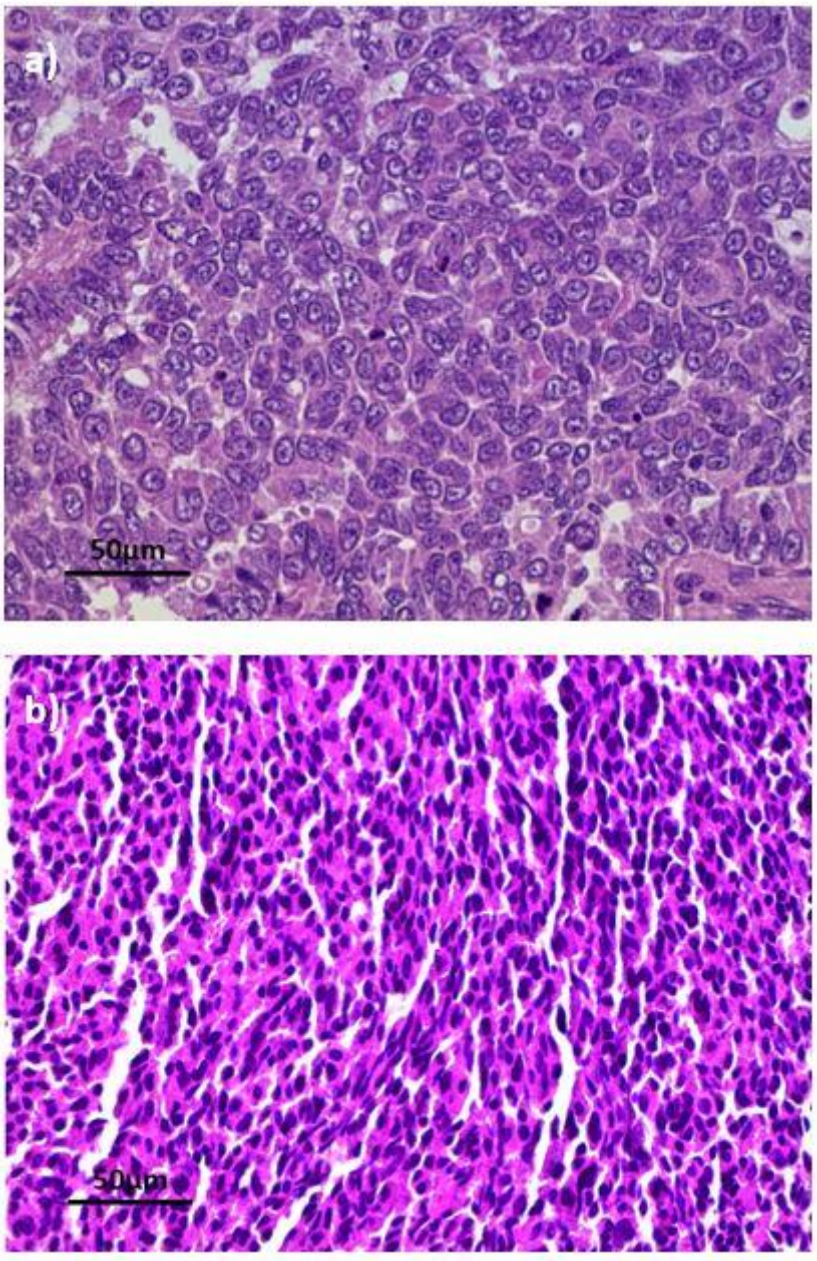

Fig.4 a) endometrial carcinoma of tissue no. 1 before the PDT procedure b) endometrial cancer tissue after PDT

Tissue image no. 1, before PDT, shows cells with a nucleus with a clearly thickened nuclear membrane and nucleoli. Visible elements of nuclear chromatin. Eosinophilic cytoplasm, mostly homogeneous. Slightly marked cell dysohesion. The tumor is solid. Low-differentiated cancer.

The PDT procedure was followed by condensation of nuclear chromatin with completely invisible elements of the nucleus. Homogeneous cytoplasm. The color is more intense. The testes changed after the PDT procedure was used. Chromatin became homogeneous, with no visible nuclei and no membranous chromatin structures.

Figure 5a) shows the image of endometrial cancer tissue no. 2 before the PDT procedure. Whereas in figure 5b) the image of endometrial cancer tissue after PDT.

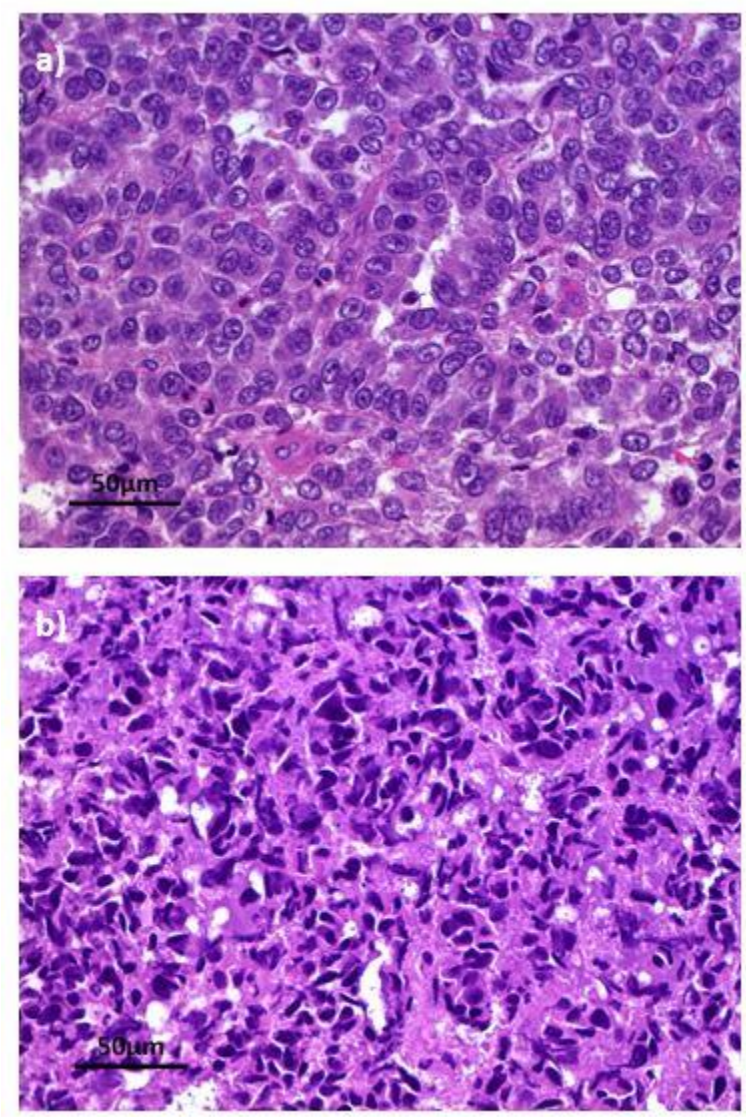

Fig.5 a) endometrial carcinoma of tissue no. 2 before the PDT procedure b) endometrial cancer tissue after PDT

Tissue image no. 2 before PDT shows well the cellular structure of endometrial cancer. A patient with adenocarcinoma with intermediate endometrial differentiation. The photo shows the nuclear membrane and fine-grained eosinophilic cytoplasm. Visible structures in the form of relative chromatin in the nucleus. Membrane unevenly thickened. The testicles, on the other hand, are irregularly enlarged.

PDT damaged endometrial cancer cells. The structure and shape of the neoplastic cell nuclei were disturbed. Significant discohesion of neoplastic cells. The image shows numerous defects in the cell membrane (the tissue looks like a syncycium). Grains of various sizes and shapes. They have a completely obliterated structure of an opaque character with invisible nucleoli.

Figure 6a) shows the image of endometrial cancer tissue no. 3 before the PDT procedure. Whereas in figure 6b) the image of endometrial cancer tissue after PDT.

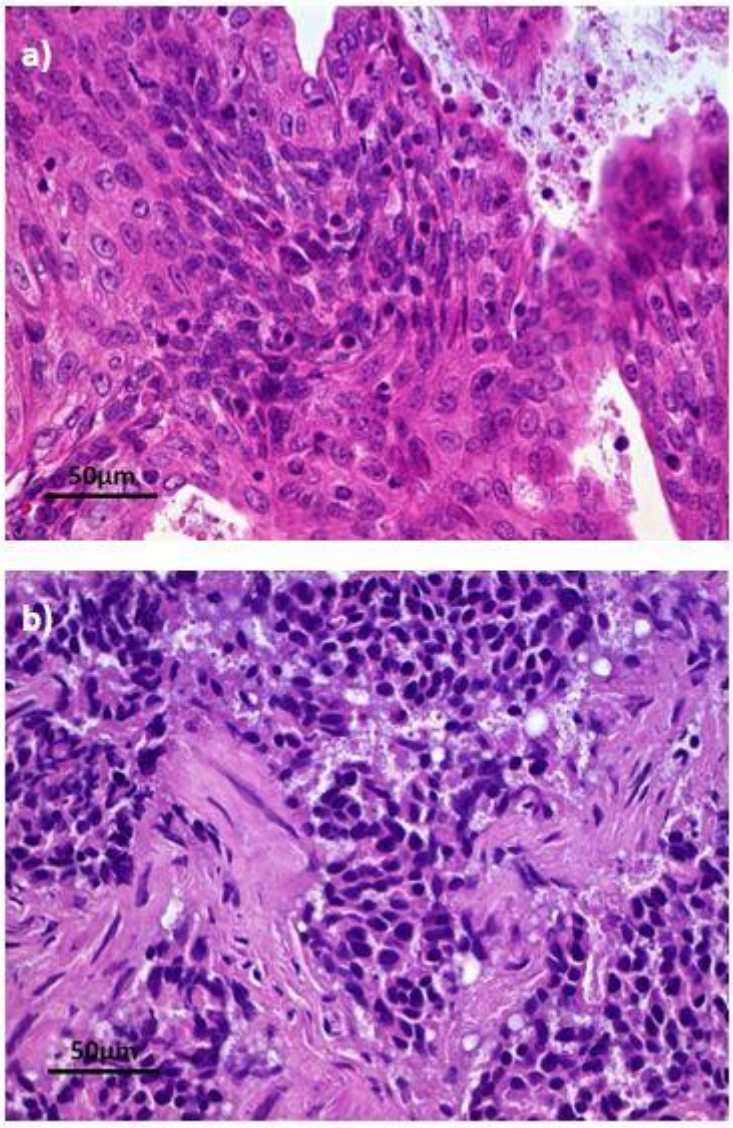

Fig.6 a) endometrial carcinoma of tissue no. 3 before the PDT procedure b) endometrial cancer tissue after PDT

Tissue image no. 3 before the PDT procedure shows the clearly visible structure of tumor cells and nuclei. The tissue came from a patient with endometrial adenocarcinoma with clearly differentiated fields. The cytoplasm of eosinophilic neoplastic cells is more homogeneous. Nuclei of various sizes and shapes with transparent chromatin with visible elements of thickened nuclear membrane and numerous nucleoli. Changes of varying severity have been observed after PDT. Some of the cells were rendered harmless to a greater extent. Condensation and homogenization of nuclear chromatin of cancer cells are visible (of varying severity). There was also an obliteration of the nuclear structure and the cytoplasm of the cell. There was cell discohesion with deeper eosinophilicity. Cell nuclei of various sizes and shapes. Visible homogenization of the nucleus structures. The structure of the nucleus, cell membrane and nucleolus is difficult to locate.

4. Discussion

Histology showed that nuclear chromatin condensation can be visualized in endometrial cancer tissue after PDT. Microscopic observation of endometrial cancer cells before and after PDT were performed. We observed visible nuclei with a distinct thickened nuclear membrane, granular chromatin and nucleoli. The advantages of PDT are its low systemic toxicity and the ability to selectively destroy tumors accessible to light and surpass it over other conventional cancer treatments. Due to these numerous activities, PDT is gaining more and more recognition as a potential tool in conventional cancer treatments. Several preclinical studies and some clinical studies suggest that the use of PDT in combination with established treatments or with newly developed treatments may be beneficial over individual treatments. Koren et al., was used hematoporphyrin in the therapeutic effect of PDT. A laser with a wavelength of 632 nm and a power of 2.5W was applied. After the experiment, the physiology of the tumor was assessed at given time intervals over a period of 22 months [35]. ALA photosensitizer is also used for selective ablation of the endometrium. It is also used as a marker for fluorescence detection in the photAklLLLLodiagnosis of cancer PD [36-37]. Wyss et al. in his experiment he used PDD diagnostics in the assessment of endometrial cancer [38]. They presented the conclusions that PDD can be used to more accurately diagnose endometrial lesions. PDT has many features that make it innovative. Direct toxicity to neoplastic cells, damage to tumor blood vessels and anti-tumor immunological activity are the main mechanisms of its beneficial effects. According to Mhawech et al., Fehr et al. and Wyss et al., PDT is a helpful tool in endometrial ablation. Various photosensitizers have been used in animal models as an experimental test to perform PDT. The effectiveness of the research was good. Which confirmed the importance and role of PDT in the treatment of endometritis [39-41]. PDT is also an endometrial cancer treatment tool that spares fertility. According to studies cited by Won et al., PDT has been on the list of the leading fertility-preserving treatments since 2013 [42]. Min Chul Choi et al. evaluated the effectiveness of photodynamic therapy (PDT) as a conservative fertility-sparing treatment in young women with early-stage endometrial cancer. PDT was used in 11 patients as primary treatment and in 5 patients as secondary treatment for recurrence after primary

hormonal therapy. Complete remission was observed in 12 (75%) of the 16 patients. Of the 7 women who attempted to get pregnant, 4 had 7 successful pregnancies, resulting in 6 live births [43]. In turn, Steiner et al., the pharmacokinetic behavior of topically administered 5-aminolevulinic acid (ALA) and the morphological characteristics of ALA-induced PDT were analyzed in an animal model of the rat. As cells are differ in their ability to produce PP IX, ALA may be an element of selectivity for PDT. Cell specificity was assessed by monitoring the spatial distribution of Pp IX in frozen uterine sections. Endometrial damage was measured by assessing the reproductive capacity of the rats treated with PDT. The muscle damage of the uterus was significant. However, the applicability of the experiment to clinical trials is uncertain. Therefore, according to the authors, further analysis and work is necessary [44]. Researchers at Tohoku University Hospital also drew conclusions regarding the future of PDT and its use in the treatment of adenomyosis. In their research, photodynamic therapy with ALA caused extensive death of cells derived from human adenomyosis. They are sure that photodynamic treatment with ALA in the future may become a new method of treating patients with uterine adenomyosis [45]. Gannon et al., using PDT, selectively destroyed the disease, confirming the role of PDT in targeted therapy [46]. Raab et al. were based on an endometrial cancer cell line treated with PDT [47]. Most of the cells treated with the photosensitizer and exposed to light died within the first 12-24 hours. A low decrease in service life was recorded over the second and third day. The relatively quick reduction in the number of viable cells was due to damage to the cell membrane. In turn, the subsequent decrease in vitality was a result of the destructive effect of PDT on internal metabolic processes [48]. Kim et al., using cells from the HEC-1-A line of endometrial neoplastic tissue, conducted research with the use of PDT. After the therapy, an increased apoptosis process was observed as compared to the control groups. PDT enhanced apoptotic signaling pathways (leading to the activation of PARP polymerase and caspase-9) and reduced the frequency and intensity of tubular formation in cells. Additionally, PDT inhibited cell invasion, reducing the likelihood of metastasis [49]. Schneider-Yin et al., also used the HEC-1-A cell line. The authors showed that the combination of the photosensitizer, which was hypericin with a white light source, has an extremely phototoxic effect on endometrial cancer cells. An increased number of dead cells was observed [50]. One of the major limitations of PDT, as with any cytotoxic modality, is the initiation of tumor cell reactivation pathways that favor the limitations of treatment with this form of therapy. Incomplete treatment may start the cancer cell spreading process by initiating metastasis. In the case of in vitro tests, the above limitation does not apply. In in vitro and in vivo tests, the limited depth of penetration of both the photosensitizer and light is a difficulty. Our experiment confirmed the changes caused by PDT in tissues and cells treated in vitro. In PDT are various photosensitizers, some of them are clinically approved and some are still in clinical trials (table 1.). PDT relies on accumulation of the photosensitizer in diseased tissue as well as localized light delivery. Therefore, an important factor that needs to be considered when planning a therapy is the photosensitizer. Structures of tetrapyrrole, such as porphyrins, chlorins, bacteriochlorins and phthalocyanines with appropriate functionalization have been extensively studied in PDT and several compounds have gained clinical approval. Other molecular structures were investigated, including synthetic dyes classes, transition metal complexes, and natural products such as hypericin, riboflavin and curcumin [51-66]. In treatment of endometrial cancer in animals there were mostly used ALA (5-aminolevulinic acid) and Verteporfin photosensitizers [39-41,52].

Table 1 Clinically approved and tested photosensitizers with their excitation wavelengths.

Photosensitizer	Drug	Stage	Wavelength [nm]	References
Approved				
Porfimer sodium (HPD)	Photofrin®	FDA approved	630	[53-56, 58-59]
ALA (5-aminolevulinic acid)	Levulan®/Ameluz®	FDA approved	635	[53-54, 56, 58-59]
M-ALA (methyl aminolevulinate)	Metvix®/Metvixia®	FDA approved	570-670	[54, 56, 58-59]
HAL (hexaminolevulinate)	Hexvix®	FDA approved	380–450	[56], [59],
Verteporfin (BPD-MA)	Visudyne®	FDA approved	690	[53-56, 58-59]
Temoporfin (mTHPC)	Foscan®	EMA approved	652	[53-56, 58-59]
Talaporfin sodium/NPe6 (N-aspartyl chlorin e6)	Laserphyrin®	MHLW approved	664	[54, 58-59]
Chlorin e6 (C e6)	Radachlorin®	MHRF approved	660	[54, 59]
Photogem	Photogem®	MHRF approved	660	[59]
In clinical trials				
Rose Bengal	Rose bengal	Phase 3	549	[54, 57, 59]
HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-alpha)	Photochlor®	Phase 2	665	[53-56, 59]

Synthetic hypericin	SGX301	Phase 3	570-650	[58-59]
LUZ11	Redaporfin®	Phase 2	749	[58-59]
Methylene blue	Methylene blue	Phase 2	665	[54, 57, 59]
Motexafin lutetium/Lutexaphyrin	LuTex/Antrin	Terminated	732	[53, 56, 59]
Padeliporfin/ Palladium bacteriopheophorbide	TOOKAD®	Terminated	763	[53-56, 59]
Rostaporfin (SnEt2)	Purlytin	Phase 2/3	660	[53, 59]
Ce6-PVP/ Photodithazine	Fotolon®/Photolon ®	Phase 2	660-670	[53-56, 59]
Sylicon phthalocyanine	Pc4	Phase 1	675	[53-56, 59]
TLD-1433	TLD-1433	Phase 2	520	[59]

Limitations of the study

The main challenge of the experiment was the biopsy procedure performed by a histopathologist. Additionally, due to the specificity of the PDT procedure, the transport and storage of biological samples also turned out to be a challenge. The procedure for applying the photosensitizer and the laser irradiation process itself has been presented many times in many scientific publications, which made it possible to test various variants of research protocols.

5. Conclusions

The use of PDT in the treatment of endometrial cancer is a significant challenge in conducting clinical trials. The conducted in vitro tests allow the use of the measurement procedure also in in vivo clinical tests. All analyzes and research on PDT make it possible to use the acquired knowledge for hospital research. Photodynamic therapy enables the selective destruction of neoplastic tissue without damaging healthy tissue. Due to the significant action of cancer cells in vitro, there is a chance that PDT will also become a common toolkit of cancer treatment in vivo in cancer patients. The study of the properties of

the photosensitizers used in PDT causes that more and more standardized methods of therapy are being developed. An important issue is the process of tissue healing after the application of PDT. The conducted research confirmed that tumor tissue and tumor tissue after PDT, based on histopathological examination, have different morphology and tissue structure. PDT therapy applied to cancer tissue caused damage to cytoplasmic membranes, resulting in damage to lysosomes and mitochondria. Tissues treated with PDT showed further degradative changes in the tumor tissue. The experiment confirmed the effectiveness of PDT therapy of cancerous tissues in vitro. Recent studies show that the use of PDT mainly violates the glandular component of endometrium. PDT is a hope for controlling metastasis. Conservative treatment is the priority in the treatment of endometrial cancer. PDT is a therapy that does not leave fibrosis and scars. It can be applied cyclically because it does not damage DNA. Due to the photosensitizers used, which combine with the mitochondria, it is these cellular organelles that are destroyed under the influence of light of the appropriate wavelength. Damage to the tumor vessels leads to its hypoxia. The result is necrosis and apoptosis of cancer cells. The main advantage of PDT is the effect of action mainly in the area of the disease focus.

Authors' contributions

Aleksandra Żołyniak-Brzuchacz: Validation, Writing—Review; Edyta Barnaś: Conceptualization, Methodology, Validation, Formal analysis, Writing—Original Draft, Visualization, Writing—Review & Editing. David Aebisher: Conceptualization, Methodology, Validation, Writing—Review & Editing. Magdalena Szpunar: Investigation, Validation, Writing—Review & Editing. Klaudia Dynarowicz: Validation, Writing—Original Draft. Elżbieta Ostańska: Validation, Methodology, Resources. Dorota Bartusik-Aebisher: Conceptualization, Project administration, Validation, Writing—Original Draft. Joanna Skręt-Magierło: Conceptualization, Methodology, Resources. Tomasz Kluz: Formal analysis, Validation. The author(s) read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article

Declarations

Acknowledgements
Not applicable

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University of Rzeszów (protocol code of 9/05/2019, number 31/05/2019). Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

References

1. Braun E, Overbeek-Wager A, Grumbo RJ. Diagnosis and management of endometrial cancer. Am Fam Physician. 2016;93(6):468-474.

2. Jonusiene V, Sasnauskiene A. Notch and endometrial cancer. Adv Exp Med Biol. 2021;1287:47-57. doi: 10.1007/978-3-030-55031-8_4.

3. World Cancer Research Fund International. Endometrial cancer statistics. 2022. https://www.wcrf.org/cancer-trends/endometrial-cancer-statistics/ [Accessed March 25, 2022].

4. Martignetti JA, Pandya D, Nagarsheth N, Chen Y, Camacho O, Tomita S, Brodman M, Ascher-Walsh C, Kolev V, Cohen S, Harkins TT, Schadt EE, Reva B, Sebra R, Dottino P. Detection of endometrial precancer by a targeted gyne-cologic cancer liquid biopsy. Cold Spring Harb Mol. Case Stud. 2018;4(6). doi: 10.1101/mcs.a003269.

5. Aoki Y, Kanao H, Wang X, Yunokawa M, Omatsu K, Fusegi A, Takeshima N. Adjuvant treatment of endometrial cancer today. Jpn J Clin Oncol. 2020;50(7): 753-765. doi: 10.1093/jjco/hyaa071.

6. Imboden S, Tapia C, Scheiwiller N, Kocbek V, Altermatt HJ, Janzen J, Mueller MD, McKinnon B. Early-stage en-dometrial cancer, CTNNB1 mutations, and the relation between lymphovascular space invasion and recurrence. Acta Obstet Gynecol Scand. 2020;99(2):196-203. doi: 10.1111/aogs.13740.

7. Bao W, Zhang Y, Li S, Fan Q, Qiu M, Wang Y, Li Y, Ji X, Yang Y, Sang Z, Xu W, Yang Y, Wu S, Zhu Y. miR 107 5p promotes tumor proliferation and invasion by targeting estrogen receptor α in endometrial carcinoma. Oncol Rep. 2019;41(3):1575-1585. doi: 10.3892/or.2018.6936.

8. Van den Heerik ASVM, Horeweg N, de Boer SM, Bosse T, Creutzberg CL. Adjuvant therapy for endometrial cancer in the era of molecular classification: radiotherapy, chemoradiation and novel targets for therapy. Int J Gynecol Cancer. 2021;31:594-604. doi: 10.1136/ijgc-2020-001822.

9. Zhang S, Gong TT, Liu FH, Jiang YT, Sun H, Ma XX, Zhao YH, Wu QJ. Global, regional and national burden of endometrial cancer, 1990-2017: results from the global burden of disease study, 2017. Front oncol. 2019;9:1440. doi: 10.3389/fonc.2019.01440.

10. Kitchener H. Management of endometrial cancer. Eur J Surg Oncol. 2006;32(8):838-843. doi: 10.1016/j.ejso.2006.03.046.

11. Park JY, Nam JH. Progestins in the fertility- sparing treatment and retreatment of patients with primary and recurrent endometrial cancer. Oncologist. 2015;20(3):270-278. doi: 10.1634/theoncologist.2013-0445.

12. Passarello K, Kurian S, Villanueva V. Endometrial cancer: an overview of pathophysiology, management and care. Semin Oncol Nurs. 2019;35(2):157-165. doi: 10.1016/j.soncn.2019.02.002

13. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016;387(10023):1094-1108. doi: 10.1016/S0140-6736(15)00130-0.

14. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of endometrial cancer risk with postmenopausal bleeding in Women: a systematic review and meta-analysis. JAMA Intern Med. 2018;178(9):1210-1222. doi: 10.1001/jamainternmed.2018.2820.

15. Trojano G, Olivieri C, Tinelli R, Damiani GR, Pellegrino A, Cicinelli E. Conservative treatment in early stage endo-metrial cancer: a review. Acta Biomed. 2019;90(4):405-410. doi: 10.23750/abm.v90i4.7800.

16. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol. 2014;15(7):e268-e278. doi: 10.1016/S1470-2045(13)70591-6.

17. Sherman ME, Sturgeon S, Brinton LA, Potischman N, Kurman RJ, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD. Risk factors and hormone levels in patients with serous and endometrioid uterine carcinomas. Mod. Pathol. 1997;10(10):963–968.

18. Yang HP, Wentzensen N, Trabert B, Gierach GL, Felix AS, Gunter MJ, Hollenbeck A, Park Y, Sherman ME, Brinton LA. Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP Diet and Health Study. Am J Epidemiol. 2013;177(2):142-51. doi: 10.1093/aje/kws200.

19. Vitale SG, Valenti G, Gulino FA, Cignini P, Biondi A. Surgical treatment of high stage endometrial cancer: current perspectives. Updates Surg. 2016;68(2):149-154. doi: 10.1007/s13304-015-0340-1.

20. Schildkraut JM. Endometrial cancer. Gynecol Oncol. 2011;120(2):165-166. doi: 10.1016/j.ygyno.2011.01.001.

21. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005;366(9484):491-505. doi: 10.1016/S0140-6736(05)67063-8.

22. Rizzo S, Femia M, Buscarino V, Franchi D, Garbi A, Zanagnolo V, Del Grande M, Manganaro L, Alessi S, Giannitto C, Ruju F, Bellomi M. Endometrial cancer: an overview of novelties in treatment and related imaging keypoints for local staging. Cancer Imaging. 2018;18(1):45. doi: 10.1186/s40644-018-0180-6.

23. Sonoda Y, Barakat RR. Screening and the prevention of gynecologic cancer: endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2006;20(2):363-377. doi: 10.1016/j.bpobgyn.2005.10.015.

24. Briki R, Cherif O, Bannour B, Hidar S, Boughizane S, Khairi H. Uncommon metastases of invasive lobular breast cancer to the endometrium: a report of two cases and review of the literature. Pan Afr Med J. 2018;30:268. doi: 10.11604/pamj.2018.30.268.16208.

25. Gaber C, Meza R, Ruterbusch JJ, Cote ML. Endometrial Cancer Trends by Race and Histology in the USA: Projecting the Number of New Cases from 2015 to 2040. J Racial Ethn. Health Disparities. 2016; doi: 10.1007/s40615-016-0292-2.

26. Sorosky JI. Endometrial cancer. Obstet Gynecol. 2012;120(2 Pt 1):383-397. doi: 10.1097/AOG.0b013e3182605bf1.

27. Allard JE, Maxwell GL. Race disparities between black and white women in the incidence, treatment, and prognosis of endometrial cancer. Cancer Control. 2009;16(1):53-56. doi: 10.1177/107327480901600108.

28. Vanderstraeten A, Tuyaerts S, Amant F. The immune system in the normal endometrium and implications for endometrial cancer development. J Reprod Immunol. 2015;109:7-16. doi: 10.1016/j.jri.2014.12.006.

29. Goebel EA, Vidal A, Matias-Guiu X, Blake Gilks C. The evolution of endometrial carcinoma classification through application of immunohistochemistry and molecular diagnostics: past, present and future. Virchows Arch. 2018;472(6):885-896. doi: 10.1016/j.jri.2014.12.006.

30. Nucci MR, Parra-Herran C. 17 - Metastatic and Miscellaneous Primary Neoplasms of the Ovary, A volume in Foundations in Diagnostic Pathology. Gynecologic Pathology (Second Edition). Elsevier. 2020;749-827.

31. Goldblum JR, Gilks B. “Uterus: Corpus” in Rosai and Ackerman's Surgical Pathology (Eleventh Edition). Elsevier. 2018;33:1294-1355.

32. Banerjee SM, El-Sheikh S, Malhotra A, Mosse CA, Parker S, Williams NR, MacRobert AJ, Hamoudi R, Bown SG, Keshtgar M. Photodynamic Therapy in Primary Breast Cancer. J Clin Med. 2020;9(2):483. doi: 10.3390/jcm9020483.

33. Gunaydin G, Gedik ME, Ayan S. Photodynamic Therapy - Current Limitations and Novel Approaches. Front Chem. 2021;9:691697. doi: 10.3389/fchem.2021.691697

34. Correia-Barros G, Serambeque B, Carvalho MJ, Marto CM, Pineiro M, Pinho E, Melo T, Botelho MF, Laranjo M. Applications of Photodynamic Therapy in Endometrial Diseases. Bioengineering (Basel) 2022;9(5):226. doi: 10.3390/bioengineering9050226.

35. Koren H, Alth G. Photodynamic therapy in gynaecologic cancer, J Photochem Photobiol B 1996;36(2):189-191. doi: 10.1016/s1011-1344(96)07370-8.

36. Kennedy JC, Marcus SL, Pottier RH. Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results. J Clin Laser Med Surg. 1996;14(5):289-304. doi: 10.1089/clm.1996.14.289.

37. Jourdain O, Joyeux P, Lajus C, Sfaxi I, Harle T, Roux D, Dallay D. Endometrial Nd-YAG laser ablation by hysterofibroscopy: long-term results of 137 cases, Eur J Obstet Gynecol Reprod Biol. 1996;69(2):103-107.

38. Wyss P, Degen A, Caduff R, Hornung R, Haller U, Fehr M. Fluorescence hysteroscopy using 5-aminolevulinic: a descriptive study, Lasers Surg Med. 2003;33(3):209-212. doi: 10.1002/lsm.10210.

39. Mhawech P, Renaud A, Sene C, Lüdicke F, Herrmann F, Szalay-Quinodoz I, van den Bergh H, Major AL. High efficacy of photodynamic therapy on rat endometrium after systematic administration of benzoporphyrin derivative monoacid ring A. Hum Reprod. 2003;18(8):1707-1711. doi: 10.1093/humrep/deg341.

40. Fehr MK, Tromberg BJ, Svaasand LO, Ngo P, Berns MW, Tadir Y. Structural and functional effects of endometrial photodynamic therapy in a rat model. Am J Obstet Gynecol. 1996;175(1):115-121. doi: 10.1016/s0002-9378(96)70260-0.

41. Wyss P, Caduff R, Tadir Y, Degen A, Wagnières G, Schwarz V, Haller U, Fehr M. Photodynamic endometrial ablation: morphological study. Lasers Surg Med. 2003;32(4):305-309. doi: 10.1002/lsm.10163.

42. Won S, Kim MK, Seong SJ. Fertility- sparing treatment in women with endometrial cancer. Clin Exp Reprod Med. 2020;47 (4):237-244. doi: 10.5653/cerm.2020.03629.

43. Choi MC, Jung SG, Park H, Cho YH, Lee C, Kim SJ. Fertility preservation via photodynamic therapy in young patients with early-stage uterine endometrial cancer: a long-term follow-up study. Int J Gynecol. Cancer. 2013;23(4):698-704. doi: 10.1097/IGC.0b013e31828b5ba2.

44. Steiner RA, Tadir Y, Tromberg BJ, Krasieva T, Ghazains AT, Wyss P, Berns MW. Photosensitization of the rat endometrium following 5-aminolevulinic acid induced photodynamic therapy. Lasers Surg Med. 1996;18(3):301-308. doi: 10.1002/(SICI)1096-9101(1996)18:3<301::AID-LSM12>3.0.CO;2-8.

45. Suzuki-Kakisaka H, Murakami T, Hirano T, Terada Y, Yaegashi N, Okamura K. Effects of photodynamic therapy using 5-aminolevulinic acid on cultured human adenomyosis- derived cells. Fertil Steril. 2007;87(1):33-38. doi: 10.1016/j.fertnstert.2006.11.066.

46. Gannon MJ, Johnson N, Roberts DJ, Holroyd JA, Vernon DI, Brown SB, Lilford RJ. Photosensitization of the endometrium with topical 5-aminolevulinic acid. Am J Obstet Gynecol. 1995;173(6):1826-1828. doi: 10.1016/0002-9378(95)90435-2.

47. Raab GH, Schneider AF, Eiermann W, Gottschalk-Deponte H, Baumgartner R, Beyer W. Response of human endometrium and ovarian carcinoma cell-lines to photodynamic therapy. Arch Gynecol Obstet. 1990;248(1):13-20. doi: 10.1007/BF02389584.

48. Wustrow TP, Jocham D, Schramm A, Unsöld E. Photodynamic destruction of in vitro cultivated squamous cell carcinoma cells of the head and neck area. Laryngol Rhinol Otol (Stuttg). 1988;67(10):532-538.

49. Kim SM, Rhee YH, Kim JS. The anticancer effects of radachlorin-mediated photodynamic therapy in the human endometrial adenocarcinoma cell line HEC-1-A. Anticancer Res. 2017;37(11): 6251-6258. doi: 10.21873/anticanres.12076.

50. Schneider-Yin X, Kurmanaviciene A, Roth M, Roos M, Fedier A, Minder EI, Walt H. Hypericin and 5-aminolevulinic acid-induced protoporphyrin IX induce enhanced phototoxicity in human endometrial cancer cells with non-coherent white light. Photodiagnosis Photodyn Ther. 2009;6(1):12-28. doi: 10.1016/j.pdpdt.2009.02.001.

51. Abrahamse H, Hamblin MR. New photosensitizers for photodynamic therapy. Biochem J. 2016;473(4):347-364. doi:10.1042/BJ20150942.

52. Wyss P, Tromberg BJ, Wyss MT, Krasieva T, Schell M. Photodynamic destruction of endometrial tissue with topical 5-aminolevulinic acid in rats and rabbits. Am J Obstet Gynecol. 1994;171(5):1176-1183. doi:10.1016/0002-9378(94)90128-7.

53. Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, Hahn SM, Hamblin MR, Juzeniene A, Kessel D, Korbelik M, Moan J, Mroz P, Nowis D, Piette J, Wilson BC, Golab J.

Photodynamic therapy of cancer: an update. CA Cancer J Clin. 2011;61(4):250-81. doi: 10.3322/caac.20114.

54. Debele TA, Peng S, Tsai HC. Drug Carrier for Photodynamic Cancer Therapy. Int J Mol Sci. 2015;16(9):22094-22136. doi: 10.3390/ijms160922094.

55. Moret F, Reddi E. Strategies for optimizing the delivery to tumors of macrocyclic photosensitizers used in photodynamic therapy (PDT). J Porphyr Phthalocyanines. 2017;21:239–256. doi: 10.1142/S1088424617300014.

56. Allison RR, Sibata CH. Oncologic photodynamic therapy photosensitizers: a clinical review. Photodiagnosis Photodyn Ther. 2010;7(2):61-75. doi: 10.1016/j.pdpdt.2010.02.001.

57. Halili F, Arboleda A, Durkee H, Taneja M, Miller D, Alawa KA, Aguilar MC, Amescua G, Flynn HW Jr, Parel JM. Rose Bengal- and Riboflavin-Mediated Photodynamic Therapy to Inhibit Methicillin-Resistant Staphylococcus aureus Keratitis Isolates. Am J Ophthalmol. 2016;166:194-202. doi: 10.1016/j.ajo.2016.03.014.

58. Alsaab HO, Alghamdi MS, Alotaibi AS, Alzhrani R, Alwuthaynani F, Althobaiti YS, Almalki AH, Sau S, Iyer AK. Progress in Clinical Trials of Photodynamic Therapy for Solid Tumors and the Role of Nanomedicine. Cancers (Basel). 2020;12(10):2793. doi: 10.3390/cancers12102793.

59. Shi H, Sadler PJ. How promising is phototherapy for cancer?. Br J Cancer. 2020;123(6), 871–873. doi: 10.1038/s41416-020-0926-3.

60. McMeekin DS. Where is the future of endometrial cancer therapy? Ann Oncol. 2009;20(11), 1757-1761. doi: 10.1093/annonc/mdp493.

61. Kawczyk-Krupka A, Bartusik-Aebisher D, Latos W, Cieślar G, Sieroń K, Kwiatek S, Oleś P, Kwiatek B, Aebisher D, Krupka M, Wiench R, Skaba D, Olek M, Kasperski J, Czuba Z, Sieroń A. Clinical trials and basic research in photo-dynamic diagnostics and therapies from the center for laser diagnostics and therapy in Poland. Photochem Photobiol. 2020;96(3):539-549. doi: 10.1111/php.13243.

62. Nkune NW, Kruger CA, Abrahamse H. Possible enhancement of photodynamic therapy (PDT) colorectal cancer treatment when combined with cannabidiol, Anticancer Agents Med Chem. 2021;21(2):137-148. doi: 10.2174/1871520620666200415102321.

63. Zhang Q, Li L. Photodynamic combinational therapy in cancer treatment. J BUON. 2018;23(3):561-567.

64. Juarranz A, Jaén P, Sanz-Rodríguez F, Cuevas J, González S. Photodynamic therapy of cancer. Basic principles and applications. Clin Transl Oncol. 2008;10(3):148-154. doi: 10.1007/s12094-008-0172-2.

65. Matoba Y, Banno K, Kisu I, Aoki D. Clinical application of photodynamic diagnosis and photodynamic therapy for gynecologic malignant diseases: a review. Photodiagnosis Photodyn Ther. 2018;24:52-57. doi: 10.1016/j.pdpdt.2018.08.014.

66. Zuluaga MF, Lange N. Combination of photodynamic therapy with anti-cancer agents. Curr Med Chem. 2008;15(17):1655-1673. doi: 10.2174/092986708784872401.