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Review Article

# Role of Photosensitizers in Photodynamic Therapy of Cancer Treatment: A Comprehensive Review

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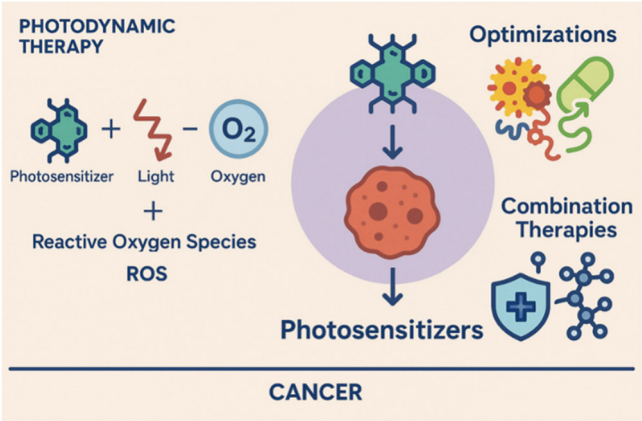
**Abstract**

Photodynamic therapy (PDT) is a clinically approved, minimally invasive treatment that uses a photosensitizer (PS), a specific wavelength of light, and molecular oxygen to induce localized cytotoxic effects in cancerous tissues. Upon light activation, the photosensitizer generates reactive oxygen species (ROS), particularly singlet oxygen, leading to oxidative damage, apoptosis, or necrosis of tumor cells. The effectiveness of PDT is critically influenced by the properties of the photosensitizer, including its absorption spectrum, photostability, tumor selectivity, and pharmacokinetics. Over the years, photosensitizers have evolved from first-generation compounds, which suffered from poor specificity and prolonged skin photosensitivity, to second- and third-generation agents with enhanced light absorption, reduced toxicity, and tumor-targeting capabilities. Recent innovations focus on nanotechnology-based delivery systems, targeted conjugates, and photoactivatable prodrugs to overcome current limitations such as non-specific accumulation, limited light penetration, and tumor hypoxia. Moreover, the combination of PDT with emerging therapies such as immunotherapy and molecular-targeted treatments is being actively explored to achieve synergistic effects and long-term tumor control. With ongoing advances in molecular design, imaging integration, and bioengineering, PDT is being refined as a more precise and effective tool in the oncologist's arsenal. This review provides a detailed examination of the central role of photosensitizers in PDT, including their mechanisms of action, classifications, challenges in clinical implementation, and the latest strategies to optimize their performance in cancer treatment.

**Keywords:** Photodynamic therapy; Photosensitizers; Cancer treatment; Reactive oxygen species; Tumor targeting; Nanotechnology




## Introduction

PDT is an emerging treatment modality that leverages the selective cytotoxicity of light-activated photosensitizers to treat various cancers. PDT involves three essential components: a photosensitizer, light, and oxygen. The photosensitizer, a light-sensitive compound, absorbs light at a specific

wavelength and, upon excitation, transfers energy to molecular oxygen, producing ROS that can induce cell death. PDT has attracted attention for its minimally invasive nature, high specificity for tumor tissue, and reduced systemic toxicity compared to traditional cancer treatments [1,2]. Recent advancements in PDT have focused on improving photosensitizer efficacy, overcoming light penetration issues, and incorporating nanotechnology to enhance treatment outcomes [3].

Cancer remains a significant global health challenge, with the World Health Organization (WHO) reporting approximately 9.6 million cancer-related deaths annually [4]. Traditional cancer therapies, including chemotherapy, radiation, and surgery, remain the standard of care but often present significant limitations, such as adverse side effects, drug resistance, and recurrence [5]. PDT, on the other hand, offers a promising alternative due to its ability to target tumors precisely with minimal damage to surrounding healthy tissues [3,7]. The successful application of PDT relies heavily on the properties of the photosensitizers used, the ability to selectively target tumor tissues, and the precise delivery of light to the treatment area [6].

A key feature of PDT is its dependence on photosensitizers, which are molecules that, when exposed to light, generate ROS capable of damaging cellular components, including DNA, proteins, and lipids [6]. ROS generated during PDT induces oxidative stress in cancer cells, triggering cell death via mechanisms such as apoptosis, necrosis, and autophagy. Singlet oxygen, a highly reactive species, is considered the most potent ROS responsible for cell damage in PDT [3,7]. For PDT to be effective, the photosensitizer must meet several criteria, including appropriate absorption properties, selective accumulation in tumor tissues, and minimal toxicity to normal tissues [5].

Early-generation photosensitizers, such as hematoporphyrin derivatives, were among the first approved for clinical use in PDT. Photofrin, a hematoporphyrin derivative, is one of the most widely studied and used photosensitizers in clinical PDT, particularly for treating cancers such as esophageal cancer and non-small cell lung cancer. However, these early photosensitizers had significant drawbacks, including poor tumor selectivity and prolonged photosensitivity, which left patients vulnerable to sunlight exposure for an extended period after treatment. As a result, recent advancements have focused on developing new-generation photosensitizers with enhanced tumor specificity, better tissue penetration, and reduced side effects [7,8].

Chlorins, phthalocyanines, and porphyrins represent newer classes of photosensitizers that have shown promise due to their improved absorption properties, allowing for deeper tissue penetration. Chlorins, for example, absorb light at longer wavelengths, enhancing PDT's ability to target tumors that are not accessible to traditional photosensitizers [9]. Recent studies have also focused on modifying these molecules to improve their solubility, stability, and selective uptake by tumor cells [5]. Additionally, the development of nanoparticles has led to significant advances in PDT. Nanoparticles, such as liposomes, micelles, and dendrimers, can enhance the delivery and biodistribution of photosensitizers, thereby increasing tumor accumulation and reducing toxicity to normal tissues [10]. The use of nanoparticles also enables co-delivery of therapeutic agents, providing an opportunity for combination therapies, such as PDT combined with chemotherapy or immunotherapy, to enhance treatment efficacy.

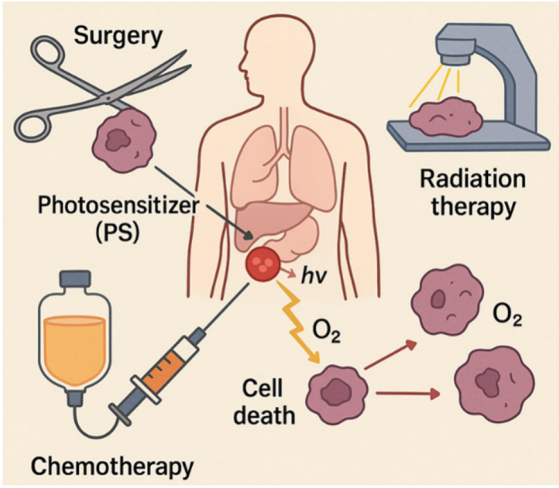



**Figure 1.** Overview of common cancer treatments incorporating photodynamic therapy.

A major challenge in PDT is the limited penetration of light into deeper tissues. Although near-infrared (NIR) light has been investigated for its ability to penetrate tissues more deeply than visible

light, PDT remains primarily effective for superficial or accessible tumors [11]. To address this issue, researchers are developing light delivery systems using fiber-optic cables, endoscopic devices, and other innovative technologies to improve light penetration into deeper tissues. Furthermore, studies have explored combination treatments in which PDT is used alongside other therapies to improve overall efficacy and overcome resistance mechanisms. For example, combining PDT with chemotherapy or radiation therapy has shown enhanced therapeutic outcomes by addressing both tumor cells and the tumor microenvironment [12,13]. The overview of common cancer treatments incorporating photodynamic therapy is illustrated in Figure 1.

Recent research also highlights the growing potential of nanotechnology-based photosensitizers in PDT. Nanoparticles offer several advantages, including the encapsulation and delivery of photosensitizers, which are more efficient in tumor tissues. Polymeric nanoparticles, for instance, can improve the solubility and stability of photosensitizers, while liposomes can facilitate the controlled release of these agents, increasing their therapeutic potential [14]. Moreover, targeted nanoparticles designed to bind to tumor-associated receptors specifically can increase the selectivity of PDT, minimizing off-target effects and improving treatment outcomes. This approach is particularly promising in overcoming the limitations of traditional PDT, such as photosensitizer accumulation in normal tissues.

PDT's ability to stimulate immune responses further enhances its potential as an anti-cancer strategy. Recent studies have shown that PDT can promote immune activation, resulting in tumor-specific immunity that may improve treatment outcomes, particularly when combined with immune checkpoint inhibitors [15]. Combining PDT with cancer vaccines is another promising avenue, as it may generate systemic anti-tumor immunity that complements the localized effects of PDT [16].

Although PDT has demonstrated significant promise in preclinical and clinical settings, challenges remain in its widespread clinical application. Tumor resistance to PDT, similar to other cancer therapies, can develop through various mechanisms, such as reduced photosensitizer uptake, increased antioxidant activity, or enhanced DNA repair. To overcome these challenges, researchers are exploring novel strategies, such as targeted drug delivery systems, to improve the selectivity and efficacy of PDT [17]. The use of PDT in combination with other therapies, such as chemotherapy, immunotherapy, or radiation therapy, holds the potential to enhance the overall therapeutic response and overcome resistance mechanisms.

Overall, PDT remains a promising and evolving cancer treatment modality. Advances in photosensitizer development, nanotechnology, and combination therapies have significantly improved the efficacy and applicability of PDT in cancer treatment. Despite challenges such as light penetration and tumor resistance, ongoing research and innovations in PDT offer hope for more effective and personalized cancer therapies. With continuous improvements, PDT is likely to become an integral part of cancer treatment regimens, providing a non-invasive, targeted, and highly effective therapeutic option for patients [18].

**Mechanism of action of photodynamic therapy**

*Photosensitizer Activation and ROS Generation*

The primary mechanism underlying PDT is the generation of ROS upon the activation of a PS. It is a compound that, when exposed to light of a specific wavelength, absorbs light energy and enters an excited electronic state. This activated state enables the PS to interact with molecular oxygen in the surrounding tissue, leading to the generation of highly reactive ROS. These ROS play a central role in the therapeutic effects of PDT by causing significant cellular damage, leading to tumor cell death.

Among the various ROS produced during PDT, the following are the most significant, including singlet oxygen ($^1O_2$), which is the most potent and long-lived ROS generated in PDT. Singlet oxygen induces substantial oxidative damage to cellular structures, such as lipids, proteins, and DNA, leading to a cascade of events, including apoptosis (programmed cell death), necrosis, and, in some cases, autophagic cell death. Singlet oxygen is responsible for most of the cytotoxic effects observed in PDT

[19]. Hydroxyl radicals (OH), which are produced in the presence of water and are highly reactive species. They can cause lipid peroxidation, compromising cellular membranes and leading to membrane rupture and cellular leakage. This radical can also contribute to oxidative damage to DNA and proteins [19]. Superoxide anion ($O_2\bullet^-$): This ROS is often generated as a precursor to other highly reactive species and can lead to cellular damage indirectly through its conversion to other ROS, such as hydrogen peroxide ($H_2O_2$), which subsequently produces hydroxyl radicals and singlet oxygen [20].

Oxidative stress caused by these ROS damages cellular components, triggering several cell death pathways, including apoptosis, necrosis, and autophagy. The generation of ROS by PDT is a powerful mechanism for disrupting tumor cell integrity, ultimately leading to tumor destruction [21]. ROS-induced DNA damage is particularly detrimental, as it impairs the cell's ability to repair itself, contributing to cell death through genetic mutations, chromosomal fragmentation, and altered cellular signaling pathways [18].

**Tumor-Specific photosensitizer accumulation**

A significant challenge in PDT is ensuring that the photosensitizer preferentially accumulates in the tumor tissue while minimizing its presence in the surrounding healthy tissues. This selective accumulation is crucial to achieving therapeutic efficacy while reducing the risk of side effects. Tumor tissues exhibit unique biological and structural features that can be leveraged to enhance the specificity of PS accumulation, primarily through the enhanced permeability and retention (EPR) effect [22]. The EPR effect is a phenomenon where tumor vasculature is often irregular, with leaky blood vessels that allow larger molecules, such as photosensitizers, to accumulate in tumor tissues more readily than in normal tissues. This preferential accumulation results from poor lymphatic drainage in tumors, which leads to the entrapment of PS molecules in the tumor microenvironment.

Several factors contribute to this enhanced accumulation, including abnormal blood vessel structure and impaired lymphatic drainage in tumor tissues, both of which are characteristic of the tumor microenvironment. Furthermore, the acidic extracellular pH of tumors and the presence of certain receptors on tumor cells can also facilitate the selective binding of PS molecules. Some newer-generation PS compounds are designed to exploit the EPR effect and are often conjugated to targeting moieties, such as antibodies or ligands, to further enhance tumor specificity [23].

The PS's ability to preferentially accumulate in tumor tissue is vital for maximizing the therapeutic outcome of PDT, ensuring that the treatment targets tumor cells while sparing normal tissues from unwanted ROS-induced damage. Moreover, research is ongoing on the development of nanoparticles and nanocarriers, which can further enhance the EPR effect by improving the solubility, stability, and tumor-targeting properties of the PS [24]. Nanotechnology-based PS formulations can enable the co-delivery of PDT agents with other therapeutic agents, such as chemotherapeutic drugs or immunomodulators, thereby improving overall therapeutic efficacy. The effectiveness of PDT is rooted in the mechanism of ROS generation via photosensitizer activation. The selective accumulation of PSs in tumor tissues, aided by the EPR effect, ensures that the ROS produced are localized to cancerous areas, thereby limiting systemic toxicity and enhancing treatment outcomes [25].

**Classification of photosensitizers**

Photosensitizers (PSs) are integral to PDT, a non-invasive modality that uses light, oxygen, and a PS to induce cytotoxic effects in malignant tissues. The classification of PSs into three generations reflects the progression in chemical sophistication, tumor-targeting ability, and therapeutic outcomes. These generations are delineated by structural differences, light-absorption characteristics, and delivery innovations.

**First-generation photosensitizers**

First-generation photosensitizers were introduced in the 1970s, with hematoporphyrin derivatives (HpD) and Photofrin® being the most well-known. These compounds are derived from porphyrins and possess photodynamic capabilities when exposed to red light at wavelengths around 630 nm [26]. While

Photofrin® is FDA-approved for certain cancers such as esophageal and bladder carcinoma, it presents several limitations: prolonged skin photosensitivity due to its slow clearance from the body, low molar absorption coefficients, and heterogeneous composition. These PSs primarily accumulate in tumors due to the EPR effect but lack active targeting capabilities. Moreover, their suboptimal absorption in the therapeutic window (650-800 nm) limits their utility for deep-seated tumors [27]. Nonetheless, their historical significance lies in establishing PDT as a viable treatment, which laid the foundation for the next generation of PS development.

**Second-generation photosensitizers**

Second-generation PSs were developed to overcome the deficiencies of first-generation agents. These compounds include chemically pure molecules such as chlorins, bacteriochlorins, phthalocyanines, benzoporphyrins, and porphycenes [28]. These PSs exhibit superior photophysical and photochemical properties, including high singlet oxygen quantum yields, stronger absorption in the NIR region (650–800 nm), and faster clearance from healthy tissues [29].

Chlorin e6 (Ce6), for instance, is widely researched due to its amphiphilic nature, ease of modification, and strong NIR absorption (~660 nm). It has shown potent phototoxicity and is compatible with a wide range of nanocarriers [29]. Similarly, aluminum phthalocyanine tetrasulfonate (AlPcS4) and zinc phthalocyanine (ZnPc) are second-generation PSs with significant light absorption near 670 nm, facilitating greater tissue penetration. However, the hydrophobicity remains a challenge for phthalocyanines, necessitating the use of surfactants or nanocarriers [28,30].

Porphycenes, which are structural isomers of porphyrins, exhibit even higher singlet oxygen generation efficiency and are being explored for PDT applications, especially for targeting hypoxic tumor environments [31]. The versatility of second-generation PSs enables formulation into liposomes, emulsions, and polymeric micelles to improve pharmacokinetics and tumor accumulation [32]. Despite their improved properties, second-generation PSs still lack specificity, which prompted the emergence of third-generation PSs.

**Third-generation photosensitizers**

Third-generation PSs represent a convergence of photodynamic efficacy and tumor-targeting precision. These systems are typically based on second-generation compounds but are conjugated with targeting ligands (e.g., antibodies, folic acid, peptides) or incorporated into smart delivery platforms such as nanoparticles, liposomes, and dendrimers [33]. The goal is to enhance selective accumulation in cancerous tissues and minimize systemic side effects.

For example, folic acid-targeted Ce6 conjugates can selectively bind to folate receptors overexpressed in several tumor types, improving photodynamic activity [34]. Similarly, epidermal growth factor receptor (EGFR)-targeted nanobody–photosensitizer conjugates have demonstrated efficient binding and internalization in EGFR-positive tumors [35]. These biofunctionalized PSs provide both active and passive targeting mechanisms, enhancing therapeutic selectivity.

The use of nanotechnology has revolutionized PDT. Nanocarriers protect PSs from degradation, enable controlled release, and facilitate co-delivery of therapeutic agents [36]. Polymeric nanoparticles, mesoporous silica nanoparticles, and lipid-based systems have been extensively investigated for the encapsulation of PSs. These carriers can also incorporate pH-responsive or enzyme-cleavable linkers that enable selective release in the tumor microenvironment [27]. Emerging modalities include upconversion nanoparticles (UCNPs), which absorb NIR light and emit visible light to activate PSs in deep tissues [37]. This approach offers an innovative solution to the limited tissue penetration of conventional light sources. Gold nanoparticles (AuNPs), on the other hand, offer photothermal and photodynamic synergy and have been engineered to deliver Ce6, thereby enhancing antitumor efficacy [38]. Additionally, third-generation PSs facilitate multimodal imaging and therapy. Theranostic systems incorporating fluorescence, MRI, or PET imaging capabilities enable real-time tracking of PS distribution and monitoring of treatment [39]. These multifunctional platforms also allow for combination therapies, such as chemo-photodynamic, photo-immunotherapy, and photothermal-

photodynamic dual strategies [40]. Despite their promise, translating third-generation PSs into clinical settings is challenged by the complexity of synthesis, scalability, the potential immunogenicity of targeting ligands, and regulatory hurdles. Nonetheless, continuous advances in nanomedicine and targeted therapy are expected to bridge these gaps, positioning third-generation PSs as the future of PDT in oncology.

**Desired properties of ideal photosensitizers**

The effectiveness of PDT is largely contingent on the properties of the PS employed. An ideal PS must exhibit physicochemical, photophysical, and pharmacokinetic properties that maximize therapeutic efficacy while minimizing side effects. In this section, we elaborate on the key features required for an optimal PS, supported by recent research insights.

**Strong absorption in the therapeutic window (600–800 nm)**

The therapeutic window between 600 and 800 nm is optimal for tissue penetration, as light in this region suffers less scattering and absorption by biological chromophores such as hemoglobin and melanin [38]. PSs that absorb strongly within this range enable activation at deeper tumor sites, allowing for the treatment of internal malignancies. Second- and third-generation PSs, such as Ce6, phthalocyanines, and bacteriochlorins, are favored for their high molar extinction coefficients and NIR absorption peaks, which allow deeper tissue targeting and better patient outcomes [41,42].

**High quantum yield of singlet oxygen generation**

The generation of ROS, particularly singlet oxygen ($^1O_2$), is the primary cytotoxic mechanism in PDT. An ideal PS must exhibit a high quantum yield of $^1O_2$ to induce oxidative damage to tumor cells upon activation [43]. Chlorin derivatives and phthalocyanines are among the top candidates due to their efficient intersystem crossing and strong energy transfer capabilities [44]. Enhancing singlet oxygen production can also be achieved through molecular engineering, as demonstrated by halogenated PSs or those conjugated with heavy atoms [45].

**Selective accumulation in tumor tissues**

Targeted delivery is essential for reducing collateral damage to healthy tissues. An ideal PS should exhibit preferential accumulation in tumor cells over normal cells. Passive targeting can be achieved via the EPR effect, while active targeting involves conjugation with ligands such as antibodies, folic acid, or peptides [46,47]. Recent developments in nanotechnology have enabled PS encapsulation in nanoparticles, liposomes, and micelles to enhance tumor localization [48]. For instance, folate-targeted Ce6 nanoparticles and EGFR-specific nanobody conjugates have shown enhanced selectivity and reduced off-target effects [35].

**Rapid clearance to minimize phototoxicity**

Prolonged circulation and retention in the body can lead to extended skin photosensitivity, a common side effect of first-generation PSs. Therefore, an ideal PS should be rapidly cleared from normal tissues while retaining sufficient tumor localization [17]. Second-generation PSs with shorter plasma half-lives and hydrophilic properties exhibit improved pharmacokinetics. Nanocarriers can further assist in achieving rapid clearance post-therapy by incorporating stimuli-responsive or biodegradable components [49].

**Chemical and photochemical stability**

PSs must remain chemically stable during storage and photochemically stable upon exposure to light until activation. Degradation or premature activation can compromise therapeutic efficacy and safety [36]. To enhance stability, PSs are often encapsulated in protective carriers or modified with stabilizing moieties. For instance, porphyrin-loaded metal–organic frameworks (MOFs) and polymeric nanoparticles have demonstrated enhanced photobleaching resistance [29].

**Minimal dark toxicity**

An ideal PS should be non-toxic in the absence of light to avoid systemic toxicity. High dark toxicity undermines the selective nature of PDT and can limit clinical use. Screening of new PSs includes rigorous evaluation of cytotoxicity under dark conditions [32]. The incorporation of PSs into smart delivery systems, such as pH-sensitive or enzyme-activated nanoparticles, ensures that they remain inactive until reaching the tumor microenvironment and are exposed to light [39]. Molecular design strategies such as modifying the hydrophobicity and charge of the PS molecule also contribute to reduced dark toxicity [37].

**Multifunctionality and imaging capabilities**

Modern therapeutic strategies demand multifunctional agents capable of simultaneous diagnosis and therapy (theranostics). PSs with intrinsic fluorescence can be used for tumor imaging and therapy monitoring [40]. Advanced formulations integrate imaging modalities like MRI, CT, and photoacoustic imaging for real-time treatment tracking. These multifunctional systems enhance clinical confidence and allow precision medicine approaches [33].

**Recent advances and future perspectives**

Recent advances in PDT have focused on enhancing the therapeutic efficacy and precision of PSs while minimizing associated side effects. One of the most notable developments is the design of PSs with higher tumor specificity and deeper tissue penetration. This has been largely facilitated by the use of NIR-absorbing PSs, which enable treatment of tumors at deeper anatomical sites due to reduced light scattering and absorption in biological tissues [38]. Researchers have developed NIR photosensitizers based on phthalocyanines, porphyrins, and cyanine derivatives that offer improved optical and therapeutic performance in preclinical models [41,42].

Multifunctional PSs have also emerged, integrating diagnostic imaging and therapeutic functions into a single molecular platform. These theranostic agents enable real-time monitoring of PS accumulation and treatment efficacy, allowing clinicians to tailor therapy to each patient. For example, photosensitizers with intrinsic fluorescence can assist in intraoperative tumor margin detection, while magnetic resonance or photoacoustic imaging-compatible formulations offer deep-tissue visualization. Hybrid nanoplatforms that combine imaging, therapy, and stimulus responsiveness are particularly promising in this regard [43-45].

The integration of PDT with other therapeutic modalities is gaining traction to overcome the limitations of monotherapy. Combination treatments with chemotherapy enhance drug penetration and cytotoxicity in hypoxic tumor regions, while photodynamic immunotherapy is being explored for its capacity to trigger antitumor immune responses by releasing tumor-associated antigens [50,51]. Gene therapy has also been incorporated into PDT regimens to modulate gene expression and sensitize cancer cells to oxidative stress [37]. In this context, PSs have been conjugated with siRNA, plasmids, or CRISPR-Cas9 components to enable photo-triggered gene modulation [35].

Nanotechnology plays a pivotal role in advancing PDT. Targeted nanocarriers such as liposomes, dendrimers, micelles, and metal-organic frameworks (MOFs) have been designed to enhance PS delivery and reduce off-target effects. These carriers can be modified with ligands like folic acid, transferrin, or monoclonal antibodies for receptor-mediated tumor targeting [34,48]. Furthermore, smart nanoparticles that respond to tumor-specific stimuli (e.g., pH, redox, enzymes) can facilitate on-site PS activation and drug release, thereby increasing therapeutic selectivity [52]. The use of biodegradable materials ensures safe elimination of carrier components post-therapy, minimizing long-term toxicity [36].

Photoactivatable prodrugs represent another innovative strategy in which PSs or chemotherapeutic agents are activated only upon exposure to specific wavelengths of light. These systems remain inert in systemic circulation and are selectively activated in the tumor site, reducing systemic toxicity and

enhancing localized action [53]. Researchers have also developed self-assembled nanoprodrugs that disassemble upon light exposure or in the acidic tumor microenvironment, releasing active agents [54].

Image-guided PDT is becoming increasingly feasible as molecular imaging and light-based treatment converge. Techniques such as fluorescence-guided resection combined with intraoperative PDT help achieve complete tumor eradication and reduce recurrence rates. Imaging tools provide feedback on PS localization and photobleaching dynamics, enabling precise control over therapeutic parameters [11,40]. Such real-time visualization allows for a more dynamic and personalized treatment approach. Looking ahead, the clinical translation of next-generation PSs will depend on overcoming regulatory and manufacturing challenges. Standardization of PS synthesis, characterization, and validation protocols is essential to ensure reproducibility and safety. Long-term toxicology studies and large-scale clinical trials are necessary to validate efficacy in diverse patient populations [32]. Personalized medicine approaches incorporating genetic and molecular tumor profiling can further guide PS selection and treatment planning.

The future of PDT is poised to benefit from interdisciplinary innovations at the interface of chemistry, nanotechnology, immunology, and biomedical engineering. The emergence of artificial intelligence and machine learning tools to optimize dosimetry, predict treatment outcomes, and analyze imaging data adds another layer of sophistication. As these technologies mature, PDT may become a cornerstone of minimally invasive, image-guided cancer therapy with improved precision and patient outcomes [8]. The recent advances in photosensitizers for cancer photodynamic therapy are listed in Table 1.

**Table 1. Recent advances in photosensitizers for cancer photodynamic therapy.**

| Photosensitizer | Delivery System | Target / Model | Key Findings | References |
|---|---|---|---|---|
| **Ce6** | Keratin nanoparticles | Osteosarcoma cells | Synergistic effect in killing osteosarcoma cells | [55] |
| **Protoporphyrin IX (PpIX)** | Polyamidoamine dendrimers | Glioblastoma cells | Improved cellular uptake and apoptosis upon light activation | [56] |
| **IRDye700DX** | Cetuximab-conjugated mesoporous silica nanoparticles | EGFR-overexpressing tumor cells | Selective killing of EGFR-expressing cells with controlled drug release | [57] |
| **Hypericin** | PLGA nanoparticles | Ovarian cancer cells | Higher photoactivity and therapeutic index compared to free PS | [58] |
| **Porphyrin-lipid conjugates** | Porphysomes (lipid-based nanoparticles) | Various cancer models | High biocompatibility and photothermal activation upon dissociation | [59] |
| **Motexafin lutetium** | Texaphyrin-based formulation | Prostate cancer | Effective PDT with deeper tissue penetration due to 732 nm activation | [60] |
| **ITIC** | Nanoparticles | Glioma cells | Near-infrared activation and targeted glioma cell killing | [61] |
| osmium | DSPE-mPEG2000 micelles | Tumor tissues | Improved luminescence and tumor selectivity | [62] |
| Phthalocyanine | dendrimers | Breast cancer cell | **Immune activation, Antigen presentation, and tumor transformation** | [63] |
| Cyanine | Liposomes | Breast cancer cell | Mitochondrial apoptosis induction and tumor-specific accumulation | [64] |
| indocyanine green | Polymeric micelles | Hepatocellular carcinoma - HuH-7 cells | Tumor-specific phototoxicity, selective tumor accumulation, and enhanced imaging capability | [65] |
| Phthalocyanine | Dendrimers | Breast cancer cells | Activate T cells, enhance antigen presentation, induce cell death, boost T-cell infiltration, convert cold to | [66] |

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|---|---|---|---|---|
| | | | hot tumors, and synergize with PDT | |
| porphyrin | Polymeric nanoparticles | Cancer cells -MDA-MB231 cells | Enhancing drug uptake, stability, and synergistic light-induced cancer cell death | [67] |
| protoporphyrin | Radiation-Activated Photodynamic Nanoparticles | Deep-Seated Tumors | Enhanced efficacy under hypoxia via singlet oxygen generation with minimal toxicity | [68] |
| protoporphyrin IX | Radiation-Activated Photodynamic Nanoparticles | Deep-Seated Tumors | Prostate radiotherapy with minimal toxicity | [69] |
| Porphyrin | Nanoparticles | Head and Neck Cancer cells | Porphysomes enable imaging, tumor ablation, and function preservation. | [70] |

## Clinical Trials

Recent clinical trials in PDT have focused on improving the efficacy and safety of various photosensitizers for cancer treatment. These studies span multiple cancer types, including brain gliomas, head and neck squamous cell carcinoma, non-small cell lung cancer, and esophageal cancer. The trials explore the use of various photosensitizers, including verteporfin, 5-aminolevulinic acid, and methylene blue, and assess their therapeutic potential when combined with PDT. With clinical phases ranging from early-stage trials to Phase III studies, the trials aim to enhance treatment precision, tumor selectivity, and patient outcomes. Key factors under investigation include the effectiveness of PDT when combined with other therapies, such as chemotherapy, as well as its impact on targeted treatment regimens. The following table summarizes some of the most recent clinical trials on PDT and their applications in cancer therapy. The clinical trials in PDT for cancer treatment are listed in Table 2.

**Table 2. Recent clinical trials on photodynamic therapy for cancer treatment.**

| Clinical Trials Registration Number | Official title | Photosensitizer/ Generation | Phase/ Status | Sponsor | Conditions | References |
|---|---|---|---|---|---|---|
| NCT01673074 | A Phase 1 Trial of Photodynamic Therapy With HPPH in Patients With Pleural Malignancy | *HPPH (Photochlor)*/ Second | Phase I/ Completed | Abramson Cancer Center at Penn Medicine | Pleural Malignancy | [71] |
| NCT03638622 | Low-cost Enabling Technology for Image-guided PDT of Oral | Aminolevulinic acid and Protoporphyrin IX/ Second | Phase I and II/ Completed | Massachusetts General Hospital | Oral cancer | [72] |
| NCT01682746 | PDT for Poor Prognosis Recurrent/Refractory Malignant Brain Tumors - A Phase I Study | Photofrin/ First | Phase I/ Completed | Harry T Whelan, MD | Brain Tumor, Recurrent | [73] |
| NCT02555501 | Laser Therapy Associated With Photodynamic Therapy in the Treatment of Oral Mucositis Induced by Chemotherapy in Young Patients: Randomized Blind Clinical Trial | Methylene blue/ Second | Phase 3/ Completed | Universidade Ceuma | Oral Mucositis | [74] |
| NCT03322293 | Tolerability and Efficacy of Daylight Aminolevulinic-acid-photodynamic Therapy (ALA-PDT) Compared With Conventional ALA-PDT for Treatment of Actinic Keratosis on the Face or Scalp | Aminolevulinic acid/ Second | Phase 1/ Completed | University of California, San Francisco | Actinic Keratoses | [75] |

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|---|---|---|---|---|---|---|
| NCT03281811 | A Pilot Study of Photodynamic Therapy in Refractory Plaques and Tumors of Mycosis Fungoides | Aminolevulinic acid/ Second | Early Phase 1/ Completed | Mayo Clinic | Refractory Mycosis Fungoides | [76] |
| NCT00122876 | A Phase 1/2 Open-Label Study to Evaluate Safety and Preliminary Evidence of Effectiveness of Tumor Ablation With Talaporfin Sodium (LS11) and Interstitial Light Emitting Diodes (LEDs) in the Treatment of Subjects With Inoperable Hepatocellular Carcinoma (HCC) | Talaporfin Sodium/ Second | Phase 1 and 2/ Completed | Light Sciences Oncology | Carcinoma, Hepatocellular Liver Neoplasms | [77] |
| NCT03003065 | Safety and Tumoricidal Effect of Low Dose Temoporfin Photodynamic Therapy in Patients With Inoperable Bile Duct Cancers (Foscan® Study) | Meso-tetrahydroxyphenylchlorin/ Second | Phase 2/ Completed | Chinese University of Hong Kong | Cholangiocarcinoma , Klatskin Tumor | [78] |
| NCT02464761 | PDT for the Treatment of Vertebral Metastases: A Prospective Phase I Clinical Trial | Visudyne/ Second | Phase 1/ Completed | Sunnybrook Health Sciences Centre | Vertebral Metastases | [79] |
| NCT00068068 | Safety and Efficacy of Treating Refractory Cancers With the Litx™ System: Phase II Safety and Efficacy Study in Patients With Liver Metastases From Colorectal Cancer That Have Failed Chemotherapy | Talaporfin Sodium/ Second | Phase 2/ Completed | Light Sciences LLC | Liver Metastasis | [80] |
| NCT01292668 | A Phase I Study for Superficial Basal Cell Carcinoma to Determine the Irradiance-Dependent Pain Threshold for Methylaminolevulinate (MAL)/PDT. | Protoporphyrin IX and Methylaminolevulinate/ Second | Phase 1/ Completed | Roswell Park Cancer Institute | Basal Cell Carcinoma of the Skin, Recurrent Skin Cancer | [81] |
| NCT00002935 | A Phase II Study of the Safety and Efficacy of Photodynamic Therapy in Carcinoma in Situ of the Esophagus | Photofrin/ first | Phase 2/ Completed | Roswell Park Cancer Institute | Esophageal Cancer | [82] |
| NCT00322699 | Sequential Whole Bladder Photodynamic Therapy (WBPDT) in the Management of Superficial Bladder Cancer | Photofrin/ first | Phase 1 and 2/ Completed | North Florida/South Georgia Veterans Health System | Superficial Bladder Cancer | [83] |
| NCT00014066 | A Phase I Study of PDT Combined With High Dose Rate (HDR) Brachytherapy for Patients With Obstructive Bronchogenic Carcinoma | Photofrin/ first | Phase 1/ Completed | Roswell Park Cancer Institute | Lung Cancer | [84] |
| NCT00978081 | Photodynamic Therapy for Premalignant and Early Stage Head and Neck Tumors | Aminolevulinic acid/ Second | Phase 1/ Completed | Abramson Cancer Center at Penn Medicine | Head and Neck Cancer, Precancerous Condition | [85] |
| NCT00002963 | Cutaneous Absorption and Intralesional Penetration of Topical Amino-Levulinic Acid in Basal Cell Carcinoma and Squamous Cell Carcinoma as Measured by In Situ Fluorescence and Intensified Video Fluorescence Microscopy | Aminolevulinic acid/ Second | Phase 2/ Completed | Roswell Park Cancer Institute | Non-melanomatous Skin Cancer | [86] |
| NCT00003923 | Phase II Study of Photodynamic Therapy With PHOTOFRIN (Porfimer Sodium) for Injection in Patients With Malignant Bile Duct Obstruction | Photofrin/ first | Phase 2/ Completed | Memorial Sloan Kettering Cancer Center | Extrahepatic Bile Duct Cancer, Gallbladder Cancer, Liver Cancer, Pancreatic Cancer | [87] |

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| NCT00453336 | A Phase II Clinical Trial on the Efficacy of Photodynamic Therapy With Porfimer Sodium (Photofrin®) for Malignant and Pre-Malignant Lesions and Condemned Mucosa Syndrome in the Upper Aerodigestive Tract | Porfimer sodium/ first | Phase 2/ Completed | University of Miami | Head and Neck Cancer, Precancerous/Nonmalignant Condition | [88] |
| NCT03033225 | Phase II Study of EUS-Guided Verteporfin PDT in Solid Pancreatic Tumors (VERTPAC-02) | Verteporfin/ second | Phase 2/ Completed | Mayo Clinic | Advanced Pancreatic Carcinoma, Metastatic Pancreatic Carcinoma, Stage IV Pancreatic Cancer AJCC v8 | [89] |
| NCT01854684 | A Phase I Study of Surgery Plus Intraoperative PDT With Temoporfin in Patients With Resectable Primary Non-small Cell Lung Cancer (NSCLC) With Ipsilateral Thoracic Nodal (N1 or N2) or T3/T4 Disease | Temoporfin/ second | Phase 1/ Completed | Roswell Park Cancer Institute | Stage IIIA Non-Small Cell Lung Cancer, Stage IIIB Non-Small Cell Lung Cancer | [90] |
| NCT01770132 | Open-label, Single-center, Non-randomized, Phase I, Dose-ranging Study of Endoscopic Ultrasound (EUS) Guided PDT With Photofrin® in Locally Advanced Pancreatic Cancer | Photofrin/ second | Phase 1/ Completed | John DeWitt | Stage III Pancreatic Cancer | [91] |
| NCT00103246 | Phase I Clinical Trial Using Topical Silicon Phthalocyanine (Pc 4) PDT for the Treatment of Pre-Malignant and Malignant Skin Conditions | Silicon phthalocyanine 4/ Second | Phase 1/ Completed | Case Comprehensive Cancer Center | Lymphoma, Non-melanomatous Skin Cancer, Precancerous Condition | [92] |
| NCT00054002 | Surgery and Intracavitary PDT for the Treatment of Malignant Pleural Mesothelioma; The Use of Light Delivery Fibers With Large Diffusers | Porfimer sodium/ Second | Phase 2/ Completed | Roswell Park Cancer Institute | Malignant Mesothelioma | [93] |
| NCT00007969 | A Phase 1/2 Uncontrolled, Open Label Study Of Photodynamic Vaccination In Patients With Stage III/IV Malignant Melanoma | Verteporfin/ second | Phase 1 and 2/ Completed | QLT Inc. | Melanoma | [94] |
| NCT00083785 | Safety and Effectiveness of Treating Cancers With the Litx™ System and Chemotherapy. Section A: Phase II Safety and Effectiveness Study in Patients With Liver Metastases From Colorectal Cancer | Talaporfin sodium (LS11)/ Second | Phase 2/ Completed | Light Sciences LLC | Hepatocellular Carcinoma | [95] |
| NCT00054171 | A Pilot Study of Short (1-2.5 h), Medium '(4-6 h) and Long (18-24 h)' Applications of 20% Topical ALA-PDT for Photodynamic Therapy of Cutaneous T and B Cell Lymphomas and Cutaneous Infiltrates of Early CLL | Aminolevulinic acid/ Second | Phase 2/ Completed | Roswell Park Cancer Institute | Leukemia, Lymphoma | [96] |

**Market-approved photosensitizers for cancer PDT**

Several PSs have been widely approved and are commercially available for clinical use in photodynamic therapy (PDT) for cancer treatment. Among these, Photofrin® (porfimer sodium) was the first PS to gain FDA approval in the United States in 1993, and it is also approved in Canada and Japan for the treatment of esophageal cancer, NSCLC, and superficial bladder cancer. Foscan (temoporfin) received approval in 2001 in the European Union for the treatment of advanced head and neck squamous cell carcinoma. Levulan® (ALA), approved by the US FDA in 1999, and Metvix® (methyl aminolevulinate, MAL), approved in 2001 in the EU and Australia, are both used for the treatment of actinic keratosis and basal cell carcinoma. Radachlorin®, a chlorin-based PS, was approved in Russia and South Korea in 2005 and is used in various solid tumors. More recently, Tookad® (padeliporfin) was approved in Europe and Israel in 2017 for the treatment of low-risk prostate cancer. These PSs approved for the market are indicators of the successful clinical translation of PDT as a cancer treatment and promote its further role in oncology practice [97-99]. They have also been approved by regulatory bodies

in various countries, further solidifying the promise of photodynamic solutions for treating specific types of cancer both therapeutically and safely.

## Conclusion

PDT has gained recognition as a minimally invasive and targeted cancer treatment modality, with the PS playing a pivotal role in determining its efficacy, selectivity, and safety. Advances from first-generation PSs like Photofrin® to second and third-generation agents have significantly improved key characteristics such as light absorption in the therapeutic window (600–800 nm), singlet oxygen yield, tumor selectivity, and rapid systemic clearance. In particular, third-generation PSs, often conjugated to antibodies or peptides or encapsulated in nanocarriers, have shown enhanced tumor targeting and reduced off-target toxicity. Preclinical and clinical research support integrating PDT with immunotherapy, chemotherapy, and gene therapy, promising synergistic antitumor effects. Despite challenges such as limited tissue penetration, tumor heterogeneity, and regulatory hurdles, the development of image-guided PDT, activatable PSs, and AI-assisted treatment planning continues to push the boundaries of this modality. With growing evidence and technological innovation, PDT, especially with next-generation photosensitizers, is poised to play a significant role in the future of precision oncology.

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## Authors contribution

None

## Declaration of interest

The authors declare no conflict of interest.

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