# Novel Targeted Therapeutic Approaches to Cancers

Editör: Dr. Asiye Gök Yurttaş

ÖZGÜR YAYINLARI

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# Novel Targeted Therapeutic Approaches to Cancers

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ÖZGÜR YAYINLARI

# *Ön Söz*

Kanser, modern toplumun en yaygın ve korkulan hastalıklarından biridir. Son yıllarda insidansı giderek artmaktadır. Kanserin moleküler özelliklerinin anlaşılmaya başlamasıyla birlikte çalışmalar hedefe yönelik tedaviler üzerine yoğunlaşmıştır. Bu kitabın amacı ise kanserlere yeni hedefli terapötik yaklaşimlara ilişkin literatürü analiz etmektir. Bu kitap temel bilim, kanserlere özgü moleküler yaklaşımlar ve sinyal yolakları, hedefli ilaçlar, klinik araştırmalar ve psikoterapi gibi alanları kapsamaktadır. Kanser veya çoklu stres tepkileri birçok insan, hayvan ve bitki hastalığının altında yatmaktadır ve bu da kitap içeriğimizin önemli bir bileşenini oluşturmaktadır. Bu kitabın konu yelpazesi, kanserle ilişkili hastalıklar dünya çapında hızla ilerledikçe büyük bir güncelliğe sahip olacaktır.

Dr. Asiye Gök Yurttaş

# *Preface*

Cancer is one of the most common and feared diseases of modern society. In recent years, its incidence has been gradually increasing. Studies have concentrated on targeted therapy as a result of the understanding of the molecular characteristics of cancer. The aim of this book is to analyze the literature on new targeted therapeutic approaches to cancers. This book covers areas such as basic science, cancer-specific molecular approaches and signaling pathway, targeted drugs, clinical trials and psychotherapy. Cancer, or multiple stress responses, underlie many human, animal, and plant diseases, and this is an important component of our book content. The range of topics of this book will have a great deal of relevance as cancer-related diseases progress rapidly in the world's environment.

Asiye Gök Yurttaş, Ph.D

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Chapter 3

# Photodyanamic Therapy in the Cervical Cancer

**Asiye Gök Yurttaş**[1]

**Abstract**

Cancer is one of the most common and feared illnesses in modern society. Its prevalence has been gradually rising in recent years. The fourth most common malignancy in women worldwide is cervical cancer (CC). Surgery, chemotherapy, and radiotherapy are examples of conventional treatments, but they are invasive and have negative side effects. In addition, metastasis is observed in roughly 70% of individuals with late-stage CC due to limits and treatment resistance. In addition to treating primary CC, photodynamic therapy (PDT) is an alternate CC treatment strategy that has been clinically shown to reduce subsequent metastasis. Because PDT is a non-invasive focused treatment with less adverse effects and reduced resistance to dose repetitions, it is believed to be much more beneficial. This review study's objective is to examine the studies on PDT's efficacy in treating cervical cancer.

## INTRODUCTION

An international health issue is cervical cancer (CC). Cervical cancer (CC) is one of the most prevalent oncological conditions nowadays and a significant public health issue. In most countries, this sickness is the main reason why women die [1].

The International Organization for Research on Cancer estimates that there were 603,863 new cases of cervical cancer worldwide in 2020, of which 341,680 were fatal [2]. The 5-year survival rate for cervical cancer patients in various nations varies from 37% to 77% in 2020 [3]. The disease's stage, the occurrence of relapses, and the development of tumor metastases all play a significant role in the suggested treatment modalities [4]. Epidemiology research on cervical cancer has revealed a 12.66% increase in cases over

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the past ten years [5]. With specific goals for the years 2020–2030, the World Health Organization (WHO) developed a draft worldwide strategy to hasten the elimination of the CC in 2019. 90, 70, and 90 key points make up the overview, according to the WHO worldwide plan. HPV is the primary factor in the emergence of CC [6]. By the age of 15, 90% of girls should have had the HPV vaccine in its entirety. Around 35 and 45 years old, 70% of women should have another high performance test screening. For disorders characterized by cervical malignant diseases, 90% of women should obtain treatment. Conventional CC treatments such radiation, chemotherapy, and surgical excision are intrusive and have negative side effects [7]. Despite increasing developments, metastasis affects 70% of patients with late-stage CC because of the limitations of all surgical excision procedures and the resistance of cervical cancer stem cell (CCSC) to repeated therapies [8, 9]. As a result, the research is needed to develop alternate treatment combinations. PDT is an alternate therapeutic approach that has the potential to both prevent secondary metastasis of CCSC and provides clinical evidence for the initial eradication of CC [10]. Furthermore, PDT is known to be a highly targeted, non-invasive, localized treatment with less side effects, quicker recovery times, and lower resistance to repeated dosage treatments when compared to traditional treatments [11]. Recent clinical trials [12,13] have shown that PDT therapy utilizing 5-aminolevulinic acid (ALA) is an effective and well-tolerated therapeutic option for CC. These clinical trials still need to be improved in order to investigate the use of cutting-edge PDT therapy to trigger particular immune responses and entirely stop CC secondary migration [14].

**Cervical cancer**

Human papillomavirus (HPV) infection is frequently linked to cervical carcinoma (CC) (HPV). The HPV family which includes more than 200 distinct DNA viruses, can be split into subgroups with low and high infection risk [15]. 99% of occurrences of cervical cancer are caused by high-risk HPV, the most common of which being HPV-16 [16].

The results revealed that HPV is the primary cause of cervical cancer; thus, while other risk factors may raise the likelihood of developing cervical cancer, this particular type of cancer cannot arise in the absence of HPV [17]. The three kinds of possible cofactors in the pathogenesis of cervical cancer include host risk factors, viral risk factors, and environmental risk factors. Hormonal birth control, smoking, and sexual activity are all environmental risk factors [18-20]. A history of HPV infection with several strains, viral load, and integration of various viruses are all viral risk

factors [21]. Endogenous hormones, genetically associated variables and essentially any element that may influence the immune system response are all considered hosts risk factors [22].

CC is a cancerous type of tumor that develops in the cervix. Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the two subtypes recognized histologically (SCC) [23]. The formation rate of SCC is almost 70% higher than that of AC [23]. Women are frequently diagnosed with CC all over the world, but mainly in low- and middle-income nations like South Africa, India, China, and Brazil. In 2020, a total of 604,127 new cases of CC were reported worldwide, of which 341 831 resulted in death [24].

Re-infection with cervical cancer is conceivable as a result of the existence of HPV in the vaginal mucosa, which is necessary for the virus' resistant persistence [25]. Thus, the discovery of therapeutic approaches that enable the eradication of the virus from all genital tract mucosal surfaces where HPV is found represents the primary challenge. It is not possible to simultaneously destroy and/or ablate relatively large areas on the surface of the cervix, vagina, and vulva due to the risk of infection at these anatomical locations. The benefit of PDT is the ability to eradicate HPV in all localizations. A non-invasive alternative approach for treating cancer is photodynamic therapy (PDT). PDT is effective in getting rid of HPV. Squamous intraepithelial lesions and cervical cancer recurrence are primarily caused by HPV persistence. According to studies, HPV persistence accounts for 40% of recurrences following surgery [26]. There was no discernible change in the incidence of recurrence following surgery in the 5-year follow-up trial. It has been demonstrated that surgical methods cannot completely eradicate HPV [26, 27].

Lack of access to medical care for successful treatment plans, public awareness, smoking, oral contraceptive use, and HIV co-infections are additional variables that may affect the overall incidence rate of CC. Atypical vaginal discharge, vaginal bleeding (especially after intercourse), pelvic discharge, and pain following intercourse are typical signs and symptoms of CC [23]. It is expected that 11 million women would be diagnosed with CC in the next 10 to 20 years, necessitating greater study into early diagnosis and therapies [23].

**Cervical Cancer Stages and Treatments**

There are four stages of CC: stage I, where the cancer is limited to the cervix; stage II, where the cancer has spread to the upper two-thirds of the vagina or to the tissue surrounding the uterus; and stage IV, where the

cancer has extended to the lower two-thirds of the vagina. Stage III cancers have spread to the lower third of the vaginal or pelvic wall, as well as to the kidneys, lymph nodes, or both; Stage IV refers to cancer that has spread outside of the pelvis or to the lining of the bladder, rectum, or other bodily areas [28].

Surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy are the currently available 5 standard kinds of conventional treatment for CC.

The stage of the CC at the time of diagnosis determines the type of treatment used alone or in combination [29]. Conization or internal radiation therapy, as well as a total or partial hysterectomy, are surgical procedures used to treat stage 1 CC. [29]. Following a combination radical hysterectomy and excision of the pelvic lymph nodes in stage II CC, radiation and chemotherapy are frequently taken into consideration. Treatments for stage III CC include low-level chemotherapy with fol excision of the pelvic lymph nodes and combination radiation and chemotherapy. The tumor is then reduced with internal radiation therapy before a complete surgical hysterectomy [29]. Chemotherapy and radiation therapy may be used as palliative care in stage IV colorectal cancer to relieve discomfort and recurrent cancer symptoms [29]. Nonetheless, concentrated immunotherapies or clinical trials of severe surgical pelvic exenteration may be additional viable treatment options for stage IV CC.

The long- and short-term adverse effects of these conventional therapy techniques are significant, notwithstanding their promise. Surgery is extremely invasive and uncomfortable at any stage of CC [28]. It is well recognized that radiation therapy damages normal, healthy cells' DNA unintentionally, impairing their ability to repair and causing irreversible harm. Similar to how chemotherapy is poisonous to healthy tissues, it has immediate adverse effects include hair loss, nausea, vomiting, diarrhea, coughing, swollen legs, and weight loss [30]. Radiation or chemotherapy can have long-term adverse effects, such as persistent leg, back, or stomach pain, trouble urinating, and fatigue [30]. Also, new therapeutic options like targeted immunotherapies are still being tested in clinical settings, so it is unclear how effective they will be in the long run.

The early diagnosis of CC is still very poor, and CC in women frequently goes misdiagnosed until the late stages due to a lack of health and education facilities (particularly in developing nations), asymptomatic patients, and poor diagnostic pap test accuracy [31]. 38% of CC patients are diagnosed at stage III or IV, compared to 44% of those that are detected at stage II [31].

As a result, one of the top main examples is Advanced CC. Inadequate early detection, a lack of effective treatment regimens brought on by treatment resistance, and recurrence are the main contributors to cancer-related mortality in low- and middle-income countries.

**Alternative Photodynamic Therapy for the Treatment of Cervical Cancer**

Surgery, radiation therapy, and chemotherapy are all part of the standard anticancer treatment for colorectal cancer (CC), yet they all have drawbacks [32].

Damage to normal tissues, structural deformations, scarring, hyperpigmentation, and systemic adverse effects are all possible complications following surgery or radiation therapy. Moreover, the use of traditional medicines may result in multidrug resistance, which could result in treatment failure and illness recurrence. Many therapy strategies have been proposed to lessen toxicity and reduce side effects. The systematic exploration has recently begun to focus on non-traditional therapies that can effectively cure CC while reducing the invasiveness, unpleasant side effects, recurrence rate and metastasis of conventional therapies.

Photodynamic therapy (PDT) is a tried-and-true alternative treatment method for curing primary CC and eliminating CCSC to halt secondary metastases [10]. Since PDT is a highly targeted, non-invasive, localized treatment with few side effects, a speedy recovery, and no aftereffects, it has numerous advantages over conventional therapies. Due to the fact that PDT enables women to keep their fertility, it can also be viewed as an alternate kind of treatment for patients. Because patients' infertility is frequently brought on by surgery, chemotherapy, and radiation therapy [10]. A light-sensitive substance (photosensitizer, PS) is systemically applied as part of the treatment, and after that, the patient is exposed to a light source with a specific wavelength. Targeted cell death results from the oxidative damage caused by this [33]. Three essential elements—PS (topically or systemically viable), light (often generated by laser sources), and molecular oxygen—are necessary for PDT activity. PS preferentially accumulates in malignant tissue. It is triggered by local illumination of the lesion with visible light calibrated to activate the PS; this results in cell death [34]. In tumor tissues, PS has minimal accumulations. They are promptly expelled from the body or the target tissue after a brief time in the bloodstream. Penetration and retention into tissues significantly increase when administered in precisely designed nanoparticle compositions [35,36]. This is as a result of better

photosensitizer targeting and defense [37,38]. A therapeutic strategy utilizing photosensitizers with nanoparticles and light activation could potentially go beyond the restrictions of photodynamic therapy for the treatment of carcinomas in light of these processes [39].

**Mechanism of Action of PDT for the Treatment of Cervical Cancer**

In PDT procedures, a patient is given a light-stimulating photosensitizer (PS), also called a photosensitizer [40]. We give the patient's body enough time for the PS to disperse. A PS can passively and specifically accumulate in tumor cells due to the enhanced permeability and retention effect (EPR) that cancer cells have [12]. A laser source is used to apply irradiation of a specific wavelength to the localized tumor in the patient's cervical region during hysteroscopy when selective accumulation of PS develops. Red laser stimulation causes localized tumor PS to transition from its single baseline state to an induced triple state [40]. Reactive oxygen species (ROS) and other free radicals are produced in the type I reaction when PS in the excited ternary state combines with biomolecules, molecular oxygen, and water in the vicinity of tumor cells [40]. In type II reactions, excited triple state PS and excited triple state oxygen ($^3O_2$) combine to form reactive single oxygen ($^1O_2$).

Oxidative stress caused by the production of cytotoxic ROS and $^1O_2$ free radical species causes cell death by necrosis or apoptosis in primary and secondary CC tumor cells [40]. These types of cell death, which are triggered by oxidative stress in tumor cells, kill a primary CC tumor by destroying a variety of internal biomolecules, such as DNA, proteins, and ligands.

PDT causes DNA damage and oxidative stress in cancer cells by inducing apoptosis and autophagy [41]. A type of programmed cell death known as apoptosis is brought on by excessive or insufficient stimulation for cell growth, proliferation, and even cell damage [42]. An intracellular catabolic degradative process is called autophagy. As a result of oxidative stress, protein recycling occurs and aids in cancer cell survival as well as programmed cell death [43]. Recent research has revealed that apoptosis and autophagy frequently take place in the same cell. Both types of cell death can be brought on simultaneously by the ROS produced by PDT [44,45]. This particular PDT treatment may also cause other anticancer immune reactions, which could damage the vascular system of the tumor. CCSC removal should be increased to prevent secondary spread [10].

PDT produces hemostasis, artery narrowing and breakdown when it targets a tumor's vascular nature. This reduces the amount of oxygen and

nutrients that a tumor receives, assisting in the main and secondary CCSC breakdown [10]. As a result, CC PDT treatment can force the destruction of localized tumor tissue as well as crucial anti-tumor responses and an acute inflammatory process. Both of that assist eradicate primary CC and stop its secondary spread.

**Recent PDT Clinical Studies for the Treatment of Cervical Cancer**

The PS deposition in the afflicted tissue and singlet oxygen quantum yield are the two main factors that determine PDT's effectiveness. Moreover, PS has a significant impact on the drug's pharmacodynamics and pharmaceutical cokinetics [46]. For usage in PDT, porphyrins, chlorines, bacteriochlorolines and phthalocyanins have all been thoroughly investigated. Clinical approval has been granted to a number of substances [47, 48]. Bacteriochlorophyll derivatives with strong absorption in the long wavelength portion of the spectrum have lately been investigated for the treatment of big or deep-seated cancers [49]. Many experimental research has been carried out to investigate the tissues and cellular targets of PS as well as its methods of action [50, 51].

During PDT, targeted and microencapsulated delivery of cytotoxic and antibacterial drugs enhances cancer therapy outcomes. Poor encapsulation and insufficient medication dose frequently thwart the success of this technology. Thus, it is crucial to create novel, trustworthy microencapsulated dosage forms that have a high level of therapeutic efficacy. 168 randomized clinical studies for the treatment of PDT in CC were conducted in 2018, according to a comprehensive review by Zhang et al. [52].

The remission rate of patients was reported to have increased greatly by PDT by 82%, although it was emphasized that additional clinical research is required to identify the PS that is the most efficient and least hazardous. One of the important studies referenced in this review said that PS (Photofrin®) PDT successfully treated 50 early-stage CC patients with a 95% improvement, however the patients also suffered unfavorable photosensitivity and inflammation. In clinical situations where CC metastasizes, researchers have also proposed that combination chemo-PDT is required [52,53]. In contrast, the researchers looked into PDT treatment using the strong FDA-approved prodrug hexaminolevulinate (HAL) in 56 CC patients. They found that 90% of the patients had a full response to treatment with no recurrence, progression and/or lesions 2 years after treatment [54]. Most recently, researchers reported 45 patients had effective PDT for CC using Photoditazine® and PhotolonTM, and 86% of those patients did not experience a relapse 5 years following treatment [11].

However, when using FDA-approved ALA as PS in the treatment of PDT in the most notable and final preclinical CC patient, researchers found that there was minimal morbidity, a low incidence of side effects, and a 94.81% remission rate after a year of treatment [55,56]. Scientists also observed that PDT utilizing ALA in clinical phase trials has emerged as the most efficient and risk-free therapy option for the current control of CC. Prior to this medication being made available to the public health system, more research is required due to the constraints of reducing secondary spread [12,13].

**Limitations and Future of PDT for Cervical Cancer Treatment**

Low-dose PDT regimens may allow CC tumor survival and may also produce anti-tumor immunity, but medium-dose PDT therapy may induce positive apoptotic tumor cell death and cause necrotic tumor ablation of high-dose PDT, according to clinical and preclinical CC PDT studies [55, 56].

Consequently, to control the local main tumor and achieve immunosuppression of secondary spread to CCSC, moderate-to-high-dose PDT is typically needed in the treatment of CC. Overall, mounting data point to CC PDT's success being based on its ability to affect tumor-host interactions while tipping the scales in favor of the activation of specific immune responses and vascular closure to halt cancer dissemination. Therefore, additional research is needed to determine how to achieve controlled high dosing, immune responses that can completely stop secondary spread and clinical trial phases with improved light sources to induce deep tissue phototoxicity and limited skin photosensitivity in comparison to CC PDT [14]. There is still space for improvement, according to additional preclinical investigations despite the fact that the most recent clinical trials have shown the huge potential of CC PDT [57]. In a more recent study, combined PDT therapy suggested methods that need further study to be fully effective in CC [57]. According to some recent combination studies, PDT for colorectal and breast cancer has been shown to be effective when combined with cannabidiol (CBD) which also inhibits migration for the main cell cancer development ablation and secondary spread [58-60].

**Conclusion**

CC is one of the most successfully treatable types of cancer when the disease is detected at an early stage. Thus, it is crucial to create efficient substitute therapies that may cure HPV-related squamous intraepithelial lesions of cervical cancer and preinvasive cervical cancer without endangering the patient's fertility. The major conclusions from this analysis

are that conventional CC treatments such surgical excision, chemotherapy, and radiotherapy are invasive and have adverse side effects [7]. Due to the constraints of surgical excision and CCSC resistance to recurrent radiation and chemotherapy, over 70% of late-stage patients still experience recurrence or metastasis despite advancements in standard CC treatments [8, 9]. As a result, there is a critical need to investigate alternate therapeutic pairings.

PDT is a complementary cancer therapy that has been shown to treat primary CC while also removing CCSC to stop secondary metastases [10]. PDT is a far more beneficial treatment for CC since it is highly targeted, non-invasive, localized, has few side effects, heals quickly without leaving scars, and is also acceptable for repeated dosing with little to no resistance [11]. According to certain studies, PDT, which is employed as PS and is reported by ALA (5-aminolevulinic acid), has emerged as the most efficient and risk-free therapy method for the current control of CC. However, additional research must be conducted before this drug may be offered [12,13]. Moreover, the most recent CC PDT clinical trials have demonstrated remarkable promise, suggesting that additional preclinical trials can still be developed [57]. The investigation of controlled high dosing, light source transmission to induce deep tissue phototoxicity with limited skin photosensitivity and advanced studies aimed at inducing particular immune responses to completely eradicate secondary propagation are just a few examples of these CC PDT clinical trials improvements [14].

This awareness has pushed research on CC PDT and conventional medicines to the fore to examine these synergistic therapies that enable the targeting of numerous cell death pathways. In order to stop primary tumor growth and fight secondary metastasis, this synergistic treatment will stimulate host immune responses. The application of PDT aids in the successful treatment of pathological foci on the mucous membrane of the cervix; the method's efficacy and safety are guaranteed by its selective action on the tissues [61,62]. PDT provides for the preservation of the normal anatomical and functional aspects of the cervix because normal surrounding tissues are not destroyed during treatment, there are no obvious scars, and there is no cervical canal stenosis. PDT enables the preservation of the normal anatomical and functional aspects of the cervix while using the procedure without causing any harm to the surrounding healthy tissues.

## References

[1]. Cohen P. A. et al. Cervical cancer. Lancet, 2019, vol. 393, no. 10167, pp. 169–182. doi: org/10.1016/S0140–6736 (18)32470-X

[2]. SungH. et al. Global cancer statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021, vol. 71, no. 3, pp. 209–249. doi: 10.3322/caac.21660.

[3]. https://gco.iarc.fr/

[4]. https://guidelines.esgo.org/cervical-cancer/guidelines/recommendations/

[5] International Agency for Research on Cancer [Internet]. GLOBOCAN 2020. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-ut eri-fact-sheet.pdf.

[6] R. Jonsson, The Nobel prize in physiology or medicine for 2008. In Scandinavian, Journal of Immunology (Vol. 68, Issue 6, (2008) 553.

[7]. Yang L, Shi P, Zhao G, et al. Targeting cancer stem cell pathways for cancer therapy. Signal Transduct Target Ther. 2020;5:8.

[8]. Chao X, Song X, Wu H, You Y, Wu M, Li L. Selection of treatment regimens for recurrent cervical cancer. Front Oncol. 2021;11:618485.

[9]. Mousavi H SR, Bannazadeh Baghi N H, Signaling pathways in cervical cancer chemoresistance: are microRNAsand long-noncoding RNAs the main culprits? Preprints. 2020;2020040294. doi: 10.20944/preprints202004.0294.v1.

[10]. Chizenga EP, Chandran R, Abrahamse H. Photodynamic therapy of cervical cancer by eradication of cervical cancer cells and cervical cancer stem cells. Oncotarget. 2019;10:4380-4396.

[11]. Ivanova VA, Verenikina EV, Nikitina VP, et al. Photodynamic therapy for preinvasive cervical cancer. J Clin Oncol. 2020;38:6035-6035.

[12]. Afanasiev M, Dushkin A, Grishacheva T, et al. The multi-course approach of photodynamic therapy to treat invasive cervical cancer IB2: a case report. Case Rep Oncol. 2021;14:506-519.

[13]. van Straten D, Mashayekhi V, de Bruijn HS, Oliveira S, Robinson DJ. Oncologic photodynamic therapy: basic principles, current clinical status and future directions. Cancers. 2017;9:19.

[14]. Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. CA Cancer J Clin. 2011;61:250-281.

[15] S. Mittal, L. Banks, Molecular mechanisms underlying human papillomavirus E6 and E7 oncoprotein-induced cell transformation, Mutation research, Rev. Mutation Res. 772 (2017) 23–35.

[16] G. Boulet, C. Horvath, D. Vanden Broeck, S. Sahebali, J. Bogers, Human papillomavirus: E6 and E7 oncogenes, Int. J. Biochem. Cell Biol. 39 (11) (2007) 2006–2011.

[17] J.M.V. Walboomers, J. M. M, M.M. Manos, et al., Human papillomavirus is a necessary cause of invasive cervical cancer worldwide, J. Pathol. 189 (1999) 8.

[18] K. Torres-Poveda, I. Ruiz-Fraga, V. Madrid-Marina, M. Chavez, V. Richardson, High risk HPV infection prevalence and associated cofactors: a population-based study in female ISSSTE beneficiaries attending the HPV screening and early detection of cervical cancer program, BMC Cancer 19 (1) (2019) 1205.

[19] A. Nersesyan, R. Muradyan, M. Kundi, M. Fenech, C. Bolognesi, S. Knasmueller, Smoking causes induction of micronuclei and other nuclear anomalies in cervical cells, Int. J. Hyg. Environ. Health 226 (2020), 113492.

[20] Y. Itarat, C. Kietpeerakool, N. Jampathong, B. Chumworathayi, P. Kleebkaow, A. Aue-Aungkul, W. Nhokaew, Sexual behavior and infection with cervical human papillomavirus types 16 and 18, Int. J. Womens Health 11 (2019) 489–494.

[21] T. Malagon, K. Louvanto, A.V. Ramanakumar, A. Koushik, F. Coutlee, E.L. Franco, T. Biomarkers of Cervical Cancer Risk Study, Viral load of human papillomavirus types 16/18/31/33/45 as a predictor of cervical intraepithelial neoplasia and cancer by age, Gynecol. Oncol. 155 (2) (2019) 245–253.

[22] Y.T. Zeng, X.F. Liu, W.T. Yang, P.S. Zheng, REX1 promotes EMT-induced cell metastasis by activating the JAK2/STAT3-signaling pathway by targeting SOCS1 in cervical cancer, Oncogene 38 (43) (2019) 6940–6957.

[23]. Hull R, Mbele M, Makhafola T, et al. Cervical cancer in low and middle-income countries. Oncol Lett. 2020;20:2058-2074.

[24]. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-249.

[25]. Hoffman S. R. et al. Patterns of persistent HPV infection after treatment for cervical intraepithelial neoplasia (CIN): A systematic review, Int.J. Cancer, 2017, no. 141 (1), pp. 8–23. doi: 10.1002/ijc.30623

[26] M.T. Bruno, N. Cassaro, S. Garofalo, S. Boemi, HPV16 persistent infection and recurrent disease after LEEP, Virol. J. 16 (1) (2019) 148, https://doi.org/10.1186/ s12985-019-1252-3.

[27] G. Bogani, V. DI Donato, F. Sopracordevole, A. Ciavattini, A. Ghelardi, S. Lopez, Recurrence rate after loop electrosurgical excision procedure (LEEP) and laser conization: a 5-year follow-up study, Gynecol. Oncol. 159 (3) (2020) 636–641, https://doi.org/10.1016/j.ygyno.2020.08.025.

[28]. Tewari KS, Monk BJ. Evidence-based treatment paradigms for management of invasive cervical carcinoma. J Clin Oncol. 2019;37:2472-2489.

[29]. Finocchario-Kessler S, Wexler C, Maloba M, Mabachi N, Ndikum-Moffor F, Bukusi E. Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective. BMC Womens Health. 2016;16:29.

[30]. PDQ Adult Treatment Editorial Board. PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002. Accessed October 6, 2021. https://www.ncbi.nlm.nih.gov/books/NBK66058/.

[31]. Mumba JM, Kasonka L, Owiti OB, et al. Cervical cancer diagnosis and treatment delays in the developing world: Evidence from a hospital-based study in Zambia. Gynecol Oncol Rep. 2021;37:100784.

[32]. Guo W. et al. Recent Developments of Nanoparticles in the Treatment of Photodynamic Therapy for Cervical Cancer, Anticancer Agents Med Chem, 2019, vol. 19. No. 15, 1809–1819. doi: 10.2174/1871520619666190411121953

[33] G. Calixto, J. Bernegossi, B. Fonseca-Santos, M. Chorilli, Nanotechnology-based drug delivery systems for treatment of oral cancer: a review, Int. J. Nanomed. 9 (2014) 3719–3735.

[34] M. Wachowska, A. Muchowicz, J. Golab, Targeting Epigenetic Processes in Photodynamic Therapy-Induced Anticancer Immunity, Front. Oncol. 5 (2015) 176.

[35] Y.Y. Huang, S.K. Sharma, T. Dai, H. Chung, A. Yaroslavsky, M. Garcia-Diaz, J. Chang, L.Y. Chiang, M.R. Hamblin, Can nanotechnology potentiate photodynamic therapy? Nanotechnol. Rev. 1 (2) (2012) 111–146.

[36] G.M. Calixto, J. Bernegossi, L.M. de Freitas, C.R. Fontana, M. Chorilli, Nanotechnology-based drug delivery systems for photodynamic therapy of cancer: a review, Molecules 21 (3) (2016) 342.

[37] E. Ricci Junior, L.B. de Oliveira de Siqueira, R.A.S. Rodrigues, F. Sancenon, R. Martinez-Manez, J.A. de Moraes, R. Santos-Oliveira, Nanocarriers as phototherapeutic drug delivery system: appraisal of three different nanosystems in an in vivo and in vitro exploratory study, Photodiagnosis Photodyn. Ther. 21 (2018) 43–49.

[38] M. Siqueira-Moura, F. Primo, A.P.F. Peti, A. Tedesco, Validated spectrophotometric and spectrofluorimetric methods for determination of chloroaluminu phthalocyanine in nanocarriers, Pharmazie 65 (2010) 9–14.

[39] M.S. Diaz, M.L. Freile, M.I. Gutierrez, Solvent effect on the UV/Vis absorption and fluorescence spectroscopic properties of berberine, Photochem. Photobiol. Sci. 8 (7) (2009) 970–974.

[40]. Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy - mechanisms, photosensitizers and combinations. Biomed Pharmacother. 2018;106:1098-1107.

[41] B. Zhu, S. Li, L. Yu, W. Hu, D. Sheng, J. Hou, N. Zhao, X. Hou, Y. Wu, Z. Han, L. Wei, L. Zhang, Inhibition of Autophagy with Chloroquine Enhanced Sinoporphyrin Sodium Mediated Photodynamic Therapy-induced Apoptosis in Human Colorectal Cancer Cells, Int. J. Biol. Sci. 15 (1) (2019) 12–23.

[42] M. Bras, B. Queenan, S.A. Susin, Programmed cell death via mitochondria: different modes of dying, Biochemistry. Biokhimiia 70 (2) (2005) 231–239.

[43] Z. Su, Z. Yang, Y. Xu, Y. Chen, Q. Yu, Apoptosis, autophagy, necroptosis, and cancer metastasis, Mol. Cancer 14 (2015) 48.

[44] S. Song, J. Tan, Y. Miao, M. Li, Q. Zhang, Crosstalk of autophagy and apoptosis: Involvement of the dual role of autophagy under ER stress, J. Cell. Physiol. 232 (11) (2017) 2977–2984.

[45] Y. Shi, B. Zhang, X. Feng, F. Qu, S. Wang, L. Wu, X. Wang, Q. Liu, P. Wang, K. Zhang, Apoptosis and autophagy induced by DVDMs-PDT on human esophageal cancer Eca-109 cells, Photodiagn. Photodyn. Ther. 24 (2018) 198–205.

[46]. Mironov A. F. et al. Synthesis and Investigation of Photophysical and Biological Properties of Novel S-Containing Bacteriopurpurinimides, J Med Chem, 2017, vol. 60, no. 24, pp. 10220–10230.doi: 10.1021/acs.jmedchem.7b00577

[47]. Abrahamse H., Hamblin M.R. New photosensitizers for photodynamic therapy, Biochem J, 2016, vol. 473, no. 4, pp. 347–64. doi: 10.1042/BJ20150942

[48]. Romanko Yu. S. et al. Efficacy of photodynamic therapy for basal cell carcinoma using photosensitizers of different classes, Voprosy Onkologi, 2016, vol. 62, no. 3, pp. 447–450.

[49]. Yuzhakov V.V. et al. Morphofunctional characteristics of rat sarcoma M-1 after photodynamic therapy with the bacteriochlorophyll a derivative, Biomedical Photonics, 2016, vol. 5, no. 4, pp. 4–14.

[50]. Kessel D. Death Pathways Associated with Photodynamic Therapy, Photochem Photobiol, 2021, vol. 97, no. 5, pp. 1101–1103. doi: 10.1111/php.13436

[51]. Romanko Y. S. et al. Relationship between antitumor efficiency of photodynamic therapy with photoditasine and photoenergy density, Bull Exp Biol Med, 2005, vol. 139, no. 4, pp. 460–464. doi: 10.1007/s10517–005–0322–2

[52]. Zhang W, Zhang A, Sun W, Yue Y, Li H. Efficacy and safety of photodynamic therapy for cervical intraepithelial neoplasia and human papilloma virus infection: a systematic review and meta-analysis of randomized clinical trials. Medicine. 2018;97:e10864.

[53]. Park YK, Park CH. Clinical efficacy of photodynamic therapy. Obstet Gynecol Sci. 2016;59:479-488.

[54]. Inada NM, Buzzá HH, Leite MFM, et al. Long term effectiveness of photodynamic therapy for CIN treatment. Pharmaceuticals. 2019;12:107.

[55]. Gunaydin G, Gedik ME, Ayan S. Photodynamic therapy for the treatment and diagnosis of Cancer-A review of the current clinical status. Front Chem. 2021;9:686303.

[56]. Li D, Zhang F, Shi L, Lin L, Cai Q, Xu Y. Treatment of HPV infection-associated low grade cervical intraepithelial neoplasia with 5-aminolevulinic acid-mediated photodynamic therapy. Photodiagnosis Photodyn Ther. 2020;32:101974.

[57]. Algorri JF, Ochoa M, Roldán-Varona P, Rodríguez-Cobo L, López-Higuera JM. Photodynamic therapy: a compendium of latest reviews. Cancers. 2021;13:4447.

[58]. Nkune NW, Kruger CA, Abrahamse H. Possible enhancement of photodynamic therapy (PDT) colorectal cancer treatment when combined with cannabidiol. Anticancer Agents Med Chem. 2021;21:137-148.

[59]. Nkune NW, Kruger CA, Abrahamse H. Synthesis of a novel nanobioconjugate for targeted photodynamic therapy of colon cancer enhanced with cannabidiol. Oncotarget. 2022;13:156-172.

[60]. R Mokoena D, P George B, Abrahamse H. Enhancing breast cancer treatment using a combination of cannabidiol and gold nanoparticles for photodynamic therapy. Int J Mol Sci. 2019;20:4771.

[61]. Yurttas AG., Sevim AM, Cinar K., Atmaca GY., Erdogmus A., & Gul A. The effects of zinc(II)phthalocyanine photosensitizers on biological activities of epitheloid cervix carcinoma cells and precise determination of absorbed fluence at a specific wavelength. Dyes And Pigments, 198, 2022, 110012.

[62]. Yurttas, AG, Okat Z., Elgun T., Ucar Cifci K., Sevim AM, Gul A, Genetic deviation associated with photodynamic therapy in HeLa cell, Photodiagnosis and Photodynamic Therapy, Volume 42, 2023, 103346,