REVIEW PAPER

JMS Journal of Medical Science

Photodynamic therapy applications – a review

Maciej Michalak
Chair and Department of Inorganic and Analytical Chemistry, Poznan University of Medical Sciences, Poland
https://orcid.org/0009-0005-1077-1671

Sandra Mazurkiewicz
Chair and Department of Inorganic and Analytical Chemistry, Poznan University of Medical Sciences, Poland
–

Jakub Szymczyk
Chair and Department of Inorganic and Analytical Chemistry, Poznan University of Medical Sciences, Poland
–

Daniel Ziental
Chair and Department of Inorganic and Analytical Chemistry, Poznan University of Medical Sciences, Poland
https://orcid.org/0000-0002-4923-9982

Łukasz Sobotta
Department of Inorganic and Analytical Chemistry, Poznan University of Medical Sciences, Poland
https://orcid.org/0000-0002-5062-4503

Corresponding author: lsobotta@ump.edu.pl

DOI: https://doi.org/10.20883/medical.e865

Keywords: photodynamic therapy, anticancer therapy, photosensitizers

Received 2023-06-05
Accepted 2023-08-02
Published 2023-08-07

How to Cite: Michalak M, Mazurkiewicz S, Szymczyk J, Ziental D, Sobotta Łukasz. Photodynamic therapy applications – a review. JMS [Internet]. 2023 Aug. 7;92(4):e865. doi:10.20883/medical.e865

ABSTRACT

Photodynamic therapy (PDT) is a treatment method gaining worldwide attention. The paper overviews studies on PDT, as it may be applied in many medical disciplines, such as dermatology, urology, gynaecology, the therapy of head and neck cancers, and age-related macular degeneration. Recently, the development of this method has sped up, which is related to the appearance of new photosensitizers and optimised dosimetry of light. Current studies indicate that PDT is a significant support for conventional treatment protocols in many cases.

Introduction

Photodynamic therapy (PDT) is a modern medical method for both diagnostic and therapeutic purposes [1–4]. It is used to combat various external and internal diseases. In PDT, a specific wavelength of light is used to excite the photosensitizer (PS), which helps make reactive oxygen species, such as singlet oxygen. A potential PS for PDT has to fulfil numerous requirements that guarantee the safety, effectiveness, and competitiveness of the treatment. It means that potential side effects related to PS are limited. Moreover, PS should be selective towards pathologically changed cells and non-toxic towards healthy ones. PS manufacturing costs are also essential [1,5,6]. Intensive research on PS preparation and potential applications with high affinity for diseased tissues is underway. One can increase PS selectivity by combining antibodies or nanoparticles with the PS molecule [7]. PSs have also been applied in medicine in diagnostics, especially in photodynamic diagnosis – PD and therapeutic methods – PDT [8]. PDT is a medical treatment that uses light-sensitive drugs called PSs, administered locally or systemically. After irradiation

with light of an appropriate wavelength, the excited PS molecule can transfer the energy to neighbouring molecules [9–12]. Thus, the excited PS molecule can transfer the energy to oxygen molecules, forming reactive oxygen species (ROS) like singlet oxygen, hydroxyl radical, or superoxide. ROS can cause several effects in cells, e.g., damage to cellular membranes or organelles, such as mitochondria or nuclei. It could lead to the activation of apoptosis or necrosis pathways [13,14]. The most desirable are PSs with maximum absorption in the so-called therapeutic window between 600 and 850 nm [15]. An appropriate laser or LED lamp is usually recommended to induce fluorescence in PD. The light source emits a wavelength of around 400 nm (near UV range/blue light), which results in the red fluorescence of a contrasting agent (PS). The identification of malignancies or lesions is possible through the accumulation of PS molecules inside affected cells. [13]. The PD has an advantage over other optically assisted diagnostic methods because of the fluorescence that makes lesions more visible due to the selective uptake of the PS molecules. This phenomenon grants PD high specificity and sensitivity, compared to other more conventional diagnostic methods (regular cystoscopy or dermatoscopy) in white light [16]. Faster diagnosis provided by PD allows for detection in the early stage of the disease and establishes the correct treatment protocol [14].

Photodynamic methods for dermatology

One of the most severe skin diseases is cutaneous melanoma, which constitutes approximately 1.7% of all malignant cancers diagnosed annually worldwide. The survival and outcomes of the treatment are strongly tied to the development stage of the malignancy, thus making regular screenings a critical aspect of preventive actions. The risk of melanoma occurrence is higher when the patient meets the following conditions: a fair skin type, multiple atypical moles, or a family history of melanoma. The most frequently used screening method is a complete body-skin examination using dermoscopy or other imaging methods, which requires a trained physician [17]. In light of the need for a fast and reliable method of skin examination, the phenomenon of melanoma cell auto-fluorescence was considered. As the melanoma tissue contains molecules that have the character of fluorophores (i.e., lipofuscin and melanolipofuscin), they can be easily differentiated from the healthy tissue in a non-invasive manner [18].

Considering the treatment strategies, traditional surgical excision is still the most common way to deal with topical lesions, as it applies to many malignancies at various developmental stages [17]. However, this approach reveals some limitations due to its highly invasive nature and limited selectivity, resulting in a high-margin area of healthy tissue that must be removed along with the cancerous tissue. As a topical skin disease, melanoma can be treated using PDT as an alternative method to traditional surgical treatment [19]. The main advantages of PDT are the appealing cosmetic effects left after the treatment and its high selectivity for malignant cells. Some limitations of PS for PDT can be further improved with nanocarrier technology. Some limitations of PS for PDT can be further improved with nanocarrier, technology. PDT was successfully used in treating IV-stage metastases of pigmented melanoma with chlorin e6 (Ce6) as the PS, resulting in an excellent outcome, no recurrence, and no after-treatment toxicity [19]. Another advantage of Ce6 is that it can be used parallelly as the PS and as the imaging agent coupled with a nanocarrier, thus leading to a precise, real-time, two-colour image with the green fluorescence protein (GFP) expressing melanoma cells of the treated region.

More importantly, this strategy also allows for the early prediction of the treatment outcome, providing information on the deposition of the active agent [20]. What needs mentioning is a possible connection between melanin content and the classical PS molecules. As melanin *in vivo* displays strong absorption in the range of 500–600 nm wavelength, it may compete with some PSs, e.g., Photofrin, which reveals absorption around 630 nm [19]. However, replacing the PS removes the inconvenience easily. For example, bacteriochlorines can be used as they reveal the characteristic Q band long-wavelength absorbance at around 770 nm that can be even further extended with different molecule transformations by adding ligands, chelating metal ions to

the core, or further modifications of the macrocyclic system, leading even to bacteriopurpurinimides with the maximum at 836 nm [21]. In this case, they present absorption maxima that do not overlap with the absorption range of the melanin and thus do not affect the efficiency of the potential treatment.

One of the key aspects influencing the effectiveness of PDT, primarily when the therapy targets the circulatory system, is the degree of oxygenation of the tissue in which the process occurs [22]. Damage to blood vessels can rapidly disrupt the delivery of oxygen to tissues and thus significantly reduce the effectiveness of PDT. Photodynamic therapy directed against some cancers in such a situation may be self-limiting. Also, in many tumours, the degree of oxygen supply to the tissues can be very inhomogeneous due to the chaotic and pathological process of angiogenesis, leading to an unevenly distributed activity of the photosensitizer, which is directly dependent on oxygen [22]. From this perspective, developing protocols enabling PDT to operate even in unfavourable conditions remains fundamental. Over the last few years, it has been proposed to implement several modus operandi, e.g., using interval exposure and chemical oxygen sources such as hydrogen peroxide. Another approach to this issue is developing photosensitisers that will generate ROS not only by type II photodynamic reaction but also by type I (less sensitive to oxygen concentrations) and type III (practically insensitive to the presence or absence of oxygen). While the number of photosensitisers based on the type III photodynamic reaction is still limited, the development of molecules generating ROS in the I and II photodynamic reactions is auspicious [23,24]. Bacteriochlorins require special attention in this context. They have many desirable features, such as high photostability, a relatively long lifetime in the excited state, and high quantum efficiency of oxygen generation. In addition, bacteriochlorins are characterised by low dark toxicity and light activity, even at low concentrations [25]. An essential aspect, however, is their ability to generate ROS by applying type I and type II mechanisms.

Zhu et al., who compared the activity of chlorins vs. bacteriochlorins vs. porphins, presented an interesting perspective. Their study indicated that bacteriochlorins revealed the highest absorption band, were the most effective anticancer agent, and simultaneously had the lowest dark toxicity in all compared macrocycles [26]. Also, in the case of skin cancer, formulations based on bacteriochlorins have brought a significant breakthrough in PDT. For a long time, the scientific community was sceptical about the use of photodynamic therapy in the treatment of melanoma. First of all, radical resection of the neoplastic lesion with a large margin of normal tissues has been considered the therapy of choice for many years. A significant challenge was melanoma cells' high concentration of endogenous pigment compounds. Their presence significantly reduces the interaction of lower-wavelength light with the photosensitizer. Therefore, using bacteriochlorins, whose absorption maximum is usually over 700 nm, proved an interesting possibility. Mroz et al. conducted ground-breaking research in 2010 on the use of bacteriochlorins to treat melanoma. Their intervention in a mouse model provided a significant survival advantage, with 20% of cures [27]. Experiments using redaporfins in Pluronic P123 produced even better results. As a result of the protocol, obtaining even a 100% long-term cure rate in B16F10 tumour-bearing mice was possible. Considering these results, the use of bacteriochlorins in treating skin lesions has up-and-coming prospects [28].

Photodynamic methods for acne treatment

Acne vulgaris is a long-lasting, inflammatory skin condition that many things can cause, mainly hyperseborrhea (excess sebum), environmental factors, dietary choices, smoking, stress, and bacterial infection with *Cutibacterium acnes* [29]. PDT is another way to treat this condition. The application of PDT allows for reducing the number of C. acnes colonies and down-regulating sebum secretion, but the entire mechanism is unknown to date [30]. Despite that, using PDT against acne exhibits promising results, especially in severe and moderate cases resistant to conventional systemic treatment strategies with antibiotics or retinoids [30]. For this purpose, aminolevulinic acid (ALA) is mainly used and researched as the PS-protoporphyrin IX (PPIX) precursor. The idea behind the phototoxic effect after ALA is applied

to the skin is that this simple molecule is a building block for heme during its biosynthesis pathway. As the topically applied ALA enters the cells, it is converted in a few steps to the PPIX, which accumulates since the ferrochelatase (the ferrous ion-inserting enzyme – creates heme) is the slowest-acting enzyme of this biochemical pathway, thus rate-limiting. The PPIX has characteristic red fluorescence and, when sun-exposed, acts as a PS [31]. As the ALA molecule is relatively polar, its permeability must be considered mainly because of the lipophilic character of the *stratum corneum*. However, this may also be its advantage since some types of lesions caused by acne tend to exist close to the surface of the dermis, resulting in easier permeability for the targeted regions [32]. In the case study of ALA-PDT, the combination of 10% ALA cream and red LED light (630 nm, 40–80 J/cm^2) was applied against severe acne in three PDT sessions performed one week apart from each other, resulting in significant improvement after one month with a persisting effect up to four months after the last treatment [30]. The side effects of this treatment were mild exfoliation, erythema, and mild oedema lasting about 2–4 days after the procedure. What is worth mentioning is that no additional scarring or pre-existing scars changed significantly. Moreover, an improvement in skin texture was reported [30].

Photodynamic methods for the treatment of oral leukoplakia

Oral leukoplakia (OL) is a pathological lesion originating from the mucosa of the oral cavity with significant potential for developing malignancy [33]. OL is a disease that benefits from developing treatment strategies since there is no clear evidence of effective treatment preventing cancerous transformation or the recurrence of OL [34]. One of the advantages of PDT is that it only affects treated regions, making it a non-invasive way to treat premalignant lesions. A 20% Ce6 and 10% dimethyl sulfoxide gel with an occlusive dressing was put directly on the damaged mucosa and the healthy tissue around it for an hour before the light treatment to see if PS Ce6 could be used. Illumination was performed with a semiconductor laser at the wavelength of 660 nm. The procedure was repeated ten times at two-week intervals, resulting in a significant mean lesion area and reduction of lesions to 79.3%. The overall efficacy of the treatment was noted at the level of 70.9% for the non-smoking group, whereas the smoking group did not respond to the treatment [33].

Besides Ce6, ALA can be used to treat the OL. For example, a 20% ALA gel was applied to the defective mucosa 2 hours before the treatment. A 395 nm UVA flashlight was used just before the treatment to check for the presence of the PPIX in the treated regions. A lesion that had exhibited red fluorescence (giving evidence of PPIX presence) could undergo the laser treatment. Local oral anaesthetic medicine – primacaine was administered prior to irradiation with light at 632 nm to decrease discomfort during the laser therapy. As a result, a high positive response to ALA-PDT was observed in 86.2% of the patients. The rest, 13.8%, responded little [34].

Photodynamic methods for urology

Prostate cancer constitutes one of the most commonly occurring malignant tumours worldwide in men, the second after lung cancer [35]. The main symptoms of prostate cancer are discomfort and difficulties during micturition, urine incontinence, pollakiuria, dysuria, hematuria, bladder pressure, and a narrow stream of urine [36]. Compared to trans-rectal ultrasonography or digital rectal examination, finding out the levels of prostate-specific antigen (PSA) in the blood is the best way to diagnose. However, if any of these examinations reveal an abnormality, prostate biopsy or multiparametric magnetic resonance imaging is recommended to properly locate and estimate the character of the malignancy [37]. The treatment options for high-risk prostate cancer are external beam radiation therapy, long-term androgen deprivation therapy, and radical prostatectomy, the last one being especially invasive and associated with many after-treatment unwanted outcomes such as nerve or muscular tissue damage involved in excretory or erectile functions resulting in, i.e., impotence, affected micturition, incontinence [35,38].

PDT may meet these clinical needs, strongly improving selectivity and, for some PSs, allowing the performing of *in vivo* image-guided PDT,

potentially improving the accuracy and the outcome. For increased selectivity, the PS molecules (Pc413 and IR700) were conjugated with peptide targeting the prostate-specific membrane antigen (PSMA), providing high-affinity PDT agents with a binding force greater than 4.6-fold compared with related Cys-CO-Glu ligand. Comparing the imaging efficiency *in vivo*, the PSMA-1-Pc413 demonstrated a much clearer image and accumulated in the murine prostate region. However, after PDT, both conjugates demonstrated significant tumour regression [38]. Another PS used for prostate cancer was padeliporfin (Tookad®), used as a vessel-targeting agent in the type of focal therapy called vessel-targeted PDT. The technique depends on the intravenous administration of the PS, resulting in the systemic presence of the pro-drug and localized activation of the PS by exciting it with appropriate light provided by optical fibres inserted into the affected prostate regions [39,40]. This approach provides excellent outcomes for patients with low-risk prostate cancer, being effective, safe, and easy to perform in ambulatory conditions and also giving the patient the comfort of being discharged on the same day of the procedure. The limitation of this approach is related to the systemic administration of the PS, making it mandatory for the patient to avoid direct sunlight exposure up to 48 hours after the procedure. The other effects are postprocedural pain and rarely urethral stricture and incontinence [39,40]. Curcumin derivatives also found their place among PSs with the potential to act against prostate cancer. The *in vitro* evaluation indicated that 7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione had a promising phototoxic effect, resulting in the high reduction of the LNCaP cell line, at the same time having the lowest dark toxicity [41]. New PS delivery mechanisms and nanoparticles, which aim to increase the solubility and bioavailability or even provide additional properties, i.e., allow for PET and optical imaging, inhibit enzymes crucial for cellular redox homeostasis or allow for radiotherapy, are being developed to improve PDT treatment efficacy [42–44]. A set of three novel fluorinated porphyrinoids (porphyrin, chlorin, and isobacteriochlorin) were synthetised, entrapped in self-assembling polyvinylopyrrolidone (PVP), giving the advantage of lower aggregation, thus better perseverance of photophysical properties of these moieties. The formulations were tested against neoplastic, androgen-independent human prostate cell line PC-3, with the highest reduction in cell viability for the formulation containing isobacteriochlorin derivative [42].

Photodynamic methods for bladder cancer

Urothelial carcinoma (UC), or bladder cancer, ranks high at fourth place, constituting 6% of the estimated new cancer cases in the USA only [45]. While a diagnosis of UC mainly relies on recognizing the first symptoms, which might be painless hematuria, dysuria, or urgency, bladder ultrasonography or cross-sectional imaging helps to identify malignancy. However, according to the European Society for Medical Oncology, the unequivocal diagnosing techniques are transurethral resection, biopsy, and histological evaluation or cystoscopy [46].

A significant improvement when using PS is the possibility of performing fluorescent cystoscopy, which up to 30% more accurately detects tumorous lesions in the bladder than a standard white light cystoscopy [47]. Commonly used precursors of PS for this type of PD are 5-aminolevulinic acid (ALA) or its hexyl ester (HAL), the main advantage being the possibility of locating them into the bladder, thus not causing systemic phototoxicity. Both of these compounds depend on the exact mechanism mentioned earlier. ALA or HAL administration results in fluorescent PPIX accumulation in the malignant tissue, which provides a contrasting and phototoxic effect while being excited with appropriate light wavelength [47]. Another molecule researched for UC PD is hypericin, which can emit fluorescence much longer (up to 16 h after the administration) [47].

Regarding diagnosis, PDT can also be successfully used against the UC, providing many advantages such as safety, high selectivity, lower systemic stress compared to conventional chemotherapy, and ease of executing the procedure [48]. The intravesicular HAL solution was administered to 17 patients with high-risk or intermediate non-muscle-invasive UC. A wide-spectrum light source was coupled with a single quartz fibre, and placed in a transurethral irrigation catheter to irradiate the bladder wall. After six months,

52.9% of patients were tumour-free. However, the long-lasting effect (21 months after the procedure) of the absence of the tumour was maintained only in 2 patients [48]. One of the challenges of the PDT of tumours is hypoxia.

For this reason, an oxygen generating MnO_2 nanoparticles (oxygen generating agent) were synthesised. They were then coupled with human serum albumin (HSA) and Chlorin e6 (the PS), forming the HSA-MnO_2-Ce6 complex, which was evaluated in the *in vitro* and *in vivo* studies [49]. The inclusion of an oxygen-generating component in the HSA-MnO_2-Ce6 nanoparticles (NPs) had a significantly enhanced cytotoxic effect while irradiated with the laser, resulting in the lowest cell viability compared to the HSA-Ce6 and HSA-MnO_2 with the second not displaying photoreactivity. Moreover, the HSA-MnO_2-Ce6 NPs provided excellent tumour-targeting ability while not exhibiting apparent accumulation in the mice with normal bladder [49].

Photodynamic methods for the ophthalmology field

The term macular degeneration refers to the age-related variations within this structure. Age-related macular degeneration (AMD) occurs in two forms: exudative (wet) and atrophic (dry) [50]. The dry form occurs significantly more often than the wet form and constitutes 80% of these types of degeneration [51]. Part of the uttermost common symptoms of the AMD wet form implicates blood stroke enclosed by the choroid, which can cause the production of vascular-fibrous membranes located beneath the retina. As a result, the oxygen supply is obstructed in the retina's outer parts, which are situated photoreceptors, leading to their degradation and generating permanent, irreversible retina devastation, termed 'disciform macular degeneration'. The cause of the dry-type macular degeneration is considered progressing thinning and atrophy of the retina close to the macula lutea. The after-effect of the described pathologies is loss of macular function and limited vision in the central part. Qualifying patients with AMD for PDT treatment comprises visual acuity tests with best correction – stereoscopic examination of the fundus with lenses after pupil dilation [52], colour fundus photography, and fluorescein angiography. Among the indications for PDT therapy is the presence of subfoveal choroidal neovascularization developing during AMD, myopia, or histoplasmosis [53].

A contraindication for PDT is a serious pigment epithelial detachment and its atrophy or fracture. After the procedure is performed, hospitalization is not required and can be completed in an outpatient clinic. Side effects of macular degeneration PDT are occasional, and their process is mild. In AMD therapy, Verteporfin is applied as a PS as lyophilized powder under the trade name VISUDYNE® [54]. Furthermore, others report the results of combining PDT with triamcinolone (tc) acetonide injections into the vitreous body. Thirteen patients with an exudative form of AMD, in whom previous PDT had not given expected improvement, underwent this procedure, and they were administered 4 mg tc into the vitreous body after 48–72 hours PDT was performed. Patients were monitored regarding initial side effects in the first and seventh days after the procedure and every three months afterwards. Improved vision has been noted in the case of 76.9 % of treated patients. These results have raised hope in patients with ineffective PDT [55].

Photodynamic methods for gynaecology

There are few gynaecological diseases in which photodynamic methods can be used. It concerns, e.g. *lichen sclerosus*, *leukoplakia vulvae*, malignancies (uterine/cervical, endometrial, ovarian) or endometrial hyperplasia [56]. The vulvar leukoplakia is a non-tumour-like lesion with an underlying chronic inflammatory skin disease of unclear aetiology. Postmenopausal and peri-menopausal females are mainly affected (approximately 3%, compared to children and men 0.1%-0.7%) with vulvar lichen sclerosus (VLS), which often manifests as itching, burning pain, and sexual dysfunction that eventually leads to decreased life quality of the patient [57].

Traditional treatment strategies leave a wide area to improve on, especially in reversing the progression and in the treatment's cosmetic outcome–lasers used to treat VLS are usually abla-

tive; thus, they cause scarring and pain during the procedure [58]. Current methods focus on alleviating or eliminating symptoms, mainly the pruritus of the vulvar regions, by topical application of corticosteroids, hormones, or retinoic acid. However, these solutions are not the best-looking long-term, especially considering the usage of corticosteroids, which may pose a risk of causing irregular skin pigmentation or atrophy; thus, surgical intervention is also a part of VLS treatment with a focus on atypical hyperplasia. [57] Consequently, it is highly recommended that PDT be applied against the VLS. A study on ALA topical application on the lesions included 30 patients who had failed prior conventional treatment.. A gel of 20% ALA concentration was administered on the affected skin and left for three hours, after which the patient was treated with a 635 nm LED light. After a six-month follow-up, patients demonstrated significant improvement in the diminished pruritus and burning pain. Out of 28 patients complaining of itching before ALA-PDT, 25 after the treatment claimed that the symptom disappeared utterly, and the remaining three patients were also relieved considerably [57]. Another study on the group of 70 patients which used ALA-PDT against vulvar leukoplakia was performed using Alasens®, as an aqueous solution of concentration 0.5% topically applied 3–4 hours before the irradiation with an LED light of the 630 nm wavelength [59]. The procedure was performed three times at an interval of 24 hours, and during the irradiation period, it was evaluated based on the decrease of fluorescence of the lesions. The decreased fluorescence intensity in the treated tissue indicates that the accumulated PPIX in the cells converts to photo-reduced forms of "photoproducts," and the photodynamic effect was reached. It shows that the method is effective and constitutes a promising alternative to treat and prevent malignant transformation of vulvar lesions [59]. Another meaningful advantage of the PDT is that it can be successfully used against uterine endometrial cancer while preserving fertility in young females (under 35) [60]. A group of 16 patients with endometrial carcinoma (EC) without myometrial invasion were retrospectively evaluated on the efficacy and overall outcome of PDT. In all cases, a derivative of hematoporphyrin (Photogem®) was used as a PS in the form of an intravenous injection of a dose of 2 mg/kg 48 hours prior to the irradiation with a laser light of 630 nm. A cylindrical optical diffusion fibre delivered the light. The fibre was inserted in the endocervical canal, or the balloon-type diffuser was installed in the endometrial cavity and filled with a standard saline solution.. Twelve of 16 patients initially demonstrated complete remission after the treatment; 4 had recurrence. However, the PDT was performed again, leaving the final positive response rate at 68% (11/16). Seven of the patients attempted pregnancy, and 4 of them had seven successful pregnancies resulting in a total of 6 live births [60]. Considering the statistics of EC incidence the statistics of EC incidence, it is far more common in females of reproductive age (1 in 359) from birth to the age of 49. This retrospective study gives hope that PDT, among the previously mentioned advantages, can also be used as a treatment strategy that preserves fertility [45,60].

Photodynamic methods for head and neck tumors

Tumours of the head and neck are mainly treated surgically. The usage of the PDT in neurosurgery was a breakthrough. In tumour surgical procedures, the surrounding tissues endure damage. PDT treatment diminished the risk of damage to healthy tissue surrounding the lesions. Once the therapy is completed, the risk of developing new poundings on the periphery of the tumour diminishes to a minimum [61].

The autofluorescence phenomenon can also be employed to diagnose neck and head cancers [62]. The discussed method reduces the possibility of making a lapse in choosing, for example, biopsy sampling locations or misdiagnosis. Cell autofluorescence is the result of the UV radiation source and endogenous compounds, for example, aromatic amino acids (tryptophan, tyrosine, phenylalanine) or coenzymes (NADH-nicotinamide adenine dinucleotide, NADPH – reduced NADH form, FAD – flavin adenine dinucleotide, FMN- flavin mononucleotide or else folic acid). The most eminent advantage of autofluorescence diagnostics has become the prospect of lesion imaging, even in patients with severe radiation-induced reactions and in advanced stages of a disease or after radiotherapy [63].

Reported experiments confirmed the described method's usefulness in oral tumour diagnostics. Forty-seven oral cancer lesions, fifty-four precancerous lesions, and thirty-nine normal oral mucosa controls were analyzed, which conducted white light images and VELscope® (Visually Enhanced Lesion Scope; LED Dental Inc., White Rock, B.C.) autofluorescence images taken with a digital camera. After detection and autofluorescence analysis, the average intensity and heterogeneity of the changed areas were calculated. The results of the presented method confirmed that it is entirely sensitive and specific for detecting cancerous lesions [64]. Among the PSs, ALA merits particular attention because it converts to PPIX and selectively accumulates in malignant glioma cells. After that, violet-blue light irradiation of PPIX leads to its excitation, which ultimately leads to the destruction of cancer cells. In head and neck surgery, the autofluorescence phenomenon is used for intraoperative diagnosis to detect remaining glioma cells in boundary surgical areas for radical removal of lesions. Based on research, the described technique called ALA-PD proves its efficacy in increasing the length of patients outliving after surgery [65]. The specific location of head and neck cancers gives rise to frequent relapses. There has been a search for possibly minimally invasive treatment methods [66], and PDT perfectly fulfils this parameter. The evaluation of the treatment of recurrent facial lesions surgical methods and radiotherapy indicates limited medication capabilities, a high risk of complications, and statisti-

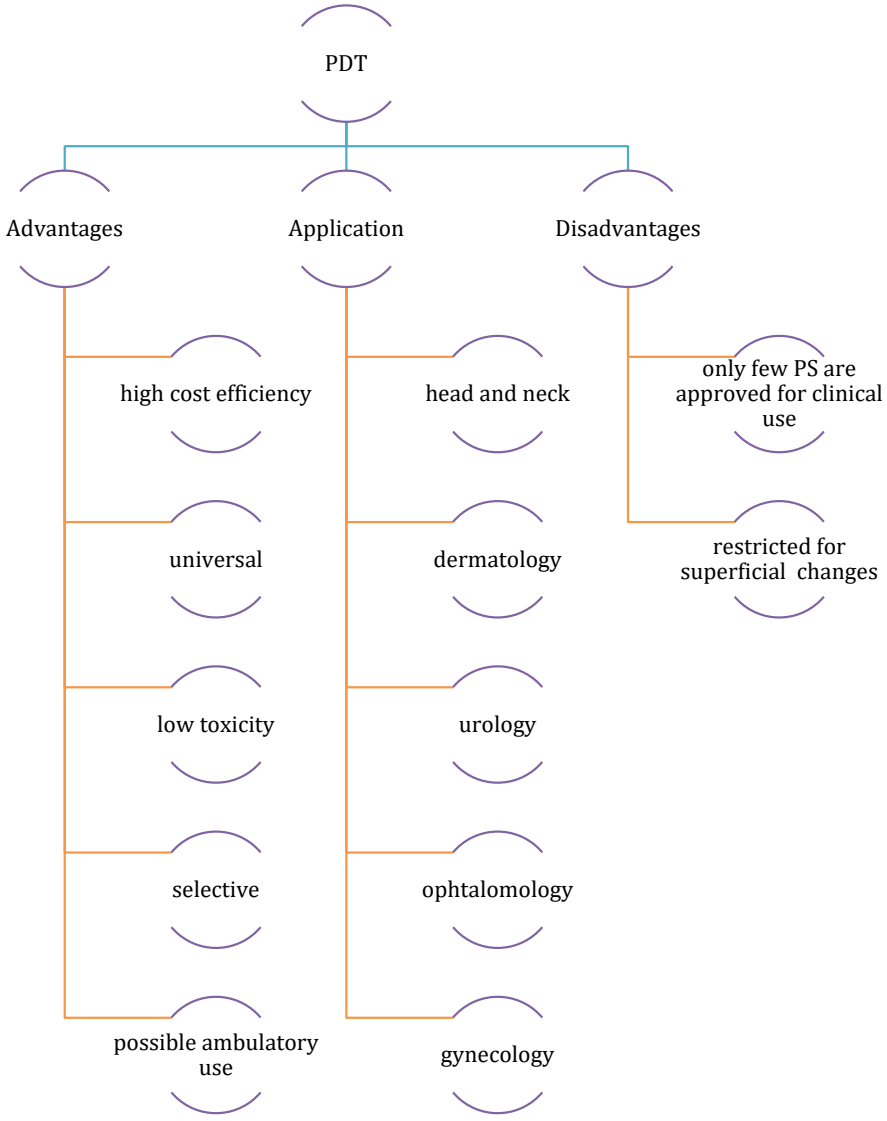

Figure 1. Summary.

cally low patient benefits. In such cases, PDT limits the prevalence of adverse and side effects of radiotherapy and enhances the prospect of complete recovery [67]. Amidst advantages in favour of PDT usage should be mentioned: the possibility of reprised procedures, local effects of PSs, and its selectivity regarding changed tissues [68,69]. The major problem is the accumulation of PSs in the body. In the event of ALA usage, PPIX accumulation occurs due to the overloading of cellular metabolisms of porphyrins. Systemically administered ALA undergoes quick elimination with a terminal half-life of about 1–3 hours [70]. Other PSs used in the treatment of head and neck tumours are HPD – sodium porfimer (Photofrin®); meta-tetra(hydroxyphenyl) chlorin (Foscan®) [71]; boronated porphyrin (BOPP®) [72]; lutetium texaphyrin (Lutex®) [73].

Summary

PDT is considered one of the most intensively developing modern treatment methods. Its main attributes are low cost, universality, low toxicity, high selectivity, and ease of use. Considering the spread of cancerous diseases, PDT development could be beneficial as a complementary approach in modern oncology. Despite the significant successes achieved with photodynamic therapy (PDT) in fighting cancer, there is still room for improvement in several areas. Further development of PDT depends on developing PSs characterised by better selectivity and improving light sources that will deliver the necessary light for therapy to hard-to-reach areas of the human body. The development of PDT holds great hope for combating tumours and improving our quality of life. **Figure 1** shows a summary.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References

1. Heerfordt IM, Philipsen PA, Wulf HC. Bringing the gentle properties of daylight photodynamic therapy indoors: A systematic review of efficacy and safety. Photodiagnosis Photodyn Ther. 2022;39:102858. doi: 10.1016/j.pdpdt.2022.102858.
2. Gunaydin G, Gedik ME, Ayan S. Photodynamic Therapy—Current Limitations and Novel Approaches. Front Chem. 2021;9:691697. doi: 10.3389/fchem.2021.691697.
3. Chilakamarthi U, Giribabu L. Photodynamic Therapy: Past, Present and Future. Chem Rec. 2017;17:775–802. doi: 10.1002/tcr.201600121.
4. Ziental D, Mlynarczyk DT, Czarczynska-Goslinska B, Lewandowski K, Sobotta L. Photosensitizers Mediated Photodynamic Inactivation against Fungi. Nanomaterials. 2021;11:2883. doi: 10.3390/nano11112883.
5. Tan G, Xu J, Yu Q, Yang Z, Zhang H. The safety and efficiency of photodynamic therapy for the treatment of osteosarcoma: A systematic review of in vitro experiment and animal model reports. Photodiagnosis Photodyn Ther. 2022;40:103093. doi: 10.1016/j.pdpdt.2022.103093.
6. Borgia F, Giuffrida R, Caradonna E, Vaccaro M, Guarneri F, Cannavò S. Early and Late Onset Side Effects of Photodynamic Therapy. Biomedicines. 2018;6:12. doi: 10.3390/biomedicines6010012.
7. Kataoka H, Nishie H, Hayashi N, Tanaka M, Nomoto A, Yano S, et al. New photodynamic therapy with next-generation photosensitizers. Ann Transl Med. 2017;5:183–183. doi: 10.21037/atm.2017.03.59.
8. Mironov AF, Zhdanova KA, Bragina NA. Nanosized vehicles for delivery of photosensitizers in photodynamic diagnosis and therapy of cancer. Russ Chem Rev. 2018;87:859–81. doi: 10.1070/RCR4811.
9. Ji B, Wei M, Yang B. Recent advances in nanomedicines for photodynamic therapy (PDT)-driven cancer immunotherapy. Theranostics. 2022;12:434–58. doi: 10.7150/thno.67300.
10. Mkhobongo B, Chandran R, Abrahamse H. The Role of Melanoma Cell-Derived Exosomes (MTEX) and Photodynamic Therapy (PDT) within a Tumor Microenvironment. Int J Mol Sci. 2021;22:9726. doi: 10.3390/ijms22189726.
11. Zhang M, Zhao Y, Ma H, Sun Y, Cao J. How to improve photodynamic therapy-induced antitumor immunity for cancer treatment? Theranostics. 2022;12:4629–55. doi: 10.7150/thno.72465.
12. Itoo AM, Paul M, Padaga SG, Ghosh B, Biswas S. Nanotherapeutic Intervention in Photodynamic Therapy for Cancer. ACS Omega. 2022;7:45882–909. doi: 10.1021/acsomega.2c05852.
13. Wang J, He H, Xu X, Wang X, Chen Y, Yin L. Far-red light-mediated programmable anti-cancer gene delivery in cooperation with photodynamic therapy. Biomaterials. 2018;171:72–82. doi: 10.1016/j.biomaterials.2018.04.020.
14. Dabrowski JM, Arnaut LG. Photodynamic therapy (PDT) of cancer: from local to systemic treatment. Photochem Photobiol Sci. 2015;14:1765–80. doi: 10.1039/c5pp00132c.
15. Yoon I, Li JZ, Shim YK. Advance in Photosensitizers and Light Delivery for Photodynamic Therapy. Clin Endosc. 2013;46:7. doi: 10.5946/ce.2013.46.1.7.
16. Russo GI, Sholklapper TN, Cocci A, Broggi G, Caltabiano R, Smith AB, et al. Performance of Narrow

Band Imaging (NBI) and Photodynamic Diagnosis (PDD) Fluorescence Imaging Compared to White Light Cystoscopy (WLC) in Detecting Non-Muscle Invasive Bladder Cancer: A Systematic Review and Lesion-Level Diagnostic Meta-Analysis. Cancers. 2021;13:4378. doi: 10.3390/cancers13174378.
17. Schadendorf D, van Akkooi ACJ, Berking C, Griewank KG, Gutzmer R, Hauschild A, et al. Melanoma. The Lancet. 2018;392:971–84. doi: 10.1016/S0140-6736(18)31559-9.
18. Bindewald-Wittich A, Holz FG, Ach T, Fiorentzis M, Bechrakis NE, Willerding GD. Fundus Autofluorescence Imaging in Patients with Choroidal Melanoma. Cancers. 2022;14:1809. doi: 10.3390/cancers14071809.
19. Baldea I, Giurgiu L, Teacoe ID, Olteanu DE, Olteanu FC, Clichici S, et al. Photodynamic Therapy in Melanoma - Where do we Stand? Curr Med Chem. 2019;25:5540–63. doi: 10.2174/0929867325666171226115626.
20. Lee C-H, Lai P-S, Lu Y-P, Chen H-Y, Chai C-Y, Tsai R-K, et al. Real-time vascular imaging and photodynamic therapy efficacy with micelle-nanocarrier delivery of chlorin e6 to the microenvironment of melanoma. J Dermatol Sci. 2015;80:124–32. doi: 10.1016/j.jdermsci.2015.08.005.
21. Grin MA, Mironov AF. Chemical transformations of bacteriochlorophyll a and its medical applications. Russ Chem Bull. 2016;65:333–49. doi: 10.1007/s11172-016-1307-1.
22. Krzykawska-Serda M, Dąbrowski JM, Arnaut LG, Szczygieł M, Urbańska K, Stochel G, et al. The role of strong hypoxia in tumors after treatment in the outcome of bacteriochlorin-based photodynamic therapy. Free Radic Biol Med. 2014;73:239–51. doi: 10.1016/j.freeradbiomed.2014.05.003.
23. Huang L, Xuan Y, Koide Y, Zhiyentayev T, Tanaka M, Hamblin MR. Type I and Type II mechanisms of antimicrobial photodynamic therapy: An in vitro study on gram-negative and gram-positive bacteria. Lasers Surg Med. 2012;44:490–9. doi: 10.1002/lsm.22045.
24. Hamblin MR, Abrahamse H. Oxygen-Independent Antimicrobial Photoinactivation: Type III Photochemical Mechanism? Antibiot Basel Switz. 2020;9:53. doi: 10.3390/antibiotics9020053.
25. Pratavieira S, Uliana MP, Dos Santos Lopes NS, Donatoni MC, Linares DR, De Freitas Anibal F, et al. Photodynamic therapy with a new bacteriochlorin derivative: Characterization and in vitro studies. Photodiagnosis Photodyn Ther. 2021;34:102251. doi: 10.1016/j.pdpdt.2021.102251.
26. Zhu W, Gao Y-H, Liao P-Y, Chen D-Y, Sun N-N, Nguyen Thi PA, et al. Comparison between porphin, chlorin and bacteriochlorin derivatives for photodynamic therapy: Synthesis, photophysical properties, and biological activity. Eur J Med Chem. 2018;160:146–56. doi: 10.1016/j.ejmech.2018.10.005.
27. Mroz P, Huang Y, Szokalska A, Zhiyentayev T, Janjua S, Nifli A, et al. Stable synthetic bacteriochlorins overcome the resistance of melanoma to photodynamic therapy. FASEB J. 2010;24:3160–70. doi: 10.1096/fj.09-152587.
28. Pucelik B, Arnaut LG, Stochel G, Dąbrowski JM. Design of Pluronic-Based Formulation for Enhanced Redaporfin-Photodynamic Therapy against Pigmented Melanoma. ACS Appl Mater Interfaces. 2016;8:22039–55. doi: 10.1021/acsami.6b07031.
29. Tuchayi SM, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC. Acne vulgaris. Nat Rev Dis Primer. 2015;1:15029. doi: 10.1038/nrdp.2015.29.
30. Ding H-L, Wang X-L, Wang H-W, Huang Z. Successful treatment of refractory facial acne using repeat short-cycle ALA-PDT: Case study. Photodiagnosis Photodyn Ther. 2011;8:343–6. doi: 10.1016/j.pdpdt.2011.07.003.
31. Thunshelle C, Yin R, Chen Q, Hamblin MR. Current Advances in 5-Aminolevulinic Acid Mediated Photodynamic Therapy. Curr Dermatol Rep. 2016;5:179–90. doi: 10.1007/s13671-016-0154-5.
32. Wortsman X, Claveria P, Valenzuela F, Molina MT, Wortsman J. Sonography of Acne Vulgaris. J Ultrasound Med. 2014;33:93–102. doi: 10.7863/ultra.33.1.93.
33. Pietruska M, Sobaniec S, Bernaczyk P, Cholewa M, Pietruski JK, Dolińska E, et al. Clinical evaluation of photodynamic therapy efficacy in the treatment of oral leukoplakia. Photodiagnosis Photodyn Ther. 2014;11:34–40. doi: 10.1016/j.pdpdt.2013.10.003.
34. Han Y, Xu S, Jin J, Wang X, Liu X, Hua H, et al. Primary Clinical Evaluation of Photodynamic Therapy With Oral Leukoplakia in Chinese Patients. Front Physiol. 2019;9:1911. doi: 10.3389/fphys.2018.01911.
35. Osuchowski M, Bartusik-Aebisher D, Osuchowski F, Aebisher D. Photodynamic therapy for prostate cancer – A narrative review. Photodiagnosis Photodyn Ther. 2021;33:102158. doi: 10.1016/j.pdpdt.2020.102158.
36. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The Epidemiology of Prostate Cancer. Cold Spring Harb Perspect Med. 2018;8:a030361. doi: 10.1101/cshperspect.a030361.
37. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71:618–29. doi: 10.1016/j.eururo.2016.08.003.
38. Wang X, Tsui B, Ramamurthy G, Zhang P, Meyers J, Kenney ME, et al. Theranostic Agents for Photodynamic Therapy of Prostate Cancer by Targeting Prostate-Specific Membrane Antigen. Mol Cancer Ther. 2016;15:1834–44. doi: 10.1158/1535-7163.MCT-15-0722.
39. Azzouzi A-R, Lebdai S, Benzaghou F, Stief C. Vascular-targeted photodynamic therapy with TOOKAD® Soluble in localized prostate cancer: standardization of the procedure. World J Urol. 2015;33:937–44. doi: 10.1007/s00345-015-1535-2.
40. Azzouzi A-R, Vincendeau S, Barret E, Cicco A, Kleinclauss F, Van Der Poel HG, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, ran-

domised controlled trial. Lancet Oncol. 2017;18:181–91. doi: 10.1016/S1470-2045(16)30661-1.
41. Kazantzis KT, Koutsonikoli K, Mavroidi B, Zachariadis M, Alexiou P, Pelecanou M, et al. Curcumin derivatives as photosensitizers in photodynamic therapy: photophysical properties and in vitro studies with prostate cancer cells. Photochem Photobiol Sci. 2020;19:193–206. doi: 10.1039/c9pp00375d.
42. Mesquita MQ, Ferreira AR, Neves MDGPMS, Ribeiro D, Fardilha M, Faustino MAF. Photodynamic therapy of prostate cancer using porphyrinic formulations. J Photochem Photobiol B. 2021;223:112301. doi: 10.1016/j.jphotobiol.2021.112301.
43. Jiang Q, Lu S, Xu X, Bai C, Yan Q, Fang M, et al. Inhibition of alanine-serine-cysteine transporter 2-mediated auto-enhanced photodynamic cancer therapy of co-nanoassembly between V-9302 and photosensitizer. J Colloid Interface Sci. 2023;629:773–84. doi: 10.1016/j.jcis.2022.05.044.
44. Tekin V, Aweda T, Kozgus Guldu O, Biber Muftuler FZ, Bartels J, Lapi SE, et al. A novel anti-angiogenic radio/photo sensitizer for prostate cancer imaging and therapy: 89Zr-Pt@TiO2-SPHINX, synthesis and in vitro evaluation. Nucl Med Biol. 2021;94–95:20–31. doi: 10.1016/j.nucmedbio.2020.12.005.
45. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics,. 2022. CA Cancer J Clin. 2022;72:7–33. doi: 10.3322/caac.21708.
46. Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33:244–58. doi: 10.1016/j.annonc.2021.11.012.
47. Przygoda M, Aebisher D. Bladder Cancer and Fluorescence Cystoscopy. IECN. 2022, MDPI;. 2022, p. 4. doi: 10.3390/IECN2022-12402.
48. Bader MJ, Stepp H, Beyer W, Pongratz T, Sroka R, Kriegmair M, et al. Photodynamic Therapy of Bladder Cancer – A Phase I Study Using Hexaminolevulinate (HAL). Urol Oncol Semin Orig Investig. 2013;31:1178–83. doi: 10.1016/j.urolonc.2012.02.007.
49. Lin T, Zhao X, Zhao S, Yu H, Cao W, Chen W, et al. O 2 -generating MnO 2 nanoparticles for enhanced photodynamic therapy of bladder cancer by ameliorating hypoxia. Theranostics. 2018;8:990–1004. doi: 10.7150/thno.22465.
50. Merry GF, Munk MR, Dotson RS, Walker MG, Devenyi RG. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. Acta Ophthalmol (Copenh). 2017;95:e270–7. doi: 10.1111/aos.13354.
51. Nowak JZ. Oxidative stress, polyunsaturated fatty acids-derived oxidation products and bisretinoids as potential inducers of CNS diseases: focus on age-related macular degeneration. Pharmacol Rep. 2013;65:288–304. doi: 10.1016/S1734-1140(13)71005-3.
52. Bressler SB, Qin H, Beck RW, Chalam KV, Kim JE, Melia M, et al. Factors Associated With Changes in Visual Acuity and Central Subfield Thickness at 1 Year After Treatment for Diabetic Macular Edema With Ranibizumab. Arch Ophthalmol. 2012;130:1153–61. doi: 10.1001/archophthalmol.2012.1107.
53. Bhavsar KV, Freund KB. Retention of good visual acuity in eyes with neovascular age-related macular degeneration and chronic refractory subfoveal subretinal fluid. Saudi J Ophthalmol. 2014;28:129–33. doi: 10.1016/j.sjopt.2014.03.001.
54. Ehmann D, García R. Triple therapy for neovascular age-related macular degeneration (verteporfin photodynamic therapy, intravitreal dexamethasone, and intravitreal bevacizumab). Can J Ophthalmol. 2010;45:36–40. doi: 10.3129/i09-243.
55. Mozolewska-Piotrowska K, Krzystolik K, Karczewicz D, Drobek-Słowik M, Kubasik-Kładna K. (41) Zastosowanie terapii łączonej PDT z iniekcjami doszklistkowymi octanu triamcinolonu u pacjentów z wysiękową postacią AMD. Doniesienie wstępne. Klin Oczna. 2011.
56. 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;24:52–7. doi: 10.1016/j.pdpdt.2018.08.014.
57. Zhang F, Li D, Shi L, Gu Y, Xu Y. 5-ALA-photodynamic therapy in refractory vulvar lichen sclerosus et atrophicus. Int J Clin Exp Pathol. 2020 Dec 1;13(12):3100-3110.
58. Yordanov A, Tantchev L, Kostov S, Slavchev S, Strashilov S, Vasileva P. Vulvar leukoplakia: therapeutic options. Menopausal Rev. 2020;19:135–9. doi: 10.5114/pm.2020.99570.
59. Sharova A, Farrakhova D, Slovokhodov E, Arakelov S, Zykov A, Sarantsev A, et al. Evaluation of vulvar leukoplakia photodynamic therapy efficiency by fluorescent diagnostics method with local «Alasens®» photosensitizer application. Photodiagnosis Photodyn Ther. 2019;27:105–10. doi: 10.1016/j.pdpdt.2019.05.018.
60. 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;23:698–704. doi: 10.1097/IGC.0b013e31828b5ba2.
61. Zastosowanie metod terapii fotodynamicznej w leczeniu zmian przednowotworowych i nowotworowych. pulsmedycyny.pl n.d. https://pulsmedycyny.pl/zastosowanie-metod-terapii-fotodynamicznej-w-leczeniu-zmian-przednowotworowych-i-nowotworowych-888116 (accessed May 27,. 2023).
62. Nguyen P, Bashirzadeh F, Hodge R, Agnew J, Farah CS, Duhig E, et al. High specificity of combined narrow band imaging and autofluorescence mucosal assessment of patients with head and neck cancer. Head Neck. 2013;35:619–25. doi: 10.1002/hed.22999.
63. Szczepkowska A, Milner P, Janas A. Autofluorescence image of post-radiation maxillary bone osteonecrosis in a 64-year-old patient – Case Report. J Pre-Clin Clin Res. 2016;10:69–72. doi: 10.5604/18982395.1208194.

64. Huang T-T, Huang J-S, Wang Y-Y, Chen K-C, Wong T-Y, Chen Y-C, et al. Novel quantitative analysis of autofluorescence images for oral cancer screening. Oral Oncol. 2017;68:20–6. doi: 10.1016/j.oraloncology.2017.03.003.
65. Kaneko S, Kaneko S. Fluorescence-Guided Resection of Malignant Glioma with 5-ALA. Int J Biomed Imaging. 2016;2016:1–11. doi: 10.1155/2016/6135293.
66. Theodoraki M-N, Yerneni S, Gooding WE, Ohr J, Clump DA, Bauman JE, et al. Circulating exosomes measure responses to therapy in head and neck cancer patients treated with cetuximab, ipilimumab, and IMRT. OncoImmunology. 2019;8:e1593805. doi: 10.1080/2162402X.2019.1593805.
67. Ahn PH, Finlay JC, Gallagher-Colombo SM, Quon H, O'Malley BW, Weinstein GS, et al. Lesion oxygenation associates with clinical outcomes in premalignant and early stage head and neck tumors treated on a phase 1 trial of photodynamic therapy. Photodiagnosis Photodyn Ther. 2018;21:28–35. doi: 10.1016/j.pdpdt.2017.10.015.
68. Chen Y, Gao Y, Li Y, Wang K, Zhu J. Synergistic chemo-photodynamic therapy mediated by light-activated ROS-degradable nanocarriers. J Mater Chem B. 2019;7:460–8. doi: 10.1039/C8TB03030H.
69. Ahn PH, Quon H, O'Malley BW, Weinstein G, Chalian A, Malloy K, et al. Toxicities and early outcomes in a phase 1 trial of photodynamic therapy for premalignant and early stage head and neck tumors. Oral Oncol. 2016;55:37–42. doi: 10.1016/j.oraloncology.2016.01.013.
70. Fukuhara H, Nohara T, Nishimoto K, Hatakeyama Y, Hyodo Y, Okuhara Y, et al. Identification of risk factors associated with oral 5-aminolevulinic acid-induced hypotension in photodynamic diagnosis for non-muscle invasive bladder cancer: a multicenter retrospective study. BMC Cancer. 2021;21:1223. doi: 10.1186/s12885-021-08976-1.
71. Berlanda J, Kiesslich T, Engelhardt V, Krammer B, Plaetzer K. Comparative in vitro study on the characteristics of different photosensitizers employed in PDT. J Photochem Photobiol B. 2010;100:173–80. doi: 10.1016/j.jphotobiol.2010.06.004.
72. Shi Y, Li J, Zhang Z, Duan D, Zhang Z, Liu H, et al. Tracing Boron with Fluorescence and Positron Emission Tomography Imaging of Boronated Porphyrin Nanocomplex for Imaging-Guided Boron Neutron Capture Therapy. ACS Appl Mater Interfaces. 2018;10:43387–95. doi: 10.1021/acsami.8b14682.
73. Al-Raqa SY, Köksoy B, Durmuş M. A novel lutetium(III) acetate phthalocyanine directly substituted with N,N'-dimethylaminophenyl groups via CC bonds and its water-soluble derivative for photodynamic therapy. Tetrahedron Lett. 2017;58:685–9. doi: 10.1016/j.tetlet.2017.01.019.