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REVIEW ARTICLE

Exploring artificial intelligence-driven photodynamic therapy to advance cancer treatment

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Abstract

Due to its multifaceted nature, cancer remains a formidable disease that continues to cause substantial mortality globally. Conventional treatments, such as surgery, chemotherapy, and radiation therapy, often fail to adequately control this aggressive disease, thereby reducing the quality of life of affected individuals. Photodynamic therapy (PDT) has emerged as a promising treatment modality that utilizes lasers to destroy cancer cells. While PDT has shown promise as a safer and more targeted treatment with fewer side effects compared to some conventional therapies, it faces certain limitations, such as limited light penetration for deep tumors and the need for tissue oxygenation in hypoxic regions. The emergence and potential use of artificial intelligence (AI)-driven technologies in PDT may offer favorable outcomes for cancer treatment by addressing some of the limitations of conventional PDT. AI uses machine learning (ML) and deep learning (DL) algorithms to continuously learn, adapt to changes, recognize abnormalities in a dataset, and make accurate predictions. In this review, we propose integrating AI tools, such as ML and DL, with PDT to combat cancer and address some of the limitations of conventional PDT. The combination of AI and PDT could improve the precision and effectiveness of PDT for cancer treatment by monitoring the effects of PDT during treatment, advancing imaging techniques for better diagnosis of specific tumor types, enabling monitoring of light in real time, and overcoming light-delivery limitations associated with deep, internal tumors, with the potential to improve overall clinical outcomes in cancer patients.

Keywords: Cancer; Photodynamic therapy; Artificial intelligence; Machine learning; Deep learning

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1. Introduction

Photodynamic therapy (PDT) is a minimally invasive treatment method used in oncology to destroy cancer cells. The technique utilizes photosensitizing agents, also known as light-sensitive drugs, which are irradiated at specific wavelengths to absorb light.[1] PDT relies on the presence of a photosensitizer (PS), oxygen, and light to produce reactive oxygen species (ROS) for therapeutic effects. The PSs' mode of action is to absorb light and excite to the excited singlet energy level (often referred to as S1). S1 can then undergo intersystem crossing to the (lowest) triplet state, which forms an

intermediate in the production of ROS, such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals.[2] The S1 state can also return to the ground (S0) state by emitting a photon (fluorescence) or by losing energy to heat through rovibrational energy transfer or internal conversion (Figure 1). Moreover, through a cascade of biochemical events, the resulting photoproducts from this process cause targeted tissue damage, leading to tumor cell death through apoptotic or necrotic pathways.[1] PDT can also damage tumor blood vessels, preventing them from receiving the blood that they need to survive.[3] In addition, it may trigger the immune system to attack the tumor cells, even in other areas of the body.

In many cases, PDT offers several clinical advantages over conventional cancer treatments. It is a minimally invasive method with fewer side effects compared to surgery or chemotherapy.[1,3] The technique is also valued for its selective ability to target diseased cells and tissues while causing less damage to normal, healthy cells through the enhanced permeability and retention (EPR) effect. The EPR effect allows nanoparticles to selectively accumulate in tumor tissue more than in normal tissue due to the leaky vasculature (caused by rapid and abnormal growth) and poor lymphatic drainage of tumors.[4] Nanoparticles conjugated to a PS can enhance this effect.[5]

In PDT, nanoparticles are utilized as carriers to deliver the PS to the target tumor site.[6] Their selective delivery of the PS is achieved by adding antibodies or ligands that recognize receptors overexpressed on the surface of tumor tissues, thus reducing off-target effects and enhancing the efficacy of PDT.[5,7] Furthermore, PDT causes little to no scarring post-treatment because it does not significantly damage the connective tissue, and unlike radiation therapy, it can be repeated multiple times in the same location.[1,8]

Despite these advantages, PDT has several important limitations. Tissue oxygenation is essential for PDT; therefore, tumor cores within dense tumor masses can be difficult to treat[1,9,10] (Figure 2). The same challenge applies to tissues within hypoxic microenvironments caused by disorganized tumor vasculature, perinecrotic areas within tumors, and poorly vascularized metastatic sites.[11] Hypoxia in PDT can reduce the treatment's efficacy. The highly abnormal vasculature, coupled with the rapid proliferation of tumor tissues, makes certain regions hypoxic due to insufficient oxygen supply. The oxygen used in PDT may also exacerbate tumor hypoxia, thus limiting the success of therapy.[12] A potential solution is the development of PSs that can function as their own oxygen source. A study by Sun *et al.*[13] demonstrated the application of an O_2-generating metal–organic framework-based hydrophobic PS delivery system (BSA-MnO_2/Ce6@ZIF-8). In their study, ZIF-8, a specialized subclass of organic frameworks, was included as a pH-responsive drug carrier. By coating the PS (Ce6@ZIF-8) with bovine serum albumin (BSA)–MnO_2 nanoparticles on its surface, the conjugated product, BSA-MnO_2/Ce6@ZIF-8, was endowed with the capacity to generate O_2 in the tumor microenvironment, thus relieving hypoxia in tumors, enhancing the efficiency of PDT, and holding great promise for application in clinical practice.

In addition, the development of Type I PSs is another potential solution to the challenges posed by hypoxia at tumor sites. Compared to Type II PSs, which require

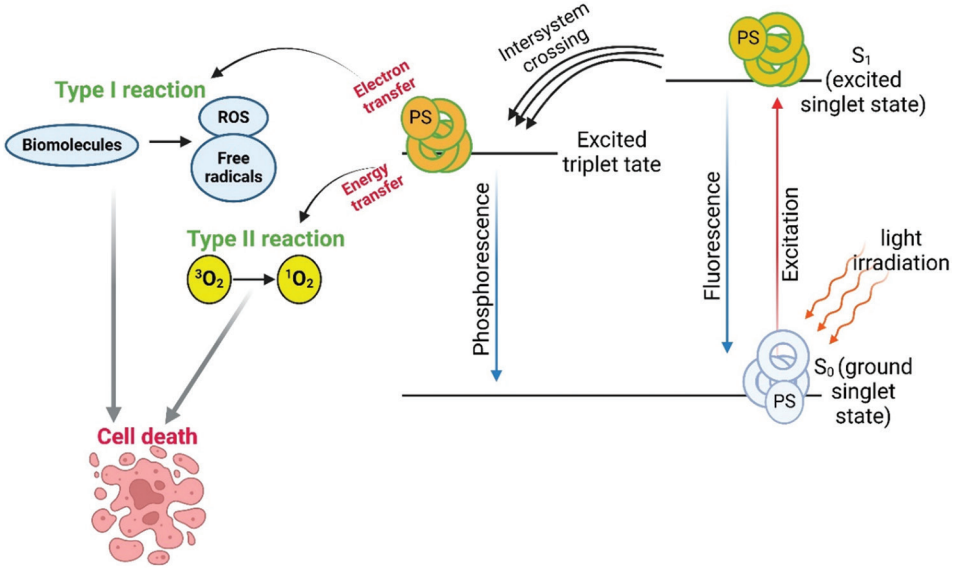

Figure 1. Schematic diagram illustrating the mechanism of action of Type I and Type II reactions in photodynamic therapy. Figure created by authors.

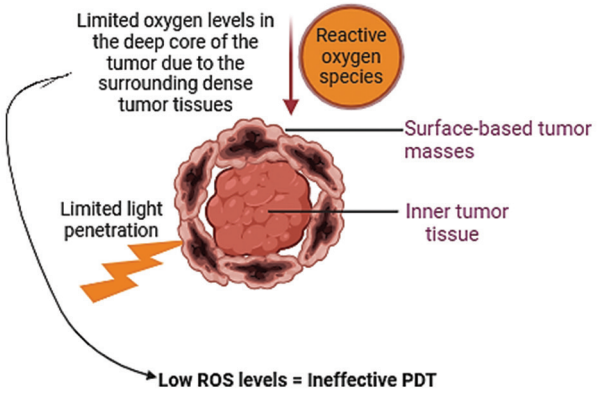

Figure 2. Light- and oxygen-related limitations in photodynamic therapy (PDT) that reduce the treatment efficacy. Figure created by authors. Abbreviation: ROS: Reactive oxygen species.

molecular oxygen to generate singlet oxygen, Type I PSs use electron or hydrogen atom transfer to generate ROS byproducts, such as hydroxyl and superoxide radicals, as well as hydrogen peroxide.[14] These species can be found in environments with limited oxygen availability. One of the current advances includes the use of crystalline, porous organic semiconducting polymers known as covalent organic frameworks (COFs), with applications in deep-tissue imaging, cancer therapy, drug delivery, and biosensing due to their excellent tunable functionalities and high structural and thermal stability.[14,15] In 2019, a study developed COFs by introducing 2D π-conjugation and used them as a novel Type I PS to improve PDT.[16] The novel COFs were synthesized by linking two previously inactive molecules, which could not generate ROS on their own, to two distinct COF types (COF-808 and COF-909). The resulting COFs showed excellent ROS production capabilities, with high porosity and surface areas of 2,270 and 2,610 m^2/g, respectively, enabling them to enhance oxygen diffusion and efficient ROS release within tumor cells while showing excellent biocompatibility and photostability. Over 80% of tumor cells were killed by COF-909, supporting the development of Type I PSs in addressing PDT challenges associated with hypoxic environments.

Another challenge in PDT is treating disseminated metastases with the current technology.[10] Accurately targeting specific tissues is crucial, but it is challenging with deep-seated tumors, particularly those that can only be reached through surgery. In PDT, light penetration depends on the irradiation wavelength, which determines how much light reaches the target tissues. Therefore, tumor depth determines the irradiation wavelength that must be selected, thereby making it challenging to directly treat larger, deeper tumors with this method.[17,18] In this case, fiber optic cables, which are thin fibers that transmit light, are employed to deliver light to various parts of the human body, typically by being inserted through an endoscope.[19] In addition, treatment efficacy is limited because PS activation occurs only at shallow tissue depths, preventing deeper tissues from receiving adequate light exposure.[10] For patients receiving PDT, this can result in partial tumor destruction and may lead to tumor regrowth.[12]

Some PSs exhibit low solubility, which may render them photodynamically inactive in aqueous solutions, thereby hindering their *in vivo* use.[12,20,21] In addition, the absorption properties of the PS in the tumor after administration can limit its homogeneous distribution throughout the tumor. This reduces the number of active PS molecules in the tumor area, thereby leading to incomplete tumor tissue destruction.[12] Furthermore, if the absorption spectrum falls outside the therapeutic window (600–700 nm), this can result in low light absorption by tumor cells and prolonged photosensitivity.[10] Thus, improving PS absorption, specificity, and distribution to enhance anti-tumor effects, while minimizing off-target effects, remains a key area for development. Artificial intelligence (AI)-mediated PDT, therefore, aims to address some of the limitations of conventional PDT.

2. AI

AI refers to the development of systems or machines to perform tasks that typically require human intelligence.[22] Such systems are developed to simulate cognitive functions such as problem-solving, prediction, learning, reasoning, and language understanding.[23] One of the key advantages of AI is its ability to anticipate and address challenges presented by users as they arise, enabling it to operate intelligently and adaptively. In addition, AI is capable of learning and identifying normal and abnormal patterns from a vast dataset and drawing reasonable conclusions.[24] Moreover, AI systems are highly autonomous and dynamic, enabling them to continuously learn and advance as new data emerges. The hierarchy and specificity of AI can be described using deep learning (DL) and machine learning (ML) systems (Figure 3).[25] In the medical field, DL algorithms are typically used to analyze medical images, such as magnetic resonance imaging (MRI) and X-ray images, and to detect conditions, such as fractures and tumors, with high accuracy, often matching or exceeding the standard performance of human radiologists.[26] DL also uses data mining and convolutional neural network (CNN) techniques to identify specific data patterns for detecting diseases in large datasets. Models used for predictive analytics, which form part of ML, rely on enormous amounts of data from electronic health records (EHRs) to forecast disease outbreaks, individual health outcomes, and

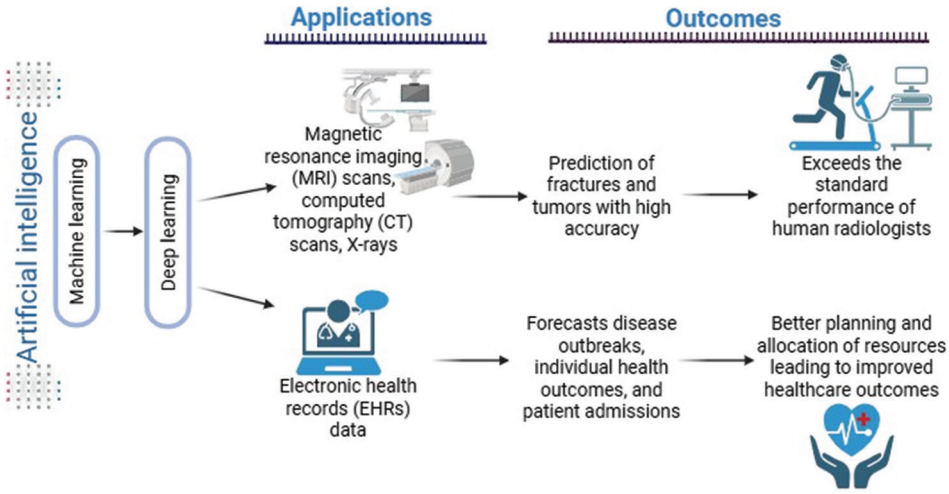

Figure 3. Artificial intelligence through machine learning and deep learning systems. Figure created by authors.

patient admissions, thereby assisting healthcare providers with planning and allocation of resources more effectively and sustainably.[27]

Another area of ML application is medical diagnostics, which addresses the challenge of effective and accurate disease diagnosis. This challenge arises from the complexities associated with various disease mechanisms. In addition, there are various stages of progression, and certain symptoms can mimic other diseases, making accurate detection difficult even at the earliest stages. The application of ML using quantitative and qualitative data is a potential solution.[28] Scientists can benefit from an easier workflow enabled by ML, which can automate specific tasks cost-effectively with a rapid turnaround time.

The use of AI may also enable personalized treatment plans by analyzing patient-specific data, which can guide and improve treatments.[25] A research study by Huang *et al.*[29] explored ML as a prediction tool using gene expression data from patients to predict their response to chemotherapeutic drugs. Their study involved gene expression data from 175 cancer patients, obtained through RNA sequencing and microarray. The models effectively predicted the patients' treatment responses with more than 80% accuracy across multiple drugs, thus demonstrating AI's promising role in predicting patients' treatment responses.[29]

Sheu *et al.*[30] used AI and EHR data to predict the differential response of 17,556 patients to four types of antidepressants over a 4- to 12-week period. Both structured and unstructured EHR information and models were used. The outcome labels from their study were acquired through expert chart review and AI-automated imputation. Different models were trained and used, including deep neural networks, a regularized generalized linear model, a gradient boosting machine, and a random forest. The performance of these models was tested and compared. All models similarly showed good predictive performance, as indicated by their predictor performance scores. The models enabled the estimation of treatment response probabilities within patients and across different classes of antidepressants for the same patient. Moreover, additional information could be obtained regarding patient-specific factors driving treatment response. The study demonstrated that AI modeling and EHR data can be effectively utilized to accurately predict the antidepressant response of each patient. The outcomes could be beneficial for guiding clinical decisions to select more effective treatments and for making the selection process less time-consuming.

However, beyond this, there are also ethical considerations that need to be addressed. Integrating AI into psychiatric decision-making raises critical concerns around data privacy, confidentiality, and misuse of EHR data. As beneficial as AI is in providing key algorithmic predictions, it must not override clinical judgment, as unintended biases in the generated data could influence the type of treatment a psychiatric patient should receive, which can be unethical. Strict measures and protection policies should be implemented to address this issue. For one, proper data storage systems and secure communication protocols should be put in place to prevent unauthorized access and misuse of critical information. In addition, the issue of unintended biases, which may lead to diagnostic errors and misleading treatment decisions, should be addressed by ensuring that the system is properly trained on data from diverse groups of individuals to develop a fair and unbiased AI system. Moreover, human specialist oversight should be maintained to preserve sensitivity,

empathy, and fairness across diverse groups of patients. In this way, these measures support the safe use of AI in healthcare and its adaptation to areas such as PDT in cancer.

3. AI-mediated PDT and its applications

In the previous section, we discussed the importance of AI across general healthcare and highlighted recent advances in the field. In this section, we will focus on the use of AI specifically in the context of PDT for cancer treatment, drawing on a variety of research studies.

3.1. AI's ability to analyze patient data and predict responses

The ability of AI to perform patient data analysis and predict responses has the potential to guide the personalization of PDT for cancer. By leveraging advanced algorithms, AI can process large amounts of data, including data acquired from EHRs, patient demographics, medical histories, imaging data, laboratory results, and previous treatment outcomes.[31] EHRs enable clinicians to use pre-existing data to improve treatment. The EHR data are primarily derived from information on all individuals who interact with the medical systems, thus allowing researchers to focus on all target groups and reducing biases.[32,33] AI can use this comprehensive repository of patient data history to track the progression of cancer by identifying patterns and correlations that may not be easily detected with traditional methods. AI can then identify relevant trends and predict possible PDT outcomes more accurately. Tools capable of this include ML models, such as neural networks and support vector machines, that identify complex patterns and correlations that may not be apparent to clinicians.[34]

3.2. Overcoming light-delivery limitations associated with deep, internal tumors

PDT offers multiple benefits for cancer treatment. However, its efficacy depends on light delivery for PS activation. This is particularly difficult in treating deep, internal tumors, as light delivery to these regions tends to be limited.[35] Wireless technologies have enabled remote light delivery to tumors. For example, biocompatible, miniaturized optoelectronic devices convert radio-frequency energy into optical energy using high-frequency or ultra-high-frequency electromagnetic waves. These devices emit light at a single wavelength to activate PSs. Despite their advantages, a key limitation is that they typically use only a single wavelength for activation. For example, Foscan has two absorption peaks at 406 nm and 652 nm, but only the 652 nm wavelength is typically used in PDT.[35] This means that 78% of the light absorbed at 406 nm does not contribute to generating oxygen-free radicals for tumor destruction. This could be due to non-radical pathways or energy dissipation mechanisms, such as fluorescence and heat production. These processes would then limit the amount of energy left to produce the radicals required to destroy the tumor cells.

A study by Kim *et al.*[35] introduced a DeepLabCut-informed, low-power wireless telemetry tool combined with a Monte Carlo thermal/light simulation system to address these key limitations. The simulator used DeepLabCut-assisted wireless telemetry with an optimized combination of light sources and wavelengths to enable adequate illumination of tumor tissues through a high-throughput (<20 mice) and multi-wavelength system. Moreover, a simulation platform was established to numerically analyze photon propagation, light absorption, and heat dissipation in tissues and tumors. Heat maps and plots were generated to show heat dissipation during illumination, indicating no significant temperature changes and thereby limiting thermal damage to surrounding tissues. The performance of hypericin and Foscan was compared based on light penetration, energy absorption, uniformity, time for targeted light energy delivery, and temperature variation. The simulations determined that the optimal PDT conditions for hypericin were achieved with a 590 nm light source and a 25% duty cycle, while for Foscan, a combination of 406 nm and 652 nm light sources with the same duty cycle was most effective. Foscan penetrated deeply into solid tumors and effectively utilized both deeply penetrating (>600 nm) and superficial (400 nm) wavelengths for photoactivation. A major challenge in PDT for treating solid cancers, particularly in hard-to-reach areas such as the gastrointestinal tract, was delivering light effectively. The proposed solution, a miniaturized, biocompatible, and low-power optoelectronic device that produces light at multiple wavelengths, could potentially expand the clinical applications of PDT. *In vivo*, Foscan-mediated PDT in cancer xenograft models resulted in substantial suppression of tumor growth and showed potential for clinical application.

3.3. Screening PDT drugs that can overcome the blood–brain barrier (BBB)

The blood–brain barrier is a selective barrier that prevents many substances and therapeutic agents, including PSs in PDT, from entering the brain. It consists of "tight junctions" between cells and specialized proteins that actively efflux certain molecules back into the bloodstream, making it difficult for drugs to reach the tumor.[36] This poses a significant challenge in treating glioblastoma. ML techniques can be used to predict which drug compounds can effectively cross the BBB based on their molecular structures, using resources such as B3DB and DeePred-

BBB.[37,38] This allows for rapid, non-invasive identification of BBB-permeable compounds that could be employed in PDT. In addition, other models, including MegaMolBART, learn from molecular representations in the Simplified Molecular Input Line Entry System format to accelerate the prediction of BBB permeability.[38] These models can extract molecular features of different drugs and use them to predict whether a novel drug can cross the BBB, enabling rapid identification of suitable drugs without extensive testing in animal or laboratory settings. Instead, researchers can use AI models to evaluate potential drugs and focus only on potential targets, making it easier to develop effective PDT treatments.

3.4. Monitoring the dynamic effects of PDT using DL

Accurately detecting how cancer cells respond to PDT during treatment is essential for monitoring and assessing treatment efficiency. However, conventional methods, including clonogenic assays, often face challenges due to the complexity of cell morphology and the inefficiency or inaccuracy of manual analysis. In addition, many of these assays are limited in their ability to capture immediate cellular responses to PDT, such as changes in shape, membrane blebbing, and cytoskeletal reorganization. Therefore, there is a need for automated and efficient methods to monitor and understand the dynamic responses of cancer cells to PDT, potentially in real time. This would assist in determining whether PDT is an effective treatment option for specific cancer types and guide future decisions on whether to proceed with or avoid its use. Furthermore, this could play a crucial role in optimizing treatment for better outcomes.

A study conducted by Rahman *et al.*[39] addressed these key limitations using the Cellpose model to assess PDT performance at different laser intensities. Cellpose is a DL, CNN model capable of segmenting cells and nuclei to allow for quick visual optimization. It is more resilient to noise and better at handling diverse cell morphologies than watershed methods. In addition to segmenting cells and backgrounds, Cellpose predicts the flow gradient toward the center of each cell, providing more comprehensive cell information. This model was employed to evaluate the performance of PDT on hepatocellular carcinoma cells treated with L-AuNP@TMT, a gold nanoparticle formulation. Images from these experiments were captured and processed with Cellpose for data analysis. There were clear changes in cell shape and size after PDT, such as shrinkage and altered forms, showing how cells respond to the treatment. The Cellpose model effectively identified these patterns. It performed well, with an accuracy of 86.43% and an R^2 value of 0.84, indicating it can reliably measure cell size. Its ability to handle different cell shapes made it useful in studying mixed cell populations. Logistic growth modeling also helped explain how PDT affects cancer cell growth and structure. The image results were quantified, and graphs were constructed, showing the influence of varying laser intensities on the averaged area, curvature, and circularity of cells over time. From the results, a clear picture emerged of how cell morphology and behavior change during and after PDT. In this way, the response of the cells to PDT could be observed in real time, providing insights not only at the end of treatment but throughout the process. This could enable adjustments to treatment parameters, such as laser intensity, exposure time, and dosage, to optimize the effectiveness of PDT based on real-time cellular responses. Therefore, DL approaches, particularly the Cellpose algorithm, can be used to analyze the effects of PDT on cancer cells. Unlike traditional methods, which suffer from noise sensitivity, DL allows for a more automated and objective approach. This approach could enhance the precision of cancer therapy evaluation and hold promise for developing personalized and more effective treatment strategies. In addition, it may be worthwhile to apply this principle to detect changes in morphology and size in healthy cells resulting solely from PS uptake. This approach would facilitate monitoring cellular alterations in the absence of irradiation to evaluate dark toxicity. While dark toxicity might not immediately cause overt cell death, certain signs of stress, including cell size and shape changes, can be detected and quantified over time. Using Cellpose for high-resolution imaging and automated cell morphology analysis could provide a quantitative assessment of different PS concentrations as a function of time. This could enable more targeted dosing of PSs, potentially identifying thresholds at which specific concentrations of PS, in the absence of irradiation, begin to adversely affect healthy cells and tissues. This could improve the precision of PDT, targeting tumors more effectively while reducing harm to surrounding healthy cells and tissues in clinical PDT.

3.5. Combating misdiagnosis in gastric tumors

Photodynamic diagnosis (PDD) endoscopy with the oral intake of 5-aminolevulinic acid detects tumors by exploiting the fluorescence of protoporphyrin IX (PpIX), the primary fluorescent metabolite of 5-aminolevulinic acid. PpIX fluoresces red under ultraviolet light due to its peak emission at 630 nm, thus allowing endoscopists to distinguish tumor tissues from non-tumor tissues. However, the classification of PDD-positive regions is subjectively determined by expert endoscopists. A previous study revealed additional lesions, categorized as tumors, in up to 13 cases using PDD endoscopy.[40] Objective methods that can reliably identify tumors are

needed to minimize the risk of overlooking lesions that can lead to misdiagnosis.

An objective method, such as defining the fluorescence characteristics of segmented regions in PDD images, could improve the accuracy and reduce missed diagnoses. A study by Yamashita *et al.*[41] addressed the problem of subjectively identifying gastric tumors from PDD images. To address this limitation, two AI-based methods were developed: one using a multi-layer neural network to identify tumor regions in LAB color space, which corresponds to human perception of color, where L represents brightness and A and B represent color tones; and method two using a CNN for tumor detection and segmentation. AI-based methods for detecting gastric tumors during PDD endoscopy showed greater potential than visual assessment by expert endoscopists. Both methods in their study proved effective at consistently identifying tumors. Method two, using a CNN, was particularly effective against photobleaching, making it more reliable for detecting subtle differences in color between adjacent regions. Importantly, the AI systems matched the performance of expert endoscopists by consistently identifying strong-positive, weak-positive, and negative lesions. For example, certain lesions initially detected by experts were accurately identified by method two, showcasing AI's potential to reduce missed diagnoses. Moreover, the methods showed tumor detection efficiencies of 77.8% for method one and 93.3% for method two. Although further validation with larger sample sizes is necessary, early results suggest that AI could significantly enhance tumor detection accuracy, especially in challenging cases. Despite current limitations such as the high cost of the 5-aminolevulinic acid-based PDD procedure and the need for further optimization, the integration of AI could make PDD endoscopy more suitable for broader clinical use, potentially improving early detection of gastric tumors.[41]

3.6. Cell viability assessment after PDT on the tumor using DL

Monitoring tumor cell death in response to PDT is vital for assessing treatment efficacy. Traditional methods, such as the methyl thiazole tetrazolium (MTT) assay and cell activity staining, are commonly used but have limitations due to optical interference from the PS and the labor-intensive preparation required for both methods.[42] In a study by Lv *et al.*,[43] it was proposed that applying stain-free bright-field imaging, combined with a DL algorithm, could provide a more efficient and accurate approach, reducing labor costs and enabling real-time cell viability assessment in clinical PDT. The application of AI in their study was introduced following the treatment of human cervical cancer cells with indocyanine green chlorin e6 nanoparticles for PDT to induce cell death. Following this treatment, cell viability was assessed using MTT and live/dead cell staining, which both confirmed the effectiveness of PDT in inducing cell death. To detect and classify cells, the researchers used both manual and automated image labeling. At first, they manually marked tumor cells to distinguish live and dead cells in fluorescence images. Since this was time-consuming, they later created an automated labeling system. This involved building an AI model that binarized images, used morphological operations to separate the cells, and added bounding boxes around each cell to train the model. The YOLOv3 (You Only Look Once) model was selected to automate cell detection, as it has proven effective in identifying small objects such as cells and provides an optimal balance between speed and accuracy for complex biomedical datasets. YOLO is a real-time object detection algorithm that divides an image into a grid and simultaneously predicts bounding boxes and class probabilities during a single evaluation of the network, hence the term "you only look once." This makes it fast and efficient for real-time detection. Using Darknet53 improved the detection accuracy for live and dead cells. After training and optimization, the model could classify cells with confidence scores, enabling the calculation of tumor cell survival rates based on live/dead counts. This DL technology was applied to recognize tumor cells and predict cell death in stain-free bright-field images, achieving a 94% mean average precision for live cells and 71.3% for dead cells. This method was faster, more efficient, and significantly reduced labor and reagent costs compared to MTT and live/dead staining. The technique is still under development, and further improvement is needed, which may be achieved using a larger dataset to train the model. This technique holds significant promise as a method for assessing post-PDT cell viability in the near future. Advances in ML can thus enhance tumor treatment evaluation by providing faster and more reliable analysis methods.[43]

4. Challenges and ethical considerations

4.1. Validation and clinical implementation through trials

The integration of AI in PDT to improve treatment methods holds great potential. However, since this is an emerging field, only a limited number of studies have been conducted. Substantially more research, testing, and validation are needed before the formal implementation of such novel treatment strategies. As previously mentioned, AI could potentially be used to tailor treatments to individual patients, optimize dosage and timing, enhance precision in targeting cancer cells, and predict patient responses.[32] Exploring this research could improve PDT

treatment for cancer, and the resulting findings could assist clinicians in making more informed and precise treatment decisions. Therefore, clinical trials should be conducted to assess the safety, accuracy, and reliability of these models across diverse patient populations and tumor types, thereby establishing their clinical utility.

4.2. Ethical considerations

Several ethical considerations must be addressed when implementing AI-driven PDT. One of the primary concerns is data privacy, as using genomic and imaging data requires strict protection policies and laws to safeguard patient information.[44] Although strict protection policies could be a potential solution, implementing them is complex and challenging. Multimodal data, including medical imaging, genomic sequences, and real-time oxygen monitoring, cannot remain fully anonymous without compromising its utility for AI models. Even when each data type is individually de-identified, combining them can create unique patterns that allow for re-identification. However, excessive de-identification risks removing important, clinically valuable information, reducing model accuracy, and limiting its applicability across patients.

Cross-institutional data sharing is another layer of concern, as hospitals and research centers often have different legal requirements, consent practices, and ethical guidelines. Addressing these issues requires effective governance frameworks that balance patient safety, regulatory and legal compliance, and the efficiency of AI-mediated PDT. Therefore, enforcing stringent policies alone is not sufficient. Future potential solutions require a combination of technical strategies and institutional governance. Federated learning, a type of ML, could be used across multiple institutions to train a shared model without sharing raw patient data, thus ensuring privacy and data protection.[45] Moreover, advanced de-identification techniques, including synthetic data generation and differential privacy, could help protect sensitive information while preserving clinically relevant information, but excessive anonymization may compromise model performance.[46] In addition, cross-institutional privacy standards and governance frameworks are crucial for ensuring responsible and safe data sharing across research facilities and hospitals. This includes setting up proper data storage systems and secure communication protocols to prevent unauthorized access and misuse of sensitive information.[44] Furthermore, transparency in AI decision-making is crucial to building trust among healthcare service providers and affected individuals. It is essential to ensure equitable access to AI-driven PDT treatments for all cancer patients, regardless of their geographical location or socioeconomic status.

Moreover, EHR data are derived from individuals who interact with the healthcare system, allowing analyses across diverse patient groups and helping to reduce selection biases.[32,33] However, AI systems that learn from extensive datasets may inherit biases present in these datasets, leading to biased or misleading outcomes. This can result in diagnostic errors and flawed treatment decisions. Therefore, it is crucial to address algorithmic biases and ensure the development of fair and unbiased AI systems that provide equitable treatment for all patients.[32,33,47] Taken together, these approaches could provide a proactive strategy for safeguarding privacy while also advancing AI-driven PDT.

5. Future directions: Research and development

Despite recent technological advancements in cancer diagnosis and treatment, concerns about the accurate detection, monitoring, and characterization of tumors remain.[48] The precise assessment of cancer radiographic images is crucially dependent on visual evaluation, which may be achieved using advanced computational systems for analysis and interpretation. AI may be employed as a qualitative method to address these critical areas by automating processes involved in the initial image assessment of tumors and by shifting the clinical workflow for radiographic detection to inform treatment decisions and determine whether to administer an intervention. Although research on AI in oncology has not been extensively validated for generalizability and reproducibility, the outcomes of ongoing studies show concerted efforts to develop AI technology for clinical use and ultimately impact the future of oncology.

As previously mentioned, cancer remains a life-threatening disease associated with substantial morbidity and mortality. Extensive research has been conducted on eradicating cancer; however, despite these efforts, fully treating it remains a challenge. With ongoing technological progress, scientists are increasingly exploring advanced tools (such as AI) for application in cancer care. At the time of initial tumor detection, accurately differentiating true tumorigenic cells from non-tumorigenic cells that mimic tumor features is essential. The classification needs to be based on biological aggressiveness to inform the intensity and type of treatment to be initiated, as well as the predicted clinical course. Ongoing research efforts to enhance AI-driven PDT capabilities focus on several key areas, such as the analysis of medical images and other diagnostic data to allow for more precise differentiation between healthy and cancer cells/tissues, thereby improving diagnosis and treatment options.[49]

In medical imaging, AI-based tools such as computer-aided detection (CADe) systems can be utilized for the initial screening of tumors to minimize clinical oversight, biases, and inconsistent reproducibility[50-52] that can arise from manual image interpretation by physicians and radiologists.[53] These CADe systems are designed using pattern-recognition algorithms, thereby highlighting regions that exhibit suspicious imaging characteristics to the interpreting clinician. This helps identify tumors that may have been missed during computed tomography (CT) or MRI screening, thereby improving sensitivity to abnormalities and the time of interpretation.[53,54] This has been applied in breast cancer, in which early detection is a challenge. CADe systems have been successfully used to locate microcalcification clusters during a mammogram, thereby improving the rate of prognosis.[55]

Moreover, efforts to enhance characterization will enable more specific targeting of tumors during PDT, ultimately minimizing collateral damage and improving the overall treatment outcomes.[32] In this context, tumors can be characterized using segmentation, diagnosis, and staging. Tumor segmentation refers to defining and delineating the boundaries of a tumor in medical imaging data from CT or MRI scans. This allows analysis of tumors' specific regions and suspicious lesions that require evaluation for signs of malignancy. The application of computer-aided diagnosis (CADx) systems is to systemically quantify tumor features, enabling more accurate and reproducible data.[48] Such detailed information can influence the type of treatment to opt for and the PS dosage to administer in PDT.

Depending on the stage of their progression, tumors can be characterized by their appearance and the extent of their spread through tissues or organs, and this will influence the clinical course to be administered. The most commonly used staging system is the tumor, node, metastasis (TNM) system, which was developed between the 1940s and 1950s.[56] With AI, newer technological systems have been employed to assess tumor multifocality. For example, a study by Song *et al.*[57] assessed maximum tumor size, multifocality, and lymph node status in 86 patients with breast cancer using ultrasound, mammography, MRI, or CT. The results were analyzed using 18-fludeoxyglucose positron emission tomography (FDG-PET) with and without CADe. The data were assessed and compared with pathological assessment results, revealing that CADe for MRI was feasible in assessing tumor multifocality in breast cancer individuals, even though it was not effective in lymph node evaluation.

Another unmet need in PDT is the development of photosensitive molecules with high singlet oxygen quantum yields (SO-QYs) to improve treatment performance. The identification and screening of such PSs using traditional methods are often time-consuming and labor-intensive. To overcome these limitations, researchers are employing ML models to build quantitative structure–property relationship (QSPR) frameworks that can accurately predict SO-QYs and provide insights into the photophysical and photochemical properties of PSs across a range of experimental conditions. This results in faster screening and the development of effective PSs for improved PDT performance. In a recent study, the researchers aimed to create more widely applicable quantitative structure–activity relationship models by including a broader range of photosensitive molecules.[58] Instead of focusing on a single core structure, they examined various molecular types that use the 1,3-diphenylisobenzofuran (DPBF) consumption method to assess SO-QY. This included diverse core structures, such as organic dyes, porphyrins, and boron-dipyrromethenes. The team also gathered important details about the testing conditions relevant to the DPBF method, including the solvents used and the excitation wavelengths. They employed two different molecular representation techniques to generate two feature matrices, which were then input into four ML algorithms, yielding eight distinct QSPR models. After assessing the performance of each model, they selected the best-performing model from each feature matrix for further analysis, particularly to evaluate feature importance. The findings from these models were compared. To validate the effectiveness of the models and the accuracy of their analyses, the researchers designed and synthesized two new photosensitive molecules and experimentally measured their SO-QYs under conditions comparable to those used for existing compounds. By comparing experimental results with model predictions, they demonstrated strong predictive performance across different testing conditions, thereby confirming the models' reliability. The application of ML models allowed for rapid identification of PSs with potentially high SO-QYs, eliminating the need for extensive experimental testing of multiple drugs simultaneously. This approach could save time, reduce lab costs, and accelerate the development of PSs, helping to improve PDT.

Another promising area is the development of AI systems to track physiological parameters, such as oxygen levels during PDT treatment, in real time and thereby adjust treatment parameters to suit the patient's needs.[59] Monitoring tissue oxygen level in PDT is vital for understanding the therapy's physiological mechanisms and optimizing light dosimetry.[60] Since the effectiveness of PDT depends on the presence of molecular O_2 in the target tissue, early research indicated that oxygen levels during PDT could predict treatment success.[61] Photochemical oxygen consumption and microvascular shutdown can

deplete oxygen, potentially affecting treatment outcomes if levels drop excessively. Monitoring oxygen levels during PDT can help predict treatment efficacy by tracking changes in tissue oxygenation over time.

Moreover, oxygen distribution in tissues involves complex convective and diffusive processes. During PDT, monitoring hemoglobin saturation is essential because oxygen depletion can affect tumor cells near blood vessels. Various *in vivo* techniques, such as Fourier-transform spectral imaging, diffuse reflectance spectroscopy, pressure of oxygen (pO_2) histography, and phosphorescence lifetime spectroscopy, measure blood and tissue oxygenation during PDT. However, direct methods tend to be invasive.[60] These methods are highly accurate but come with significant drawbacks that can negatively affect patient comfort, safety, and the overall feasibility of their use in clinical settings. For example, pO_2 histography involves inserting microelectrodes directly into the tissue to measure partial pO2 at various points. These electrodes provide localized and precise oxygen readings. This method is invasive because it requires physically penetrating the tissue, which can cause pain, discomfort, and potential tissue damage. There is also a risk of infection at the insertion sites. In addition, it is challenging to perform this technique repeatedly or in sensitive areas such as the brain or heart.

Invasive methods are typically unsuitable for continuous monitoring over long periods, which is crucial for understanding how oxygen levels fluctuate throughout PDT. One potential way to mitigate the risks associated with invasive methods is to use AI-enabled technologies that provide accurate, real-time data to optimize PDT. AI-driven oxygen management devices, including AI Compass, OxyGEN, and OxyNov, initially designed for respiratory care,[62] can be adapted for use in PDT. OxyNov, for example, is a medical device that uses a closed-loop system to dynamically adjust the flow of oxygen to maintain target peripheral capillary oxygen saturation levels during a patient's treatment. These devices use pulse oximeters to measure the patient's oxygen saturation levels. In addition, they provide real-time feedback and integrate AI algorithms to adjust the oxygen supply based on the patient's specific needs during treatment.[63] This helps prevent hypoxia or hyperoxia, ensuring precise oxygenation at targeted sites. As is known, PDT relies on the generation of ROS by a PS drug on exposure to light in an oxygen-dependent process. The ROS generated is used to eliminate cancer cells, and PSs that do not generate sufficient ROS in poorly oxygenated tissues are unlikely to eliminate all cancer cells.

It should be noted that these AI devices do not and are not intended to, generate ROS directly. Nonetheless, they are essential for optimizing the patient's physiological state during treatment.[62] By monitoring and adjusting blood oxygen saturation and other vital signs, these AI systems help maintain an optimal oxygen environment, ensuring that the PS can perform effectively. This is important in preventing issues such as hypoxia, which could cause a reduction in ROS production and reduce the therapy's effectiveness. By reducing the need for invasive monitoring, AI not only offers the potential to improve patient experiences but also increases the accessibility and applicability of advanced oxygenation monitoring in clinical practices. The potential clinical outcome would be the ability to monitor and maintain sufficient oxygen levels for ROS generation, thus ensuring effective PDT outcomes.

Finally, expanding research to a broader range of cancers, including deeper and less accessible tumors, will represent a significant milestone for AI-driven PDT. This progress will be particularly impactful by developing specialized protocols and delivery mechanisms tailored to these challenging environments. Drug development is also an interesting area of focus, where AI can be used to screen vast chemical libraries/databases to identify novel PSs with better optical properties.[64] By focusing on these key areas for AI-driven PDT, the efficacy and safety of cancer treatments can be improved, and clinically relevant advancements can be achieved across multiple oncologic domains.

6. Conclusion

The application of AI in oncology has yielded key findings that show promise for improving both cancer diagnosis and therapy. Among these were the ability of AI to enhance the precision and efficiency of PDT by monitoring its effects during treatment, advancing imaging techniques for better diagnosis of specific tumor types, improving light delivery to deep, internal tumors, and fast-tracking the process of identifying effective light parameters for PDT. Moreover, AI-driven PDT enhanced tumor targeting through medical imaging and real-time monitoring, allowing for dynamic adjustments to the treatment protocol and leading to promising clinical outcomes. The potential advancement of PDT in oncology, driven by the integration of AI, immunotherapy, and nanotechnology, holds significant promise for enhancing treatment efficacy. Future exploration of this novel technology could lead to a more precise and effective personalized treatment modality, potentially improving overall clinical outcomes. However, given the novelty of this integrated treatment, more work is needed to advance its development and validation, and with appropriate tools, it can ultimately contribute to more effective cancer treatment.

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Conflict of interest

The authors declare no conflicts of interest.

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