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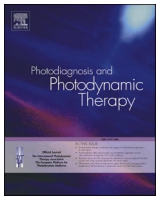

Review Article

Clinical and pre-clinical advances in the PDT/PTT strategy for diagnosis and treatment of cancer

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ABSTRACT

Photodynamic therapy (PDT) and photothermal therapy (PTT) have demonstrated great potential to diagnose and combat localized cancers. As a matter of fact, these techniques are less invasive and have fewer side effects than traditional cancer treatments like surgery, chemotherapy or radiotherapy. This review summarizes the clinical progress in the theranostics (diagnosis and treatment) of various types of regional cancers using these two light stimuli techniques, PDT and PTT. Therefore, clinical advances in cancer diagnosis based on PDT are detailed, including fluorescence-guided PDT for intraoperative cancer detection, optical coherence tomography (OCT)-guided PDT for early cancer detection, and imaging by magnetic resonance imaging (MRI) or computed tomography (CT) assisted through PDT/PTT. Moreover, clinical studies of breast, prostate, skin, gynecologic, head, neck and other varieties of cancer have been addressed to compare the main conditions of these treatments. This work also discussed the principal advantages and drawbacks of PDT and PTT in tumor targeting and cancer therapy. Finally, the usage of nanoparticles as photosensitizers (PSs) and photothermal agents (PAs) have been analyzed. In this manner, the authors have compiled relevant updated studies so that researchers interested in these areas can access it speedily.

1. Introduction

Cancer is one of the leading causes of death around the world [1]. According to the World Health Organization (WHO), cancer was responsible for an estimated 10 million deaths in 2020, making it the second cause of death globally [1]. The WHO also estimates that there are more than 18 million new cases of cancer each year, and the 70 % occurs in low and middle-income countries [1]. The burden of cancer can be seen in both, mortality and morbidity statistics, from different countries [2].

The most common types of cancers reported in 2020 were breast (2.26 million cases), lung (2.21 million cases), colorectal (1.93 million cases), prostate (1.41 million cases), skin non-melanoma (1.20 million cases), and stomach (1.09 million cases) cancers. Research is constantly being developed to find more effective treatments, giving hope to those fighting this disease [1]. Treatments used to combat cancer include surgery, chemotherapy, radiation, biomarker testing, hormone therapy, hyperthermia, immunotherapy, stem cell transplant, targeted therapy, photodynamic therapy (PDT), photothermal therapy (PTT) and synchronic PDT/PTT. Relating to last three strategies, it is worth to mention that they still being carried out only in pre-clinical studies, and due to the limited access of light, PDT and PTT are only suitable for treating localized cancers (not to systematic cancer) [3,4].

Regarding PDT, it is a non-invasive and highly selective technique used to destroy tumors and infectious agents [5–8]. It combines a photosensitizer (PS), light (in an appropriate wavelength), and oxygen to produce reactive oxygen species (ROS) such as superoxide ($O_2^{\cdot-}$), hydroxyl radical (·OH), or singlet oxygen ($^1O_2$) [9]. Since 1978, PDT has been used to treat primary and secondary skin tumors [10]; and currently, it is employed to diagnose and treat a wide range of diseases, including some forms of internal cancers in the liver (metastasis), esophagus, neck, head, and lungs [11–15]. Within PDT, the activation wavelength and period of photosensitivity are among the most essential factors. Besides, the regulation of the hydrophilicity and lipophilicity of the PSs is essential for designing pharmaceutical formulation and administration routes [16]. In fact, newer PSs have been structurally

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modified to present an amphiphilic condition. It is important to mention that second-generation PSs based on porphyrin structure, such as benzoporphyrins, purpurins, texaphyrins, phthalocyanines, naphthalocyanines, and protoporphyrin IX (PpIX), have excellent selectivity of accumulation in tumor tissue, better photosensitizing properties, and more profound photodynamic action [17]. To enhance the therapeutic effect of PDT innovative strategies such as the use of nanomaterials or nanocomposites as PSs are being developed [18]. Nanotechnology has the potential to revolutionize the detection and treatment of cancer, its role comprises improving pharmacokinetics and reducing systemic toxicities of chemotherapies by selectively targeting and delivering anticancer drugs to tumor tissue [19]. Some nanomaterials such as liposomes, micelles, dendritic macromolecules, quantum dots, and carbon nanotubes have been employed in cancer treatment [20].

With respect to PTT, it uses light-absorbing agents called photothermal agents (PTAs) to generate heat when irradiated to destroy tumor cells [21]. This therapy is a promising strategy for cancer treatment due to its localized therapeutic effect by laser irradiation. Nevertheless, a mild-temperature PTT method is necessary to ensure a stable temperature below 43 °C for minimizing thermal damage to adjacent tissue [22]. PTT has been studied extensively since it efficiently inhibits the growth of solid tumors and accelerates photochemical reactions during hyperthermia which can trigger the immune response of the host [23,24].

On the other hand, PDT/PTT synergistic treatment represents a cutting-edge innovation in cancer therapy. By combining PDT's light-activated generation of ROS to damage cancer cells with PTT's localized heat induction to induce cell death, this dual approach enhances therapeutic efficacy [25]. Nanomaterials often serve as carriers to optimize light absorption, ensuring precise targeting and minimizing damage to healthy tissues. The synergy between PDT and PTT amplifies tumor destruction, overcoming limitations of each therapy alone, such as hypoxia in PDT and heat resistance in PTT, offering a promising strategy for more effective, minimally invasive cancer treatments [26,27].

Against this background, this review compiled the recent clinical developments within the last few years regarding the diagnose and treatment of different types of cancer by PDT, PTT, and synchronic PDT/PTT strategies. Therefore, we have divided this paper into four main sections. The first one comprises cancer diagnosis from PDT and PTT strategies including: (i) fluorescence-guided PDT for intraoperative cancer detection, (ii) optical coherence tomography (OCT)-guided PDT for early cancer detection, and (iii) perspectives in the diagnosis based on PDT/PTT along with magnetic resonance imaging (MRI) or computed tomography (CT). Then, we reported several clinical studies regarding the application of PDT/PTT in the treatment against breast, prostate, skin, ginecological, head, neck, and other types of cancer comparing the principal conditions of these treatments. The advantages and drawbacks of PDT and PTT in tumor targeting and cancer therapy were also discuseed. Finally, we addressed the perspectives for future clinical applications of PDT/PTT using nanomaterials. In this manner the authors aim to present an updated state of art of the diagnosis and treatment of cancer by these light stimuli techniques being PDT and PTT or both.

2. Clinical progress in cancer diagnosis based on PDT and PTT strategies

PDT studies in cancer diagnosis have been carried out since the 1960s. In that decade, Lipson et al. (1967) [28], carried out practical work using hematoporphyrin as PS to diagnose malignant neoplasms based on PDT, which were detected by emitting red fluorescence, while healthy tissue was shown in shades of gray [28,29]. Although PDT has been widely used as a treatment strategy, there have been significant advances in the application of PDT for cancer diagnosis. Some notable studies are mentioned below, including those related to the perspectives of PDT/PTT along with magnetic resonance imaging (MRI) or computed tomography (CT).

2.1. Fluorescence-guided PDT for intraoperative cancer detection

Fluorescence-guided PDT allows real-time visualization and detection of cancerous tissues during surgery. Therefore, it is possible to distinguish malignant tissues from normal ones, helping to mark specific body areas that must be removed in the operating room [30]. This fluorescence-based tool allows greater tissue preservation and causes minimal damage. For example, PSs like indocyanine green (ICG), 5-aminolevulinic acid (5-ALA), or methylene blue have been administrated in patients to obtain fluorescence emission upon light activation, and this signal is detected by special equipment such as fluorescence microscopy camera. Hence, surgeons can identify and selectively treat tumor cells [31]. This approach has been investigated in various types of cancer [32]. For instance, Dupont et al. (2019) [32], carried out a clinical study to diagnose glioblastoma. They employed 5-ALA to use the fluorescence phenomenon produced by the PpIX, a photosensitive molecule that targets tumor cells because of exogenous 5-ALA; thus, when the surgical cavity was irradiated with blue light (375–440 nm), the tumor tissues glowed red simplifying their localization [32]. As a matter of fact, malignat tissues of cancers in breast, colorectal, vulvar, lung, gastric, esophageal and melanoma have been detected by sentinel lymph node (SLN) mapping from fluorescence-guided PDT [33–35]. Fig. 1 depicts some examples of the obtained images from this approach.

Portable instruments for fluorescence-guided PDT have also been fabricated. For instance, Khan et al. (2019) [38], and Siddiqui et al. (2022) [39], designed a low-cost arrangement for the detection of oral cancer. It consisted of obtaining fluorescence images (after the irradiation of a light-emitting diode (LED)) using a conventional smartphone camera (see Fig. 2). For this porpuse these studies used PpIX (induced by 5-ALA), and blue LED of 405 nm in a dose of 100 J/cm^2. This approach helped to guide and follow-up the treatment of early oral cancer (surface lessions). In addition, it comprises a widely available and low risk platform with great potential to be integrated in telemedicine [38,39].

Therefore, when resection is the chosen alternative to treat cancer or it comprises the crucial first step capable of reducing the risk of tumor recurrence, fluorescence-guided PDT results very attractive. In addition to the benefits mentioned above, this tool could significantly improve the eradication of residual tumors owing to the synchronous delimitation of the tumor and its visualization during surgery. Nevertheless, it must be considered that some current PSs do not always discriminate the tumor well and surgical resection may be compromised; thus, the selection of PS is a key decision in this procedure.

2.2. Optical coherence tomography-guided PDT for early cancer detection

Conventional OCT is a no-contact and noninvasive imaging technology that provides high-resolution cross-sectional *in vivo* three-dimensional (3-D) images, based on low coherence interferometry, typically using NIR light, without impacting the analyzed tissue [40]. The resolution of the OCT is better than that of other medical imaging methods like ultrasound or MRI. OCT can be integrated into small probes and catheters (contact/invasive technology), allowing access to internal organs for cancer imaging and diagnosis. Regarding the latter, it is notably valuable when conventional microscopic tissue diagnosis, such as biopsy, is impossible. The advantage of OCT is its high soft-tissue contrast based on refractive index differences [41]. The effectiveness of OCT in the detection and diagnosis of cancer was first demonstrated through *in vitro* cell imaging, followed by a series of *in vitro/ex vivo* and *in vivo* studies on a broad spectrum of malignancies. Thus, when OCT is combined with PDT, clinicians can identify early-stage cancer lesions and precisely deliver light-based therapy. This approach has shown promise in detecting and treating early-stage skin cancers, the oral cavity, and the gastrointestinal tract [42,43].

A clinical study illustrated the potential of OCT in monitoring the application of 5-ALA by PDT using red, green, blue (RGB) LEDs with various correlated color temperatures to treat oral squamous cell

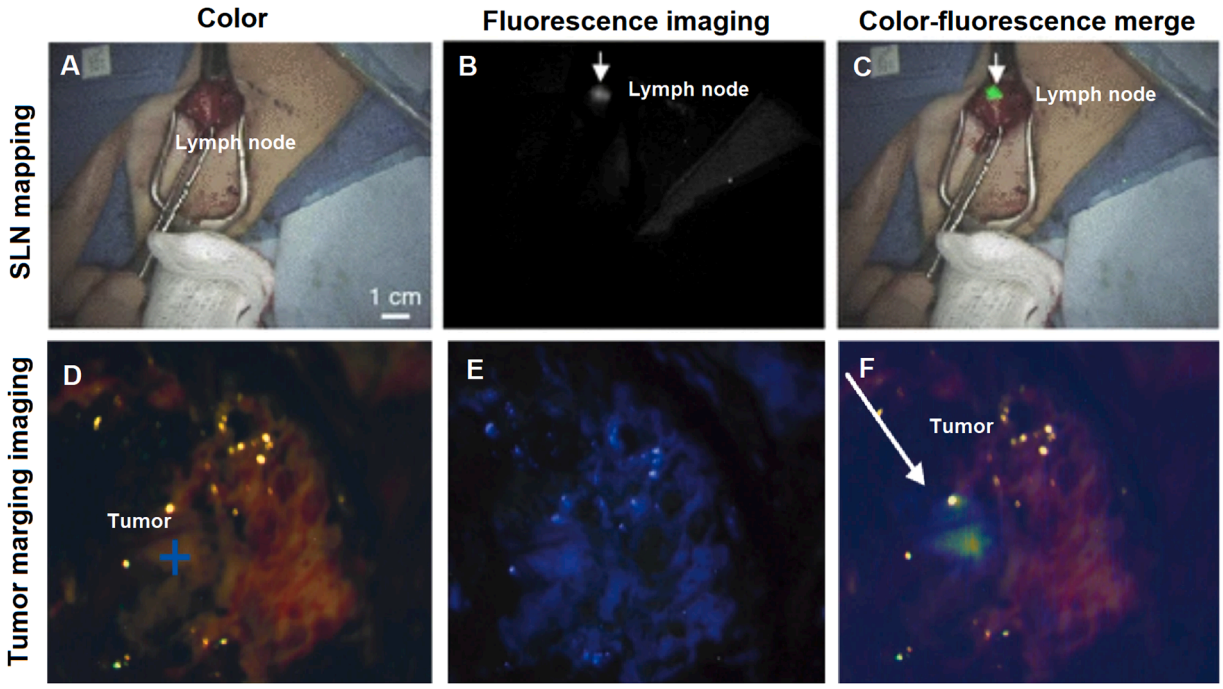

Fig. 1. (a-c) Breast tumor: (a) color image, (b) near infrared (NIR) fluorescence image, (c) merged image from (a) and (b). (d-f) Brain tumor in surgical resection of glioblastoma multiforme: (d) color image, (e) visible fluorescence image, (f) merged image from (d) and (e). Reproduced with permission from [33,36,37].

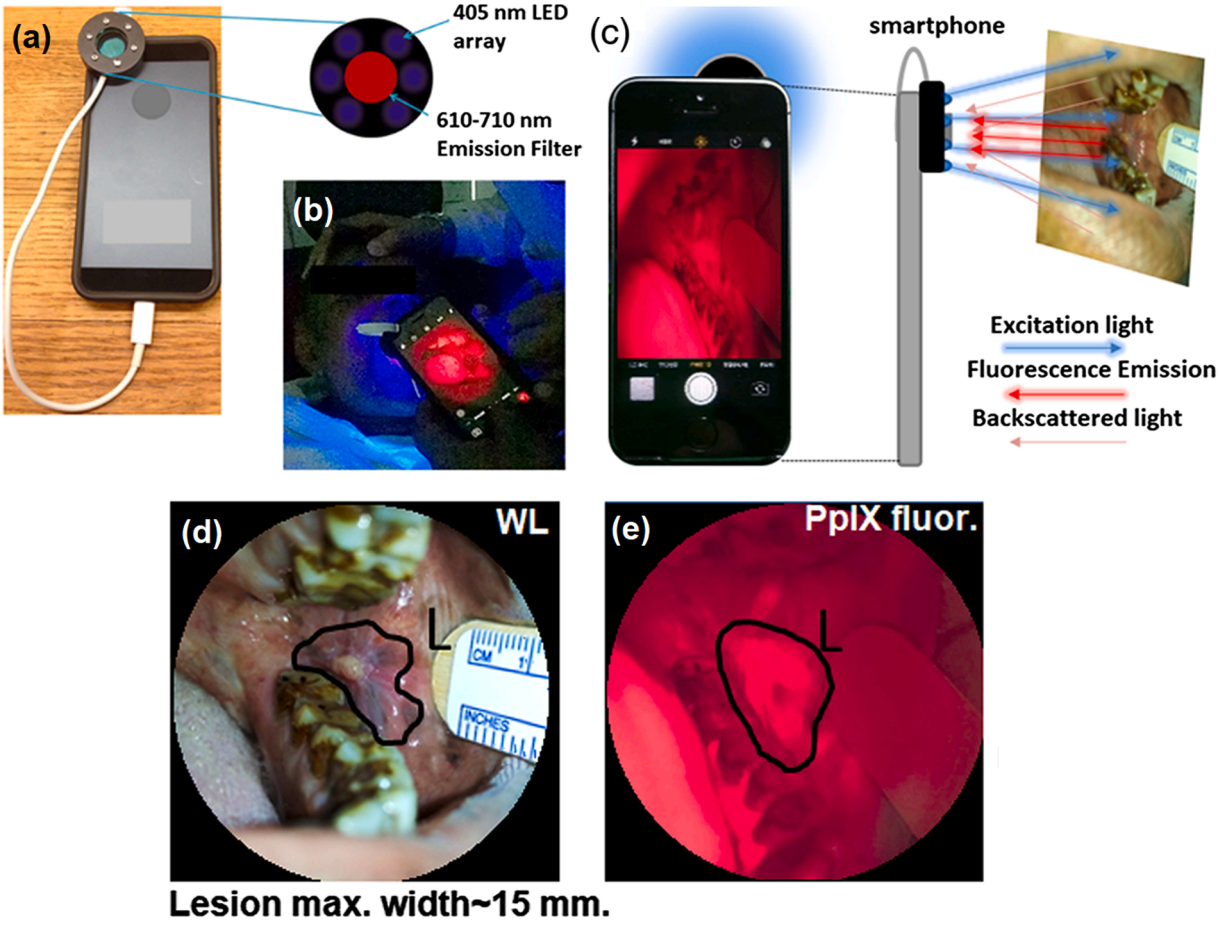

Fig. 2. (a) Smartphone attached with LED array and fitted with an emission filter, (b) PDT treatment: LED irradiaton to obtain PpIX fluorescence, (c) Light responses to LED irradiation, (d) Image with light (WL) and (e) fluorescence image. Adapted with permission of [39].

carcinoma (SCC). In the study carried out by Wang et al. (2013) [44], it was observed that in cross-sectional OCT images of cancerous oral tissues, the boundary between the epithelial (EP) and lamina propria (LP) layers disappeared. One week after the initial ALA-PDT treatment, the EP-LP boundary was not distinctly visible. However, after the third ALA-PDT treatment, OCT images obtained one week later clearly showed the re-establishment of the EP-LP boundary, indicating a favorable treatment response of oral cancer to ALA-PDT [44].

Similarly, it was illustrated that OCT has the technical capability to map the precise boundaries of tumors and could observe the alterations using PDT in patients with skin cancer in real time. In this clinical study conducted by Hamdoon et al. (2021) [45], metatetra(hydroxyphenyl) chlorine (mTHPC) was intravenously administered (dose of 0.05 mg/kg) in patients 48 h before illuminating the tissue. During PDT, a 652 nm diode laser was used, delivering a dosage of 20 J/cm^2 per treatment site. The OCT images captured after PDT revealed noticeable changes in the tissue structure, including the formation of swelling (edema) and the shedding of dead tissue (necrotic slough). These effects were particularly prominent in the initial weeks following treatment. Additionally, by OCT, it was possible to distinguish between the various layers of the tumor and the skin above it, with a maximum penetration depth of 1.5–2.0 mm in the specific model used for the study [45]. In Fig. 3 is depicted the obtained images by this study.

Likewise, Niculescu (2017) et al. [43], developed a pilot study using ALA- and methyl aminolevulinate (MAL)-PDT treatment with ten patients (3 male, 7 female) with superficial basal cell carcinoma (BCC) lesions. They indicated that OCT improved accuracy in detecting residual BCC lesions. Besides, they confirmed an excellent response after PDT compared with clinical inspection alone. The employed treatment was detectable, and completely cured lesions that were clinically suspicious for BCC and identified correctly [43].

Hence, significant advantages of OCT in cancer detection and treatment were evidenced, particularly when combined with PDT. OCT's high-resolution imaging, superior to other modalities like ultrasound or MRI, allows for precise tumor mapping and monitoring of treatment efficacy. The ability to visualize tissue response in real-time, as demonstrated in various clinical studies, underscores OCT's potential to enhance cancer treatment outcomes. However, while these findings are promising, further research is needed to standardize OCT's application across different cancer types and to explore its long-term impact on patient outcomes.

2.3. *Perspective in the diagnosis based on PDT/PTT along with magnetic resonance imaging or computed tomography*

MRI is a non-invasive, non-ionizing, tomographic imaging modality that is particularly useful for detecting and characterizing soft tissue pathologies like cancer [46]. Zheng T. et al. (2019) [47], prepared a

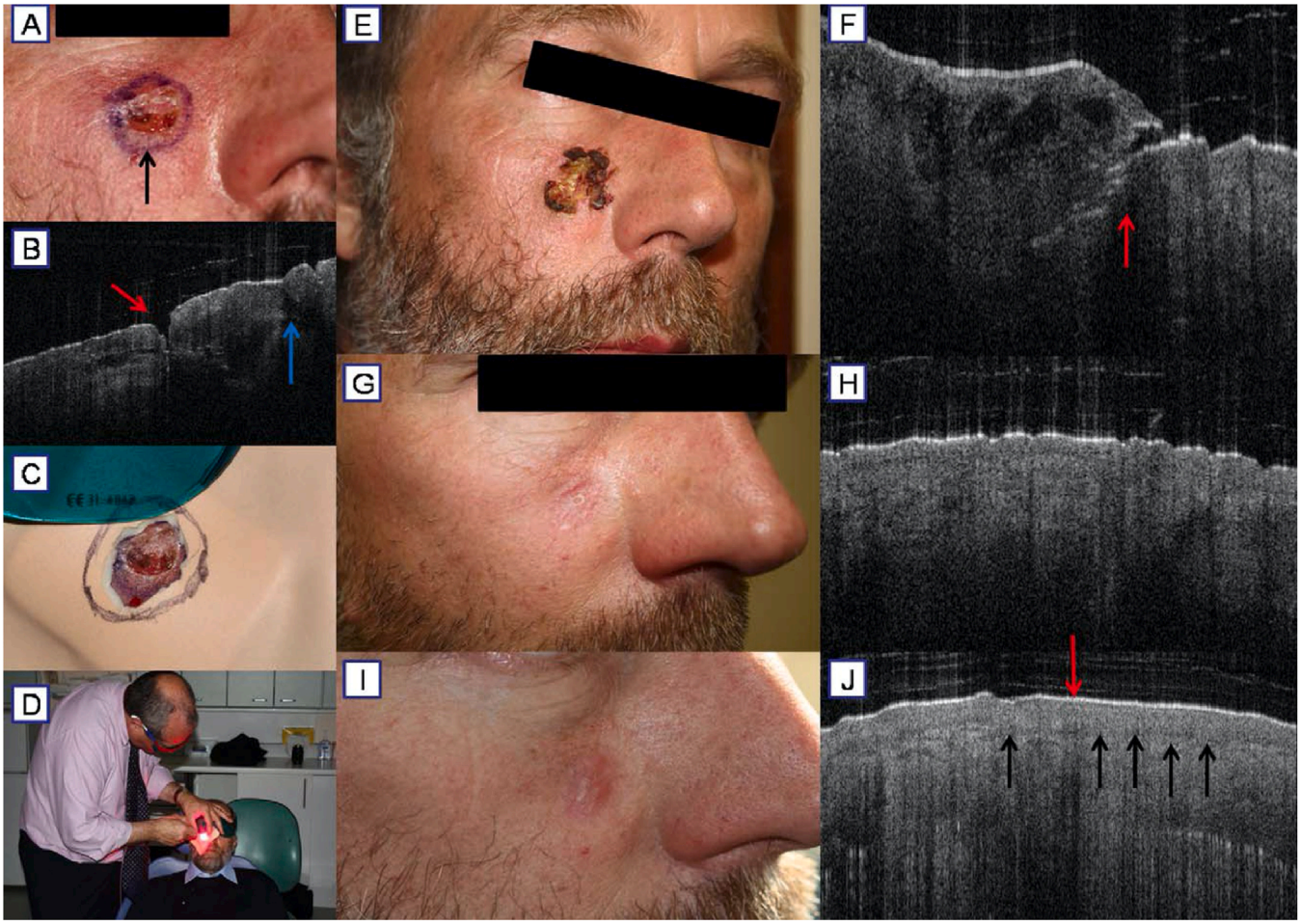

Fig. 3. OCT-PDT applied in skin cancer: (a) SCC face lession (black arrow); (b) OCT image showing the tumor margin (red arrow) and a vertical cleft with non-visible damage beyond the margin (blue arrow); (c) Real margins of SCC determined by OCT to fabricate a custom made template; (d) PDT; (e) SCC lession after 1 month; (f) OCT image of (e) showing vertical cleft with multiple empty spaces which indicate necrotic changes (red arrow); (g) SCC lession after 3 months; (h) OCT image of (g) showing healing with granulation tissue formation (slight poor differentiation in skin layer as the area is in state of healing); (i) SCC lession after 6 month; and (j) OCT image showing early differentiation of epidermal and dermal layers with distinctive dermo-epidermal junction (black arrows) and very thin stratum corneum layer (red arrow). Reproduced with permission from [45].

nanosystem for clinical anticancer applications against HeLa tumor-bearing mice using Prussian blue (PB, T_1-weighted MRI). The nanosystem exhibited excellent biocompatibility and good absorption in the NIR region, and their photothermal conversion was 25.73 % upon irradiation with 650 nm laser light (1.5 W/cm^2). This study verified that the nanosystem achieved a visualized synergistic therapy with the aid of MRI (see Fig. 4) [47]. Another material that was successfully employed to achieve the same aim comprises Fe_3O_4-core, which was used as a T_2-weighted MRI; Zhang H. et al. (2017) [48], could take images of tumor-bearing mice in the coronal and axial plane by MRI [48]. Therefore, from a single agent, it is possible to generate multiple functions such as PDT/PTT and responsiveness theranostic (combination of diagnosis and therapy) for MRI due to an exogenous light stimulus [46]. On the other hand, CT could briefly be used to analyze the position of metastasis of the lymph node and to refine the therapeutic regimens throughout PTT. It is possible to track the distribution of the PTA in the tumor sites for CT contrast agents for angiography and organic imaging in real time [49].

In this manner, PDT/PTT can be combined with targeted imaging to detect specific biomarkers of cancer cells to enhance safety and therapeutic efficacy. This approach enables non-invasive visualization and quantification of molecular markers associated with cancer progression [50,51]. Developing new imaging probes for cancer diagnosis is critical for early disease detection and management; therefore, techniques such as MRI and CT have been coupled with PDT/PTT. The use of nanoparticles for these diagnostic techniques is in the *in vitro/in vivo* phase and has good prospects for its use in the future.

3. Clinical progress in PDT/PTT for tumor destruction

Studies are currently underway to evaluate the effectiveness of PDT and PTT in the treatment of cancer. At the moment, PTT, although it has shown promising results, is still at the stage of *in vitro/in vivo* studies; while PDT is more established and consolidated, with several clinical trials being carried out for different types of cancer and disseminated worldwide [52]. Below are the clinical advances for PDT-based cancer treatments by body section.

3.1. Breast cancer

Breast cancer has the highest incidence in the USA, according to the American Cancer Society. It was estimated that in 2023, approximately 298 thousand women and 3 thousand men were diagnosed with invasive breast cancer, resulting in 43,700 deaths [53]. In women, the occurrence of breast cancer has been increasing since 2020 by 0.5 % due to factors such as weight gain after the age of 18, physical inactivity, and hormonal therapies in menopause. In addition, non-modifiable factors such as inherited genetic mutations (BRCA1 or BRCA2 genes), high density of breast tissue, a history of ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS), and receiving high-dose radiation to the chest before age 30, are risk factors for the occurrence of breast cancer [53].

Patients who underwent a mastectomy for breast cancer frequently experience recurrence as a side effect in the chest wall. Wyss et al. (2001) [54], and Cuenca et al. (2004) [55], employed PDT to treat this type of metastatic lesions, **providing** an excellent clinical response with minimal morbidity [54,55]. The first study treated the lesions of patients with 0.10 mg/kg of mTHPC intravenously PS. They were irradiated with a 652 nm laser diode and a light dose of 10 J/cm^2, producing an elimination of tumor lesions with minimal scarring after 8 to 10 weeks, which resulted in complete response in all patients. In the second work, 64 % of complete responses were obtained using 8 mg/kg of intravenously photofrin irradiated with a 630 nm laser diode and 150 to 200

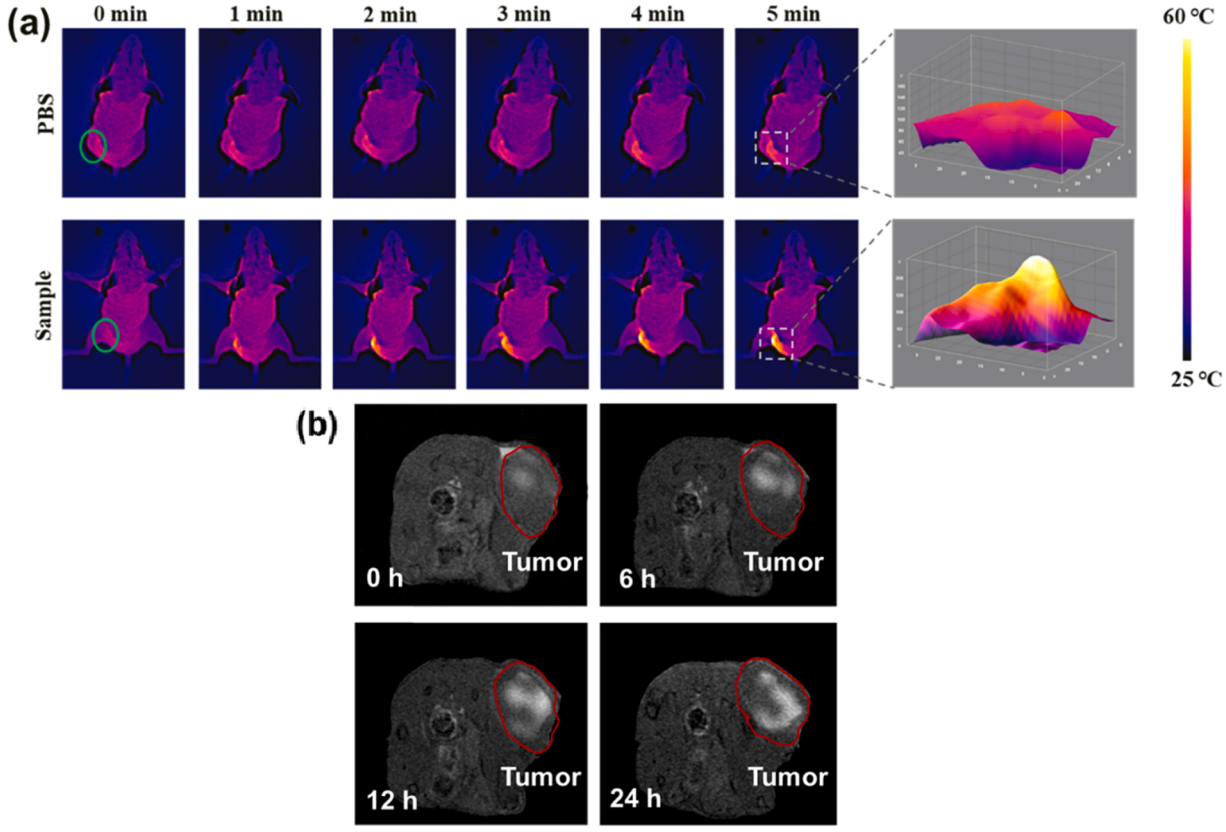

Fig. 4. (a) Thermal imaging of HeLa tumor-bearing mice treated with phosphate-buffered saline PBS (top) and nanosystem (sample-bottom) before and after tail vein injection under 650 nm laser irradiation (1.5 W/cm^2, 5 min); (b) *In vivo* T1-weighted MRI in HeLa tumor-bearing mice before and after tail vein injection of nanosystem. Adapted with permission from [47].

J/cm^2 doses. After 190 days of treatment, epithelial growth was observed without lesions [55].

One interesting clinical trial for treating primary breast cancer by PDT was reported in recent years by Banerjee et al. (2018) [56]. This work employed verteporfin (0.4 mg/kg) as PS. Fig. 5 shows that a 1 mm fiber laser with a 1 cm diffuser tip of 690 nm and 150 mW/cm power was used to irradiate the tumor. Complete tumoral necrosis resulted from a dose of 50 J [57].

PDT has been recognized as a significant treatment option for breast cancer due to its ability to target cancerous cells precisely while minimizing damage to surrounding healthy tissue. As a highly localized treatment, PDT offers promising outcomes, particularly for patients with early-stage breast cancer or those seeking alternatives to traditional methods. The importance of PDT is underscored by the growing number of breast cancer cases, since the new cases diagnosed annually demand for innovative and less aggressive treatments, like PDT, which is more pressing than ever.

3.2. Prostate cancer

This type of cancer is the fifth leading cause of cancer-related death in men worldwide [58]. While PDT shows promise as a potential treatment for prostate cancer, it is still considered an experimental or investigational therapy. Clinical trials and research studies are ongoing to evaluate the safety and effectiveness of PDT. Conventionally, prostate cancer is treated by radiotherapy or surgery [59].

Tookad, also called padoporfin, is one of the most used PS in clinical studies for prostate cancer treatment based on PDT. This PS is activated with NIR light at 753 nm. Azzouzi et al. (2017) [60], applied this vessel-targeted PS to treat low-risk localized prostate cancer using 4 mg/kg and irradiation of 753 nm, 150 mW/cm for 22 min 15 s. As a result, 41 % obtained a definitive absence of cancer at 24 months [60]. Likewise, Noweski et al. (2018) [61], used the same conditions of PS and irradiation (753 nm, 200 J), with a higher light dosage than the first study, achieving an efficacy of 75 % [61]. Thus, this vascular-targeted photodynamic therapy (VTP) is a promising tissue-preserving treatment that reduces side effects while maintaining oncological efficacy. It works by inducing focal ablation of tumor lesions through cell necrosis, targeting tumor vasculature with the photosensitizer WST-11 and a low-power NIR laser. Besides, it was demonstrated that the oncologic outcomes were superior for VTP compared to active surveillance over a two-year follow-up. The literature also highlights VTP's effectiveness in optimizing treatment parameters, making it a valuable option for prostate carcinoma by balancing therapeutic benefits with reduced harm.

3.3. Skin cancer

The WHO estimates that each year, there are 2 to 3 million non-melanoma skin cancers, and 132,000 melanoma skin cancers diagnosed worldwide. Melanoma is the most dangerous form of skin cancer. It has a higher potential to spread to other body parts if not detected and treated early. In the USA, the American Cancer Society estimated that in 2023, there were about 106,110 new cases of melanoma and 7180 deaths from this disease. Non-melanoma skin cancers (keratinocyte cancers), among others, include BCC and SCC. These types of skin cancer are generally less aggressive than melanoma and have a high cure rate. The exact number of non-melanoma skin cancer cases worldwide is difficult to determine, but estimates suggest that they account for most skin cancer cases. For decades, the conventional treatment consisted of surgical excision; nevertheless, this option can cause co-morbidities, and potential intolerance for repeated excisions. Likewise, topical treatments have also been employed using 5-Fluorouracil, imiquimod, and PDT, among others.

International guidelines recommend topical PDT as a treatment option to treat BCC, SCC, *in situ* (known as Bowen's disease), and actinic keratosis (AK) for lesions less than 2 mm thick due to natural barriers that restrict the penetration of the cream [62–65]. Generally, a PS, at topical cream or solution, is applied to the skin, which is selectively absorbed by cancer cells, taking a few hours. The PS is activated by exposing it to a specific wavelength of light, typically a laser or LEDs, to generate ROS that causes cell death in the cancerous tissue. This process helps to destroy the cancer cells while the surrounding healthy tissue is preserved. After PDT, the treated area may develop redness, swelling, and crusting, which usually resolves over time. Patients may require multiple sessions of PDT depending on the extent and type of skin cancer being treated. It is worth noting that PDT is primarily used for superficial skin cancers, and its effectiveness may vary depending on factors such as the size and location of the tumor.

Some frequent PSs used in PDT to treat skin cancer are MAL, 5-ALA, and photofrin. While 5-ALA is usually recommended for the treatment of BCC, AK, and Bowen's disease, MAL is commonly used for non-melanoma skin cancer treatment, such as thin nodular BCC and SCC, due to its methylation may penetrate the skin more effectively and enhance the accumulation of PpIX in cancer cells. Finally, photofrin is an injectable PS drug that circulates throughout the body and preferentially accumulates in cancerous tissues; photofrin-PDT may be used for more advanced or extensive skin cancers.

In Brazil, a multicenter clinical study was developed to treat BCC-type lesions using topical MAL-PDT in two sessions with an interval of seven days. Based on the results of this program, it was possible to obtain approval for the incorporation of PDT as an option for treating BCC-type injuries in the Brazilian public health system. The results proved cost-effective, as they present high efficacy rates in outpatient procedures, which do not require specialized professionals for application and do not present serious side effects that require medical interventions (see Fig. 6) [66,67]. Some new protocols have been developed to optimize the treatment protocol and make the outpatient routine more viable and

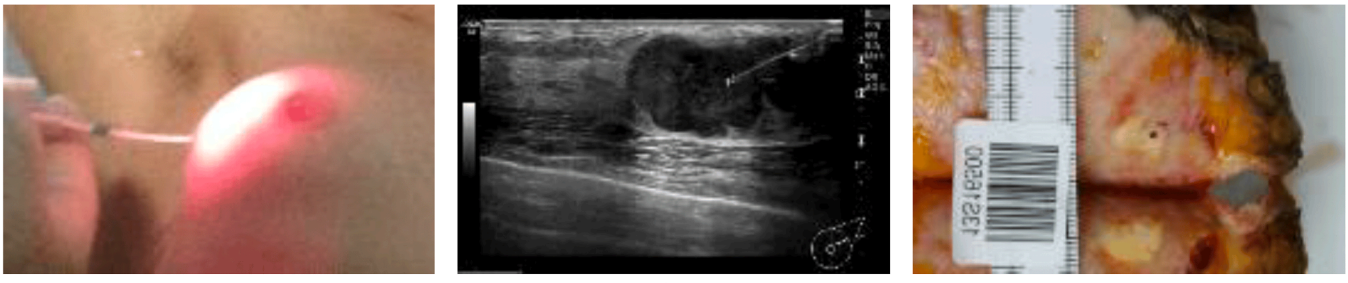

Fig. 5. (a) Laser fiber inserted into the tumor (under the armpit); (b) Ultrasound image of the laser fiber into the tumor; (c) Fiber track under microscope as a uniform, pale patch of PDT-induced necrosis in the resected tissue that has been sliced perpendicular to the needle track. The bottom uniform, pale region is on the cut's opposite side. Reproduced with permission of [57].

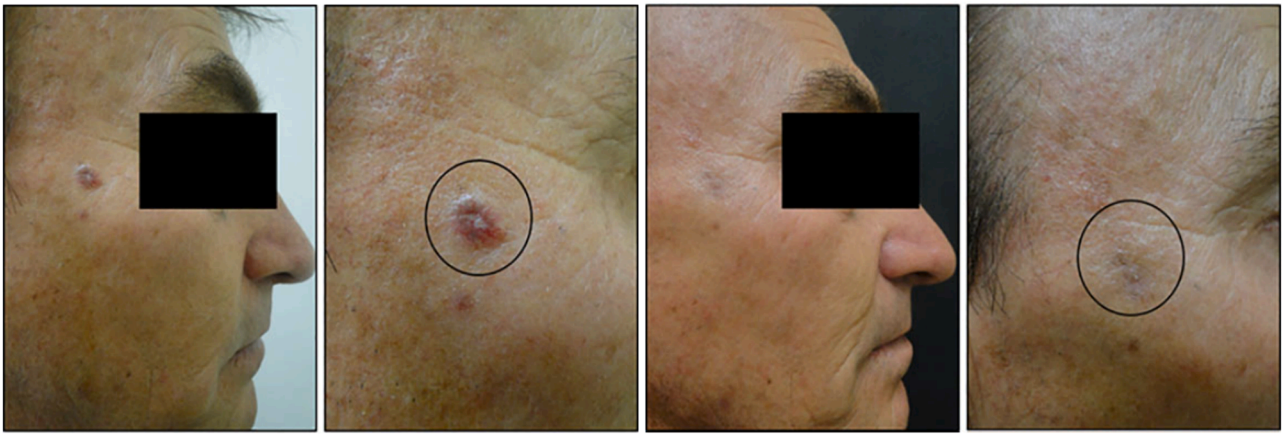

Fig. 6. Nodular BCC lesion located in zygomatic region, photos before and 30 days after the PDT. The circles mark the treated region. Reproduced with permission of [66].

comfortable for patients, demonstrating similar efficacy rates to the conventional protocol. A developed protocol, called single visit, established two treatment sessions to be carried out on the same day, the first incubation time being 3 h and the second immediately after the first irradiation, lasting 1.5 h [68,69]. Another protocol that has been studied is based on the single-visit protocol, but the second session is carried out at home using a portable device. After the first irradiation, the patient is discharged with an occlusive dressing containing MAL cream and the system positioned over the lesion. This device has lower irradiance, and although the treatment requires more time, the patient performs it in the comfort of their home and feels less pain inherent to the treatment [70, 71].

Seeking to overcome the skin's natural barriers and improve drug delivery to the lesion, physical and chemical strategies have been explored to increase the concentration and availability of PS in the target cell [72]. These strategies can both increase the effectiveness of the treatment and make the treatment suitable for thicker lesions. Hexaminolevulinate (HAL) is also an esterified derivative of 5-ALA with increased lipophilicity, authorized for sale in Europe [73]. Just as changes can be made to the molecules, physical methods can also be used to facilitate the penetration of the drug, as well as curettage and debulking of the lesion and delivery methods using dermograph and microneedles [72].

The incorporation of PDT into treatment protocols, as evidenced by successful outcomes in Brazil's public health system, highlights its cost-effectiveness and minimal side effects. Innovations in treatment protocols, such as single-visit sessions and home-based therapies, further enhance patient comfort and accessibility. Ongoing research into improving drug delivery methods and enhancing the effectiveness of photosensitizers promises to expand PDT's applicability to thicker and more challenging lesions. As international guidelines continue to support PDT, it remains a promising approach for managing non-melanoma skin cancers, combining efficacy with patient-centered care.

3.4. Gynecological cancers

Uterine corpus cancer is one of the most frequently diagnosed gynecological malignancies. This cancer is the sixth most diagnosed cancer in women and is associated with infection caused by human papillomavirus (HPV) [74]. This virus can affect the cervix, vulva, vagina, perineum and anus women [74].

While PDT is commonly used for certain types of cancer, such as skin cancer, its use in uterine corpus cancer (also known as endometrial cancer) is limited [75]. The standard treatment for uterine corpus cancer typically involves surgery, radiation therapy, and/or chemotherapy. Surgical removal of the uterus (hysterectomy) is often the primary treatment for early-stage uterine corpus cancer [75].

For the treatment of cervical cancer in women, PS ALA has been tested with irradiation of red light resulting in 76 to 90 % efficacy, as demonstrated by Wang et al. (2022) [76], who successfully healed cervical intraepithelial neoplasia (CIN) with vaginal intraepithelial neoplasia (VAIN) [76]. Likewise, Wu et al. (2021) [77], treated high-grade squamous intraepithelial lesions (HSIL)-CIN, applying 20 % of 5-ALA as a gel with a 2 % concentration of dimethylsulfoxide followed by light irradiation of 100 J/cm^2 at 635 nm [77]. Other studies that used PDT to treat patients with CIN associated with HPV observed the PDT effect after the first procedure (see Fig. 7) and confirmed that 88.2 % of the women presented a complete regression of the dysplasia foci using Chlorin e6 (Ce6) as an intravenous administrated PS [78].

Regarding the application of PDT in pre-invasive vaginal cancer, Ivanova V. et al. (2021) [79], treated 20 patients using a light dose of 40 to 100 J/cm^2 and an irradiation from 10 to 30 min, depending on the number of irradiation fields. The PDT effect was assessed with extended colposcopy, and the evaluation comprised a normalization of the colposcopy picture and the absence of atypical cells. After 3 months, a complete regression was registered in 100 % of patients. In other work, PDT was used against VAIN, Cai et al. (2020) [80], performed a lesion treatment using ALA as PS, which was irradiated after 3 h with light at a wavelength of 635 nm and a density of 80 mW/cm^2. The treatment was assessed using HPV-DNA tests along with liquid-based cervical cytology. As a result, 67 % of women were HPV negative on retesting 3–4 months after ALA-PDT, and most patients showed no signs of recurrence during the follow-up period. A study has also shown that the PDT intervention in CIN I increased the number of lesion regressions when compared to the placebo group, in which patients are only monitored without treatment, as recommended by the Brazilian health system [81]. In a case study by Castro et al. (2020) [82], it was observed that the viral load of a patient with CIN 3 (high grade) was eliminated when treated with two PDT sessions [82].

Vulvar intraepithelial neoplasia (VIN) is a non-invasive precursor lesion usually found in 50–70 % of patients affected by vulvar squamous cell carcinoma (VSCC). PDT has also treated VIN lesions for surgical excision and laser ablation [53]. Likewise, PDT allows the maintain vulvar anatomy and excellent cosmetic outcomes since it causes minimal destruction of the tissues.

PDT is appearing as a hopeful treatment for various gynecological cancers, particularly those associated with HPV, such as CIN, VAIN, and VIN. Unlike traditional treatments, PDT offers significant advantages. It effectively treats pre-invasive lesions, leading to high rates of lesion regression and viral load reduction while preserving the anatomical and functional integrity of the cervix. This is crucial for maintaining female fertility. PDT's ability to minimize tissue damage and preserve organ

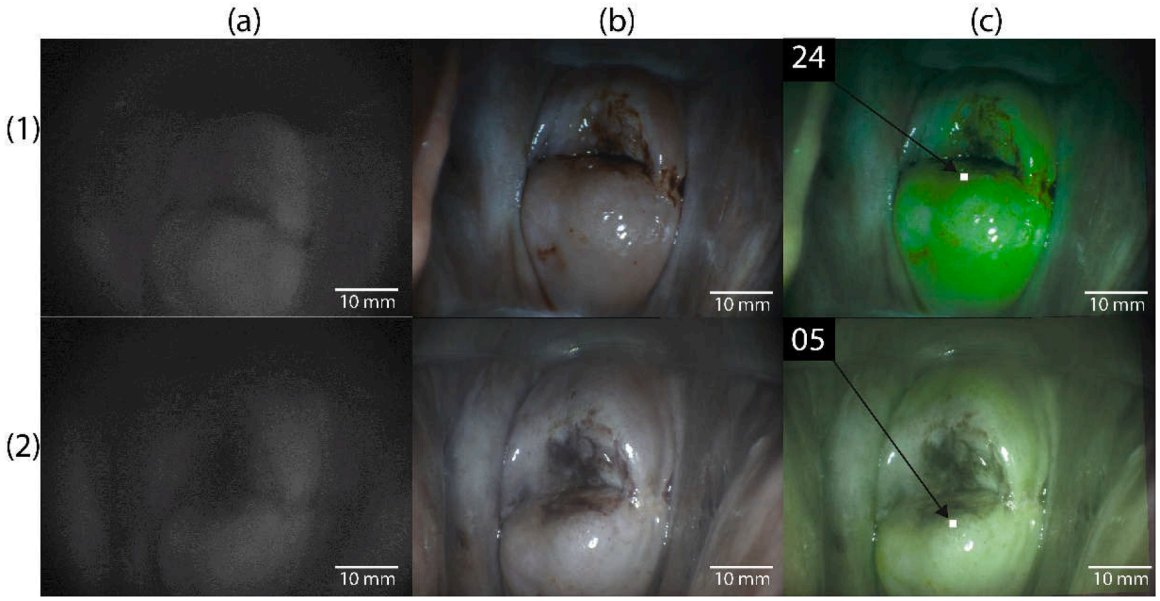

Fig. 7. Images of cervical tissue from a patient with CIN III: (1) Before PDT, (2) After PDT. (a) Black and white mode. (b) Color mode. (c) Combined mode (in the upper left corner is the fluorescence index in rel. units). Reproduced with permission of [78].

structure makes it a valuable option in gynecological oncology. As research continues, PDT has the potential to play a key role in managing gynecological cancers, offering a safer alternative to conventional treatments and improving patient outcomes.

3.5. Head and neck cancer

Head and neck cancers are the seventh most common cancer globally, accounting for approximately 4 % of all new cancer cases [83]. These refer to a group of cancers that develop in the squamous cells lining the mucosal surfaces of the head and neck region, including the oral cavity, throat, voice box, sinuses, and nasal cavity. Head and neck cancers are often categorized based on location and may include the oral cavity, oropharyngeal, laryngeal, nasopharyngeal, and others [84]. PDT is often used in combination with other treatments, such as surgery, radiation therapy, or chemotherapy, to provide a comprehensive approach to treating head and neck cancer. It can be used for early-stage cancers or as palliative treatment to relieve symptoms in advanced cases [84,85].

Santos et al. (2018) [86], reported a successful treatment using PDT with redaporfin (0.75 mg/kg) and irradiation of 749 nm laser light (dose of 50 J/cm^2), followed by immune checkpoint inhibition with an anti-PD1 antibody. Even though the patient had undergone surgery, radiotherapy, and multiple lines of systemic treatment without response, PDT with redaporfin achieved the destruction of all visible tumors, and the sequential use of an immune checkpoint inhibitor allowed a sustained complete response. Subsequently, the treatment was supplemented with nivolumab (3 mg/kg) and partial removal of the bone, and in this way, a reduction in the tumor load was achieved, and in subsequent evaluations, no progression of tumor size was evidenced (see Fig. 8) [86].

Likewise, a clinical trial demonstrated the benefits of PDT after surgery in close or positive resection margins in head and neck cancer. Patients underwent surgery (54 cases), and PDT was carried out using mTHPC at 0.15 mg/kg. A 652 nm red laser light with a dose of 20 J/cm^2 was employed for the irradiation. The progression-free survival rate was 30 %, the disease-free survival rate was 28 %, and the overall survival rate was 51 % at 2 years. The better disease-free survival was verified with a time interval between surgery and PDT of at least one month and a half, concluding that PDT can be applied as auxiliary therapy in head

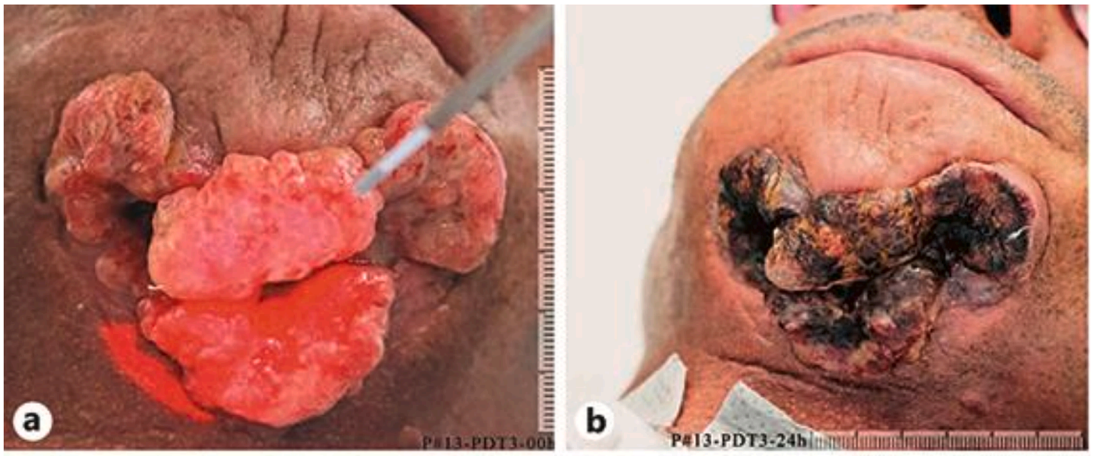

Fig. 8. Clinical evolution of tumor spots, with a 3 cm diameter each, after perfusion with redaporfin 0.75 mg/kg, in the second PDT session with treatment intent. (a) Pre-dose); (b) 24 h after PDT. Reproduced with permission of [86].

and neck cancer after surgery with tumor-positive resection margins [87].

In 2022, Jerjes et al. [88], developed an exploratory study that evaluated the effect of PDT with mTHPC in the head and neck area to improve the quality of life of 38 patients and was successful in all patients [88]. The patients were treated for various head and neck pathologies using mTHPC-PDT and completed the questionnaire during an average 56-day follow-up. One month after PDT, improvements were observed in swallowing, speaking, visual symptoms, and breathing, and in the following weeks, enhancements in daily life activities and social life were reported [88].

In this way, it was confirmed that PDT is viable for use in both early and advanced stages, delivering effective tumor reduction and symptom relief. Clinical trials have proven its effectiveness, including the successful application of redaporfin-PDT in combination with immune checkpoint inhibitors, which resulted in lasting tumor destruction in patients who had previously not responded to standard treatments. Furthermore, PDT has been shown to enhance quality of life by improving essential functions such as swallowing, speaking, and breathing. Its use as an additional therapy after surgery, particularly in cases with positive resection margins, has also been associated with improved disease-free survival rates. These results highlight PDT's potential as a valuable tool in the comprehensive treatment of head and neck cancers.

3.6. Studies and clinical trials reported in the literature

There are currently hundreds of clinical trials with favorable results in treating solid tumors based on PDT, registered in the Clinical Trials Database of the US National Library of Medicine. Some of the trials with favorable results are presented in Table 1, where the clinical trials are organized by section of the body.

Based on the reported data of Table 1, it is evident that PDT has considerable versatility in the treatment of various types of cancer, including different stages. Table 1 presents the use of different PSs, being Photofrin, WST11, and ALA the most employed. Besides, it was determined that each PS is paired with a specific wavelength for optimal activation. On the other side, most of the drugs are administered intravenously, with doses ranging from 0.15 to 4 mg/kg, emphasizing the need for dose customization based on disease progression and tumor characteristics. The variability in light intensity, from 20 to 1200 J/cm^2, suggests that the optimal efficacy is related to the optical properties of the tissues. Furthermore, the flexibility in treatment time indicates that PDT can be tailored to the patient's specific clinical needs. This data highlights the precision required in PDT, where drug selection, wavelength, and light dose are carefully modulated to maximize tumor treatment while preserving normal tissue function.

3.7. Advantages and disadvantages of PDT and PTT in tumor targeting and cancer therapy

PDT and PTT have gained considerable attention in cancer treatment due to their precision, minimal invasiveness, and reduced side effects compared to conventional therapies like surgery, chemotherapy and radiotherapy. These therapies offer significant advantages in tumor targeting, as both PDT and PTT selectively target cancerous tissues, sparing healthy cells and minimizing systemic toxicity. As stated before, PDT uses PSs that upon light exposure generate ROS to induce tumor cell death and activate the immune system. On the other hand, PTT leverages light-activated PTAs to produce localized heat, effectively destroying tumor cells. Their high specificity allows for better patient outcomes with fewer adverse effects [117].

Despite the clear benefits of PDT and PTT, these therapies have some inherent limitations. The most significant drawback of PDT is the restricted light penetration, which limits its efficacy in treating deep-seated or large tumors. Furthermore, the accumulation of PS in non-target tissues, combined with tumor hypoxia, can reduce the overall effectiveness of the therapy. Similarly, PTT also faces challenges with selective targeting and is less effective against metastatic disease. While both therapies are highly localized, their impact on larger or more advanced tumors is limited, and there is also a risk of local toxicities, such as edema, when treating larger tumor masses. These limitations point out the need for further refinement and combination with other cancer treatment strategies [118–120].

Facing this scenario, the potential of PDT and PTT lies in their integration with other therapeutic approaches, such as chemotherapy and immunotherapy. In the literature it has shown that combining PS with chemotherapeutic agents or immunotherapeutic drugs can produce a multi-mechanistic anti-tumor response, overcoming some of the limitations of PDT and PTT. This approach enhances tumor targeting, reduces the risk of tumor recurrence, and potentially improves long-term survival rates. As ongoing research continues to refine these therapies, PDT and PTT could become central components of a more personalized and comprehensive cancer treatment strategy in developing more effective treatments. There are several current studies aimed at identifying the best combination strategies. [17,18].

4. Perspectives for PDT/PTT based on nanoparticles for future clinical applications

Nanoparticles have been used as PS and nanocarriers within PDT, this approach enhances the stability, targeting ability, and uptake by cancer cells [121,122]. Additionally, nanoparticles can be designed to accumulate in tumors selectively through passive or active targeting strategies, thereby improving the specificity of PDT. This approach allows for precise spatiotemporal control of treatment, minimizing damage to surrounding healthy tissues [123]. Likewise, PTT has employed nanoparticles as gold nanoparticles, iron nanoparticles, and carbon nanotubes, which possess photothermal properties [124–127]. Nanoparticles can be functionalized to specifically accumulate in tumors, enabling targeted PTT [128]. As stated before, PDT and PTT can be synergistically combined to enhance treatment outcomes; thereby, it is possible to incorporate PSs and PTAs into nanoparticles, such as a single system that can provide dual-modal therapy or use nanoparticles as PSs and PTAs. This combined approach offers the potential for enhanced cancer cell-killing efficacy through complementary mechanisms of action. Furthermore, nanoparticles can be engineered to respond to specific triggers, such as pH or enzymes, to improve treatment selectivity and effectiveness [129,130].

Nanoparticles (*e.g.*, magnetic iron oxide nanoparticles [131]) have also been employed in imaging and theranostic applications using irradiation to activate them [131]. As imaging agents, nanoparticles enable real-time monitoring of treatment efficacy and tumor response, which can be modified by incorporating imaging or contrast agents for various imaging modalities, like optical, magnetic resonance, or computed tomography. The theranostic capability of the nanoparticles allows, in addition to tracking tumor foci and delimiting their volumes, for personalized and targeted treatment monitoring, facilitating the optimization of therapy and minimizing unnecessary side effects [132].

Based on these facts, it is evident that nanoparticles have great potential in photoactivated clinical applications. However, researchers must address toxic side effects to make it an effective mode of cancer treatment [133]. Below is summarized the recent advances in this topic within breast and prostate cancer in pre-clinical tirals. Nevertheless, it is worth mentioning that nanoparticles have also been employed in skin cancer (hafnium oxide nanoparticles) [126], glioblastoma [127], and so on.

4.1. Nanoparticles for breast cancer treatment based on PDT/PTT

Carbon-based nanomaterials have been employed to treat breast cancer. In the study of Yang et al. (2020) [134], they prepared a

Table 1
Treatments approved for clinical trials.

Section	Condition or disease-treated	Drug	Procedure	Dose and via	Wavelength, dose and time	Ref
Breast	Adenocarcinoma of the breast	mono-L-aspartyl chlorin e6 (Npe6)	PDT	2.5 and 3.5 mg/kg, intravenous	664 nm, 100 J/cm^2	[89]
	Breast cancer recurs in the skin	Photofrin	PDT	0.8 mg/kg, intravenous	630 nm, 100, 200, 400 and 800 J/cm^2	[90]
	Breast neoplasms	Verteporfin	PDT	0.4 mg/kg, intravenous	690 nm, 20 −90 J/cm^2	[91]
Prostate	Prostate cancer	WST11 (TOOKAD®)	VTP	Prostate size <60 mL, 4 mg/kg; and ≥60 mL, 6 mg/kg, intravenous	753 nm, 200 or 300 J/cm^2	[92]
	Localized prostate cancer	WST11 (TOOKAD®)	VTP	4 mg/kg via intravenous	753 nm, 200 J/cm^2	[93]
	Unilateral low-risk prostate cancer	WST11 (TOOKAD®)	VTP	3.66 mg/kg via intravenous	753 nm, 200 J/cm^2	[94]
Skin	BCC and SCC	Npe6	PDT	2.5 and 3.5 mg/kg, intravenous	664 nm, 100 J/cm^2	[95]
	BCC	5-ALA	PDT	Topically	blue light, ~20 J/cm^2, 30 min	[89]
	Skin cancer	5-ALA	PDT	20 %, topically	633 nm	[96]
	Nonmelanoma skin cancer	Levulan Kerastick (ALA)	PDT	Topically	417 nm, 1000 s	[97]
	Superficial non-melanoma skin cancer	MAL or Metvix® (Galderma)	Fractional ablative CO_2 laser + MAL PDT	Topically	630 nm, 37 J/cm^2, 10 min	[98]
	AK in photodamaged skin of the face	MAL	Daylight PDT	Topically	Daylight for 2 h, 5 sessions	[99]
	AK photoaging solar elastosis	Metvix ®, Galderma France	PDT	Topically	635 nm, 37 J/cm^2, 3 sessions	[100]
	AK	Levulan Kerastick	PDT	20 %, topically	Blue light, 10 J/cm^2	[101]
	AK	Vitamin D (Calcipotriol ointment 50 mcg/g) + MAL 16 % (Metvix, Galderma France)	Calcipotriol assisted PDT	Topically	635 nm, 37 J/cm^2	[102]
Cervical Cancer	CIN 1/2	HAL	PDT	HAL 5 % topically	629 nm, 100 J/cm^2	[103]
Head and neck	SCC of the head and neck	Temoporfin	PDT	0.15 mg/kg, intravenous	652 nm, 200 s	[104]
	Carcinoma *in situ* and stage I carcinoma of the oral cavity and the larynx	Photofrin	PDT	2 mg/kg, intravenous	630 nm, 50 or 75 J/cm^2	[105]
	Brain tumor, high-grade gliomas	Photofrin	PDT	2.5 mg/kg, intravenous	630 nm, 240 J/cm^2	[106, 107]
	Oral cavity SCC	2-1[Heyloxyethyl]-2-Devinylpyropheophorbide-a (HPPH)	PDT + Therapeutic conventional surgery	4 mg/kg, slow intravenous	665 nm, 140 J/cm^2	[105]
Esophagus	Early stage esophageal adenocarcinoma in Barrett esophagus	Photofrin	Endoscopic mucosal resection + PDT	2 mg/kg, intravenous	630 nm	[108]
	Esophagogastric cancer with moderate to severe dysphagia	WST11 (TOOKAD®)	PDT with an endoscopy procedure	4 mg/kg, intravenous	753 nm	[108]
Lung	Lung cancer with endobronchial obstruction	Photofrin	PDT by bronchoscopy	2 mg/kg, slow intravenous injection	630 nm, 200 J/cm^2	[109]
	Solid lung tumor	Photofrin	PDT by bronchoscopy	2 mg/kg, intravenous	630 nm, 200 J/cm^2	[110]
Bladder	Non-muscle invasive bladder cancer	TLD1433	TLD1433 infusion + PDT	0.70 mg/kg, infused into the bladder	532 nm, 90 J/cm^2	[111]
	Superficial bladder cancer	Photofrin	PDT	1.5 mg/kg, infused intravenously	630 nm, target light doses of 1200 J/cm^2	[112]
Kidney	T1a renal tumors	WST11 (TOOKAD®)	Vascular targeted PDT	4 mg/kg single IV administration	753 nm, 200 J/cm^2	[113]
Liver	Hilar cholangiocarcinoma	Photofrin	Stenting procedure + PDT + chemotherapy	2 mg/kg, intravenous	630 nm, 180 J/cm^2 after 92–96 h and 120 J/cm^2 at 3-month intervals + chemotherapy	[114]
	Bile duct cancer	Photosan-3(R)	PDT	2 mg/kg, intravenous	633 nm, 200 J/cm^2, 550 s	[115]
	Bile duct cancer	Hematoporphyrin derivative	PDT	2 mg/kg, intravenous	633 nm, 492 s	[116]

composite of Gd^{3+} and Ce6-loaded single-walled carbon nanohorns coated with amphiphilic polymers. *In vitro* experiments used breast cancer cells (4T1) and 50 μg /mL of the composite. The authors demonstrated a significant decrease in cell viability using PTT, PDT, and PTT/PDT techniques. The combination of PTT and PDT resulted in the lowest cell viability. For the *in vivo* study, mice of orthotopic breast cancers were intravenously injected with the composite at a dosage of 10 mg kg^{-1}; then, the tumor area was irradiated at 650 nm laser (40 mW cm^{-2}) for PDT, and at 808 nm laser (1.5 W cm^{-2}) for PTT, both for 10 min in sequence. Following laser irradiation, the growth of the treated tumors was quickly halted, and five days later, they disappeared [134].

Another study carried out by Lyles et al. (2020) [135], focused on polysilsesquioxane (PSilQ) nanoparticles conjugated with PpIX for PDT of breast cancer. The *in vivo* experiments used an orthotopic model of triple-negative breast cancer, showing that PSilQ effectively reduced the tumor burden when treated with PDT using a 630 nm LED and a total fluence of 88.2 J/cm^2. The results highlight the phototherapeutic efficacy of PSilQ in lowering the tumor burden and provide valuable insights into the potential of these nanoplatforms for breast cancer therapy [135]. Likewise, Li et al. (2019) reported an amino-modified biodegradable nanomaterial based on MoS_2 quantum-dots-doped disulfide-based SiO_2 nanoparticles loaded with hyaluronic acid and Ce6. This nanocomposite was used for clearable imaging-guided PTT/PDT combination tumor therapy and was applied in 4T1 tumor-bearing mice, exhibiting strong fluorescence and inducing a significant temperature increase (from 25 °C to 56.8 °C) under NIR radiation (808 nm, 1.5 W/cm^2). Besides, the nanocomposite showed low cytotoxicity and high ROS generation capacity, highlighting their potential for effective breast cancer treatment [136,137]. Several authors have developed *in vivo* and *in vitro* studies of tumor elimination based on carbon-based materials [138].

Similarly, Liu et al. (2018) [139], developed functional Ce6-gold nanorods for combined PTT/PDT breast cancer treatment. The nanorods were synthesized using seed-mediated growth, and mesoporous silica was used as the covering. *In vitro* experiments on human breast cancer cells (MCF-7) proved considerable cytotoxicity and apoptosis induction under combined PTT (808 nm and 2 W laser for 5 min) and PDT (650 nm and 50 mW laser for 5 min) treatment. *In vivo* studies using breast cancer xenografts in mice further validated the efficacy of the nanocomposite in treating breast cancer [139]. Other research, that demonstrated the effectiveness of the nanoparticles in destroying cancer cells was published by Shao et al. (2020) [140]; they reported an acceptor-oriented molecular design of donor-acceptor–donor conjugated small molecule-based phototheranostic agent with isoindigo (IID) as selective acceptor, and triphenylamine (TPA) as donor IID-TPA-based nanoparticles for synergistic PTT/PDT treatment under a single NIR laser irradiation of 671 nm, 1 W/cm^2 for 5 min. The nanomaterial showed high photothermal conversion efficiency and singlet oxygen quantum yield. *In vivo* experiments were successfully assessed on orthotopic 4T1 tumor-bearing mice [140].

The growing research on this type of nanomaterials highlights their significant potential as innovative therapeutic agents in breast cancer treatment. The aforementioned studies demonstrate the effectiveness of nanostructures in achieving substantial tumor reduction through the synergistic application of PDT and PTT. The results observed in both *in vitro* and in *vivo models* suggest that the combination of these modalities not only enhances cancer cell apoptosis but also improves treatment outcomes by halting tumor growth and facilitating complete regression in animal models. The development of novel nanomaterials underlines the versatility of these platforms in leveraging targeted therapy and improving phototherapeutic efficacy.

4.2. Nanoparticles for prostate cancer treatment based on PDT/PTT

Nanomaterials such as gold nanoparticles, magnetic nanoparticles, quantum dots, up-conversion nanoparticles, and carbon-based nanomaterials have been used in PDT/PTT for prostate cancer treatment. Thus, Choi et al. (2018) [141], developed multifunctional Fe_3O_4 magnetic nanoparticles conjugated with a Ce6 and folic acid (FA) to treat PDT prostate cancer (PC-3 cells) *in vivo* tests by a 660 nm long-wavelength light source. Fe_3O_4—Ce6-FA showed good biocompatibility and had significant anticancer effects by inducing apoptosis. This result was demonstrated in the analysis of the translocation of the plasma membrane, nuclear fragmentation, and activities of caspase-3/7 in the prostate cancer cells [141]. Likewise, Bhattarai et al. (2017) [142], prepared self-assembled nanoparticles on porphyrin grafted lipid (PGL) with cyanine dye DiR for PDT/PTT against prostate cancer testing *in vitro* and *in vivo* asssays. The authors demonstrated that more ROS was generated when the PGL-DiR nanoparticles were first irradiated by 760 nm, followed by 650 nm, and there was a considerable synergistic effect on tumor growth inhibition. Similarly, Ji et al. (2017) [143], synthesized human serum albumin-based nanoparticles loaded with Ce6 and ICG for prostate cancer evaluating *in vitro* and *in vivo* studies. The results demonstrate that ICG could quench the fluorescence of Ce6; only when the nanoparticles first received 808 nm light irradiation did ICG degrade and convert light energy into heat energy to kill cancer cells. Followed by 660 nm irradiation, Ce6 produces lots of ROS for PDT [143]. Thus, this approach also has promising effects in healing prostate cancer.

Therefore, these studies demonstrate the potential of diverse nanoparticles to treat prostate cancer using PDT/PTT; nevertheless, further research and clinical trials are warranted to fully explore the translational potential of these nanoparticle-based approaches. Several challenges need to be addressed for successful translation to clinical applications. These include optimizing nanoparticle design for efficient tumor targeting, ensuring biocompatibility and safety, establishing standardized protocols, and conducting rigorous clinical trials to evaluate efficacy and long-term outcomes. In summary, PDT and PTT based on nanoparticles offer exciting opportunities for clinical applications in cancer treatment. These approaches provide targeted and localized therapies with the potential for enhanced efficacy and reduced side effects. Continued research and development efforts are crucial to overcome technical and clinical challenges and enable the successful translation of these approaches into routine clinical practice [144].

5. Conclusions

Over the past few decades, several PDT and PTT strategies have been tested and developed to diagnose and combat various types of cancer. This review focuses on current advances in PDT and PTT theranostics.

In terms of diagnosis, approaches such as fluorescence-guided PDT, OCT-guided PDT, and imaging via MRI or CT assisted by PDT/PTT were discussed. These alternatives show promise in improving the eradication of residual tumors by allowing synchronous delimitation and visualization of tumors during procedures like surgery. Additionally, they enable precise tumor mapping and treatment monitoring. However, the development of new imaging probes for cancer diagnosis remains critical for early disease detection and management. Furthermore, additional research is needed to standardize their application across different cancer types and to explore their long-term impact on patient outcomes.

Regarding cancer treatment through PDT and PTT, these strategies have been used in both preclinical and clinical settings, demonstrating favorable results against breast, prostate, skin, gynecologic, head, neck, and other cancer types. For instance, PDT is considered versatile due to the wide variety of PSs available, with Photofrin, WST11, and ALA being the most commonly employed. Each PS must be paired with a specific wavelength and dosage for optimal activation. Thus, it is crucial to emphasize the need for dose customization based on disease progression and tumor characteristics. The flexibility of PDT suggests that this treatment can be tailored to the patient's specific clinical needs. Although PDT is effective, its use is not yet widespread. Several explanations for this include high costs, inconsistent clinical outcomes, lack of superior efficacy compared to alternative local ablation techniques or

surgery, and the complexity of the treatment, which involves both medication and a device. Therefore, researchers in biomedical optics technology are encouraged to develop light sources that are both more powerful and cost-effective. Furthermore, it is important to emphasize that PDT and PTT are viable strategies when cancer does not present as a systemic disease. This is due to the inherent challenges in directing light effectively, which are related to the nature of neoplasia.

It is also worth mentioning that nanomaterials offer ways to overcome the significant limitations of traditional PS delivery, thereby enhancing the overall efficacy of PDT cancer treatment. Specifically, in PDT and PTT, nanomaterials have emerged as a promising field of study for cancer therapy. Research into photoactivated nanomaterials is crucial for advancing cancer treatments. Various nanoparticles, including those based on carbon, gold, copper sulfide, iron oxide, and others, have demonstrated potential applications. This approach has greatly improved the quality of life and patient outcomes. Light-activated strategies are less invasive and less likely to damage healthy tissue while effectively targeting cancer cells. Research into the development, mechanisms, and applications of PS systems must continue. Future directions for PDT/PTT research point toward combined treatments and the usage of nanomaterials, which could enhance therapeutic efficacy and reduce side effects, though this topic is beyond the scope of this review.

6. Acronyms and abbreviations

AK: Actinic keratosis.
ALA: Aminolevulinic acid.
BCC: Basal cell carcinoma.
Ce6: Chlorin e6.
CIN: Cervical intraepithelial neoplasia.
CT: Computed tomography.
DCIS: Ductal carcinoma in situ.
EP: Epithelial.
FA: Folic acid.
ICG: Indocyanine green.
IID: Isoindigo.
HAL: Hexaminolevulinate.
HPV: Human papillomavirus.
HPPH: 2-1[Heyloxyethyl]-2-Devinylpyropheophorbide-a.
HSIL: High-grade squamous intraepithelial lesions.
MAL: Methyl aminolevulinate.
MRI: Magnetic resonance imaging. mTHPC: Metatetra(hydroxyphenyl)chlorine.
NIR: Near-infrared.
Npe6: Mono-L-aspartyl chlorin e6.
LCIS: Lobular carcinoma in situ.
LED: Light-emitting diode.
LEDs: Light-emitting diodes.
LP: Lamina propria.
OCT: Optical coherence tomography.
PBS: Phosphate-buffered saline.
PDT: Photodynamic therapy.
PGL: Porphyrin grafted lipid.
PpIX: Protoporphyrin IX.
PS: Photosensitizer.
PSilQ: Polysilsesquioxane.
PSs: Photosensitizers.
PTA: Photothermal agent.
PTAs: Photothermal agents.
PTT: Photothermal therapy.
RGB: Red, green, blue.
ROS: Reactive oxygen species.
SCC: Squamous cell carcinoma.
SLN: Sentinel lymph node.
TPA: Triphenylamine.
VAIN: Vaginal intraepithelial neoplasia.
VIN: Vulvar intraepithelial neoplasia.
VSCC: Vulvar squamous cell carcinoma.
VTP: Vascular-targeted photodynamic therapy.
WHO: World Health Organization.
WL: With light.
3-D: Three-dimensional.
5-ALA: 5-aminolevulinic acid.

CRediT authorship contribution statement

Coralía Fabiola Cuadrado: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Karina J. Lagos:** Writing – review & editing, Writing – original draft. **Mirian Denise Stringasci:** Writing – review & editing. **Vanderlei Salvador Bagnato:** Writing – review & editing, Supervision. **María Paulina Romero:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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References

[1] World Health Organization Cancer Available online: https://www.who.int/news-room/fact-sheets/detail/cancer (accessed on 13 August 2024).
[2] L. Rezakhani, M. Darbandi, Z. Khorrami, S. Rahmati, F.K. Shadmani, Mortality and disability-adjusted life years for smoking-attributed cancers from 1990 to 2019 in the North Africa and Middle East Countries: a systematic analysis for the global burden of disease study 2019, BMC Cancer 23 (2023) 80, https://doi.org/10.1186/s12885-023-10563-5.
[3] X. Guo, L. Li, W. Jia, C. Zhang, W. Ren, C. Liu, Y. Tang, Composite nanomaterials of conjugated polymers and up conversion nanoparticles for NIR-triggered photodynamic/photothermal synergistic cancer therapy, ACS Appl. Mater. Interfaces (2023) 16, https://doi.org/10.1021/acsami.3c12553.
[4] National cancer institute types of cancer treatment - NCI Available online: https://www.cancer.gov/about-cancer/treatment/types (accessed on 13 August 2024).
[5] R.R. Allison, G.H. Downie, R. Cuenca, X.-H. Hu, C.J. Childs, C.H. Sibata, Photosensitizers in clinical PDT, Photodiag. Photodyn. Ther. 1 (2004) 27–42, https://doi.org/10.1016/S1572-1000(04)00007-9.
[6] V.T. Anju, B. Siddhardha, M. Dyavaiah, Nanostructures for antimicrobial and antibiofilm photodynamic therapy. Nanotechnology in the Life Sciences, Springer Science and Business Media B.V., 2020, pp. 305–325.
[7] M. Awad, N. Thomas, T.J. Barnes, C.A. Prestidge, Nanomaterials enabling clinical translation of antimicrobial photodynamic therapy, J. Controll. Release 346 (2022) 300–316, https://doi.org/10.1016/j.jconrel.2022.04.035.
[8] G.C. Chaves Lamarque, D.A.C. Méndez, A.A. Matos, T.J. Dionísio, M.A.A. M. Machado, A.C. Magalhães, R.C. Oliveira, T. Cruvinel, In vitro effect of curcumin-mediated antimicrobial photodynamic therapy on fibroblasts: viability and cell signaling for apoptosis, Lasers Med. Sci. 36 (2021) 1169–1175, https://doi.org/10.1007/s10103-020-03150-8.
[9] G. Calixto, J. Bernegossi, L. De Freitas, C. Fontana, M. Chorilli, Nanotechnology-based drug delivery systems for photodynamic therapy of cancer: a review, Molecules 21 (2016) 342, https://doi.org/10.3390/molecules21030342.
[10] T.J. Dougherty, J.E. Kaufman, A. Goldfarb, K.R. Weishaupt, D. Boyle, A. Mittleman, Photoradiation therapy for the treatment of malignant tumors, Cancer Res. 38 (1978) 2628–2635.
[11] A.F. Dos Santos, D.R.Q. De Almeida, L.F. Terra, M.S. Baptista, L. Labriola, Photodynamic therapy in cancer treatment - an update review, J. Cancer Metastasis. Treat. (2019), https://doi.org/10.20517/2394-4722.2018.83. *2019*, N/A-N/A.
[12] K. Wang, B. Yu, J.L. Pathak, An update in clinical utilization of photodynamic therapy for lung cancer, J. Cancer 12 (2021) 1154–1160, https://doi.org/10.7150/jca.51537.
[13] T. Yano, K.K. Wang, Photodynamic therapy for gastrointestinal cancer, Photochem. Photobiol. 96 (2020) 517–523, https://doi.org/10.1111/php.13206.
[14] H. Wu, T. Minamide, T. Yano, Role of photodynamic therapy in the treatment of esophageal cancer, Digest. Endosc. 31 (2019) 508–516, https://doi.org/10.1111/den.13353.
[15] J. Sun, S. Kormakov, Y. Liu, Y. Huang, D. Wu, Z. Yang, Recent progress in metal-based nanoparticles mediated photodynamic therapy, Molecules 23 (2018) 1704, https://doi.org/10.3390/molecules23071704.
[16] L. Fan, Z. Jiang, Y. Xiong, Z. Xu, X. Yang, D. Gu, M. Ainiwaer, L. Li, J. Liu, F. Chen, Recent advances in the HPPH-based third-generation photodynamic agents in biomedical applications, Int. J. Mol. Sci. 24 (2023) 17404, https://doi.org/10.3390/ijms242417404.

[17] T. Vo-Dinh (Ed.), Biomedical Photonics Handbook, 2nd ed., CRC Press, 2014. ISBN 9780429139222.

[18] T. Hu, Z. Wang, W. Shen, R. Liang, D. Yan, M. Wei, Recent advances in innovative strategies for enhanced cancer photodynamic therapy, Theranostics 11 (2021) 3278–3300, https://doi.org/10.7150/thno.54227.

[19] National Cancer Institute Nanotechnology Cancer Therapy and Treatment - NCI Available online: https://www.cancer.gov/nano/cancer-nanotechnology/treatment (accessed on 13 August 2024).

[20] C. Jin, K. Wang, A. Oppong-Gyebi, J. Hu, Application of nanotechnology in cancer diagnosis and therapy - a mini-review, Int. J. Med. Sci. 17 (2020) 2964–2973, https://doi.org/10.7150/ijms.49801.

[21] D. Zhi, T. Yang, J. O'Hagan, S. Zhang, R.F. Donnelly, Photothermal therapy, J. Controll. Release 325 (2020) 52–71, https://doi.org/10.1016/j.jconrel.2020.06.032.

[22] J. Oh, H. Yoon, J.-H. Park, Nanoparticle platforms for combined photothermal and photodynamic therapy, Biomed. Eng. Lett. 3 (2013) 67–73, https://doi.org/10.1007/s13534-013-0097-8.

[23] W. Li, J. Peng, L. Tan, J. Wu, K. Shi, Y. Qu, X. Wei, Z. Qian, Mild photothermal therapy/photodynamic therapy/chemotherapy of breast cancer by Lyp-1 modified docetaxel/IR820 co-loaded micelles, Biomaterials 106 (2016) 119–133, https://doi.org/10.1016/j.biomaterials.2016.08.016.

[24] A.B. Bucharskaya, N.G. Khlebtsov, B.N. Khlebtsov, G.N. Maslyakova, N. A. Navolokin, V.D. Genin, E.A. Genina, V.V. Tuchin, Photothermal and photodynamic therapy of tumors with plasmonic nanoparticles: challenges and prospects, Materials 15 (2022) 1606, https://doi.org/10.3390/ma15041606.

[25] T. Yan, G. Alimu, L. Zhu, H. Fan, L. Zhang, Z. Du, R. Ma, S. Chen, N. Alifu, X. Zhang, PpIX/IR-820 dual-modal therapeutic agents for enhanced PDT/PTT synergistic therapy in cervical cancer, ACS Omega 7 (2022) 44643–44656, https://doi.org/10.1021/acsomega.2c02977.

[26] A. Urazaliyeva, P. Kanabekova, A. Beisenbayev, G. Kulsharova, T. Atabaev, S. Kim, C.-K. Lim, All organic nanomedicine for PDT–PTT combination therapy of cancer cells in hypoxia, Sci. Rep. 14 (2024) 17507, https://doi.org/10.1038/s41598-024-68077-4.

[27] C. Kong, B. Xu, G. Qiu, M. Wei, M. Zhang, S. Bao, J. Tang, L. Li, J. Liu, Multifunctional nanoparticles-mediated PTT/PDT synergistic immune activation and antitumor activity combined with Anti-PD-L1 immunotherapy for breast cancer treatment, Int. J. Nanomed. 17 (2022) 5391–5411, https://doi.org/10.2147/IJN.S373282.

[28] R.L. Lipson, E.J. Baldes, M.J. Gray, Hematoporphyrin derivative for detection and management of cancer, Cancer 20 (1967) 2255–2257, https://doi.org/10.1002/1097-0142(196712)20:12<2255::AID−CNCR2820201229>3.0.CO,2-U.

[29] R.L. Lipson, The photodynamic properties of a particular hematoporphyrin derivative, Arch. Dermatol. 82 (1960) 508, https://doi.org/10.1001/archderm.1960.01580040026005.

[30] J. He, L. Yang, W. Yi, W. Fan, Y. Wen, X. Miao, L. Xiong, Combination of fluorescence-guided surgery with photodynamic therapy for the treatment of cancer, Mol. Imaging 16 (2017) 153601211772291, https://doi.org/10.1177/1536012117722911.

[31] M.V. Marshall, J.C. Rasmussen, I.-C. Tan, M.B. Aldrich, K.E. Adams, X. Wang, C. E. Fife, E.A. Maus, L.A. Smith, E.M. Sevick-Muraca, Near-infrared fluorescence imaging in humans with indocyanine green: a review and update, Open Surg. Oncol. J. 2 (2010) 12–25, https://doi.org/10.2174/1876504101002010012.

[32] C. Dupont, M. Vermandel, H.-A. Leroy, M. Quidet, F. Lecomte, N. Delhem, S. Mordon, N. Reyns, Intraoperative photodynamic therapy for glioblastomas (INDYGO): study protocol for a phase I clinical trial, Neurosurgery 84 (2019) E414–E419, https://doi.org/10.1093/neuros/nyy324.

[33] A. Buda, B. Bussi, G. Di Martino, P. Di Lorenzo, S. Palazzi, T. Grassi, R. Milani, Sentinel lymph node mapping with near-infrared fluorescent imaging using indocyanine green: a new tool for laparoscopic platform in patients with endometrial and cervical cancer, J. Minim. Invasive Gynecol. 23 (2016) 265–269, https://doi.org/10.1016/j.jmig.2015.09.022.

[34] S. Schipmann, M. Müther, L. Stögbauer, S. Zimmer, B. Brokinkel, M. Holling, O. Grauer, E. Suero Molina, N. Warneke, W. Stummer, Combination of ALA-induced fluorescence-guided resection and intraoperative open photodynamic therapy for recurrent glioblastoma: case series on a promising dual strategy for local tumor control, J. Neurosurg. 134 (2021) 426–436, https://doi.org/10.3171/2019.11.JNS192443.

[35] H.L. Stewart, D.J.S. Birch, Fluorescence guided surgery, Methods Appl. Fluoresc. 9 (2021) 042002, https://doi.org/10.1088/2050-6120/ac1dbb.

[36] S.L. Troyan, V. Kianzad, S.L. Gibbs-Strauss, S. Gioux, A. Matsui, R. Oketokoun, L. Ngo, A. Khamene, F. Azar, J.V. Frangioni, The FLARE™ intraoperative near-infrared fluorescence imaging system: a first-in-human clinical trial in breast cancer sentinel lymph node mapping, Ann. Surg. Oncol. 16 (2009) 2943–2952, https://doi.org/10.1245/s10434-009-0594-2.

[37] P.A. Valdés, F. Leblond, V.L. Jacobs, B.C. Wilson, K.D. Paulsen, D.W. Roberts, Quantitative, spectrally-resolved intraoperative fluorescence imaging, Sci. Rep. 2 (2012) 798, https://doi.org/10.1038/srep00798.

[38] S. Khan, M.A.B. Hussain, A.P. Khan, H. Liu, S. Siddiqui, S. Mallidi, P. Leon, L. Daly, G. Rudd, F. Cuckov, et al., Clinical evaluation of smartphone-based fluorescence imaging for guidance and monitoring of ALA PDT, in: Proceedings of the 17th International Photodynamic Association World Congress 11070, SPIE, 2019, p. 163. Hasan, T.

[39] S.A. Siddiqui, S. Siddiqui, M.A.B. Hussain, S. Khan, H. Liu, K. Akhtar, S.A. Hasan, I. Ahmed, S. Mallidi, A.P. Khan, et al., Clinical evaluation of a mobile, low-cost system for fluorescence guided photodynamic therapy of early oral cancer in India, Photodiag. Photodyn. Ther. 38 (2022) 102843, https://doi.org/10.1016/j.pdpdt.2022.102843.

[40] J.F. Bille, High Resolution Imaging in Microscopy and Ophthalmology, Springer International Publishing: Cham, 2019. Bille, J.F.ISBN 978-3-030-16637-3.

[41] J. Wang, Y. Xu, S.A. Boppart, Review of optical coherence tomography in oncology, J. Biomed. Opt. 22 (2017) 1, https://doi.org/10.1117/1.JBO.22.12.121711.

[42] M. DeCoro, P. Wilder-Smith, Potential of optical coherence tomography for early diagnosis of oral malignancies, Expert Rev. Anticancer Ther. 10 (2010) 321–329, https://doi.org/10.1586/era.09.191.

[43] G. Hüttmann, Optical coherence tomography (OCT) for early diagnosis of tumors and online-control of photodynamic therapy (PDT), Photodiag. Photodyn. Ther. 8 (2011) 152, https://doi.org/10.1016/j.pdpdt.2011.03.100.

[44] H.-C. Wang, M.-T. Tsai, C.-P. Chiang, Visual perception enhancement for detection of cancerous oral tissue by multi-spectral imaging, J. Opt. 15 (2013) 055301, https://doi.org/10.1088/2040-8978/15/5/055301.

[45] Z. Hamdoon, W. Jerjes, D. Rashed, S. Kawas, A.A. Sattar, R. Samsudin, C. Hopper, In vivo optical coherence tomography-guided photodynamic therapy for skin pre-cancer and cancer, Photodiag. Photodyn. Ther. 36 (2021) 102520, https://doi.org/10.1016/j.pdpdt.2021.102520.

[46] B. Brito, T.W. Price, J. Gallo, M. Bañobre-López, G.J. Stasiuk, Smart magnetic resonance imaging-based theranostics for cancer, Theranostics 11 (2021) 8706–8737, https://doi.org/10.7150/thno.57004.

[47] T. Zheng, T. Zhou, X. Feng, J. Shen, M. Zhang, Y. Sun, Enhanced plasmon-induced resonance energy transfer (PIRET)-mediated photothermal and photodynamic therapy guided by photoacoustic and magnetic resonance imaging, ACS Appl. Mater. Interfaces 11 (2019) 31615–31626, https://doi.org/10.1021/acsami.9b09296.

[48] H. Zhang, Y.-H. Li, Y. Chen, M.-M. Wang, X.-S. Wang, X.-B. Yin, Fluorescence and magnetic resonance dual-modality imaging-guided photothermal and photodynamic dual-therapy with magnetic porphyrin-metal organic framework nanocomposites, Sci. Rep. 7 (2017) 44153, https://doi.org/10.1038/srep44153.

[49] R. bhole, A comprehensive review on photodynamic therapy (PDT) and photothermal therapy (PTT) for cancer treatment, Turk. J. Oncol. 36 (2021) 125–132, https://doi.org/10.5505/tjo.2020.2400.

[50] T. Kato, C. Jin, D. Lee, H. Ujiie, K. Fujino, H.-P. Hu, H. Wada, L. Wu, J. Chen, R. Weersink, et al., Preclinical investigation of folate receptor-targeted nanoparticles for photodynamic therapy of malignant pleural mesothelioma, Int. J. Oncol. 53 (2018) 2034–2046, https://doi.org/10.3892/ijo.2018.4555.

[51] X. Wang, D. Luo, J.P. Basilion, Photodynamic therapy: targeting cancer biomarkers for the treatment of cancers, Cancers (Basel) 13 (2021) 2992, https://doi.org/10.3390/cancers13122992.

[52] H.O. Alsaab, M.S. Alghamdi, A.S. Alotaibi, R. Alzhrani, F. Alwuthaynani, Y. S. Althobaiti, A.H. Almalki, S. Sau, A.K. Iyer, Progress in clinical trials of photodynamic therapy for solid tumors and the role of nanomedicine, *Cancers* 12 (2020) 2793, https://doi.org/10.3390/cancers12102793.

[53] R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, CA Cancer J. Clin. 73 (2023) 17–48, https://doi.org/10.3322/caac.21763.

[54] P. Wyss, V. Schwarz, D. Dobler-Girdziunaite, R. Hornung, H. Walt, A. Degen, M. Fehr, Photodynamic therapy of locoregional breast cancer recurrences using a chlorin-type photosensitizer, Int. J. Cancer 93 (2001) 720–724, https://doi.org/10.1002/ijc.1400.

[55] R.E. Cuenca, R.R. Allison, C. Sibata, G.H. Downie, Breast cancer with chest wall progression: treatment with photodynamic therapy, Ann. Surg. Oncol. 11 (2004) 322–327, https://doi.org/10.1245/ASO.2004.03.025.

[56] A.N. Banerjee, Graphene and its derivatives as biomedical materials: future prospects and challenges, Interf. Foc. 8 (2018) 20170056, https://doi.org/10.1098/rsfs.2017.0056.

[57] S.M. Banerjee, S. El-Sheikh, A. Malhotra, C.A. Mosse, S. Parker, N.R. Williams, A. J. MacRobert, R. Hamoudi, S.G. Bown, M.R.S. Keshtgar, Photodynamic therapy in primary breast cancer, J. Clin. Med. 9 (2020) 483, https://doi.org/10.3390/jcm9020483.

[58] M.A. Jain, S.W. Leslie, A. Sapra, Prost. Cancer Screen. (2024).

[59] PDQ adult treatment editorial board prostate cancer treatment (PDQ®): patient version available online: https://www.cancer.gov/types/prostate/patient/prostate-treatment-pdq (accessed on 14 August 2024).

[60] A.-R. Azzouzi, S. Vincendeau, E. Barret, A. Cicco, F. Kleinclauss, H.G. van der Poel, C.G. Stief, J. Rassweiler, G. Salomon, E. Solsona, et al., Padeliporfin vascular-targeted photodynamic therapy *versus* active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial, Lancet Oncol. 18 (2017) 181–191, https://doi.org/10.1016/S1470-2045(16)30661-1.

[61] A. Noweski, A. Roosen, S. Lebdai, E. Barret, M. Emberton, F. Benzaghou, M. Apfelbeck, B. Gaillac, C. Gratzke, C. Stief, et al., Medium-term follow-up of vascular-targeted photodynamic therapy of localized prostate cancer using TOOKAD soluble WST-11 (Phase II Trials), Eur. Urol. Focus 5 (2019) 1022–1028, https://doi.org/10.1016/j.euf.2018.04.003.

[62] C.A. Morton, R.-M. Szeimies, N. Basset-Séguin, P.G. Calzavara-Pinton, Y. Gilaberte, M. Hædersdal, G.F.L. Hofbauer, R.E. Hunger, S. Karrer, S. Piaserico, et al., European dermatology forum guidelines on topical photodynamic therapy 2019 Part 2: emerging indications – field cancerization, photorejuvenation and inflammatory/infective dermatoses, J. Eur. Acad. Dermatol. Venereol. 34 (2020) 17–29, https://doi.org/10.1111/jdv.16044.

[63] D. Berker, J.M. McGregor, M.F. Mohd Mustapa, L.S. Exton, B.R. Hughes, P. M. McHenry, K. Gibbon, D.A. Buckley, I. Nasr, C.E. Duarte Williamson, et al., British association of dermatologists' guidelines for the care of patients with

actinic keratosis 2017, Brit. J. Dermatol. 176 (2017) 20–43, https://doi.org/10.1111/bjd.15107.
[64] L.R. Braathen, R.-M. Szeimies, N. Basset-Seguin, R. Bissonnette, P. Foley, D. Pariser, R. Roelandts, A.-M. Wennberg, C.A. Morton, Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus, J. Am. Acad. Dermatol. 56 (2007) 125–143, https://doi.org/10.1016/j.jaad.2006.06.006.
[65] C. Liao, G. Zhang, P. Wang, X. Sun, X. Wang, Combination curettage and modified ALA-PDT for multiple basal cell carcinomas of the face and head, Photodiag. Photodyn. Ther. 35 (2021) 102393, https://doi.org/10.1016/j.pdpdt.2021.102393.
[66] H.H. Buzzá, L.T. Moriyama, J.D. Vollet-Filho, N.M. Inada, A.P. da Silva, M. D. Stringasci, M.B. Requena, C.T. de Andrade, K.C. Blanco, D.P. Ramirez, et al., Overall results for a national program of photodynamic therapy for basal cell carcinoma: a multicenter clinical study to bring new techniques to social health care, Cancer Control 26 (2019) 107327481985688, https://doi.org/10.1177/1073274819856885.
[67] D.P. Ramirez, C. Kurachi, N.M. Inada, L.T. Moriyama, A.G. Salvio, J.D. Vollet Filho, L. Pires, H.H. Buzzá, C.T. de Andrade, C. Greco, et al., Experience and BCC subtypes as determinants of MAL-PDT response: preliminary results of a national Brazilian project, Photodiag. Photodyn. Ther. 11 (2014) 22–26, https://doi.org/10.1016/j.pdpdt.2013.11.001.
[68] D.P. Ramirez, L.T. Moriyama, E.R. de Oliveira, N.M. Inada, V.S. Bagnato, C. Kurachi, A.G. Salvio, Single visit PDT for basal cell carcinoma – a new therapeutic protocol, Photodiag. Photodyn. Ther. 26 (2019) 375–382, https://doi.org/10.1016/j.pdpdt.2019.04.016.
[69] A.G. Salvio, D.B. Veneziano, L.T. Moriyama, N.M. Inada, C. Grecco, C. Kurachi, V. S. Bagnato, A new photodynamic therapy protocol for nodular basal cell carcinoma treatment: effectiveness and long-term follow-up, Photodiag. Photodyn. Ther. 37 (2022) 102668, https://doi.org/10.1016/j.pdpdt.2021.102668.
[70] A.G. Salvio, M.D. Stringasci, M.B. Requena, V.S. Bagnato, The use of a portable device for photodynamic therapy at home decreasing the patient's stay at hospital for small nodular basal cell carcinoma treatment, Photodiag. Photodyn. Ther. 41 (2023) 103449, https://doi.org/10.1016/j.pdpdt.2023.103449.
[71] A.G. Salvio, M.D. Stringasci, M.B. Requena, B.A. Fregolenti, M.M. Medeiro, C. da, R.G. Santos, V.S. Bagnato, Long-term follow-up results of a pilot study for nodular basal cell carcinoma with PDT using partial home treatment protocol, Photodiag. Photodyn. Ther. 45 (2024) 103930, https://doi.org/10.1016/j.pdpdt.2023.103930.
[72] M. Barreto Requena, M. Denise Stringasci, J. Dirceu Vollet-Filho, V. Salvador Bagnato, Strategies to improve drug delivery in topical PDT. Photodynamic Therapy - From Basic Science to Clinical Research, IntechOpen, 2021.
[73] N. Fotinos, M.A. Campo, F. Popowycz, R. Gurny, N. Lange, 5-aminolevulinic acid derivatives in photomedicine: characteristics, application and perspectives, Photochem. Photobiol. 82 (2006) 994–1015, https://doi.org/10.1562/2006-02-03-IR-794.
[74] K.D. Miller, L. Nogueira, A.B. Mariotto, J.H. Rowland, K.R. Yabroff, C.M. Alfano, A. Jemal, J.L. Kramer, R.L. Siegel, Cancer treatment and survivorship statistics, 2019, CA Cancer J. Clin. 69 (2019) 363–385, https://doi.org/10.3322/caac.21565.
[75] G. Correia-Barros, B. Serambeque, M.J. Carvalho, C.M. Marto, M. Pineiro, T.M.V. D. Pinho e Melo, M.F. Botelho, M. Laranjo, Applications of photodynamic therapy in endometrial diseases, Bioengineering 9 (2022) 226, https://doi.org/10.3390/bioengineering9050226.
[76] B. Wang, Y. Su, C. Zhang, M. Zhou, S. Yuan, M. Zhang, L. Zhang, Y. Zhou, L. Cao, M. Zhang, et al., The effect of local photodynamic therapy with 5-aminolevulinic acid in treating different grades of cervical intraepithelial neoplasia, Photodiag. Photodyn. Ther. 40 (2022) 103196, https://doi.org/10.1016/j.pdpdt.2022.103196.
[77] A. Wu, Q. Li, J. Ling, L. Gu, Z. Hong, W. Di, L. Qiu, Effectiveness of photodynamic therapy in women of reproductive age with cervical high-grade squamous intraepithelial lesions (HSIL/CIN2), Photodiag. Photodyn. Ther. 36 (2021) 102517, https://doi.org/10.1016/j.pdpdt.2021.102517.
[78] A. Gilyadova, A. Ishchenko, A. Ishenko, S. Samoilova, A. Shiryaev, A. Kiseleva, N. Petukhova, K. Efendiev, P. Alekseeva, E. Stranadko, et al., Analysis of the results of severe intraepithelial squamous cell lesions and preinvasive cervical cancer phototheranostics in women of reproductive age, Biomedicines 10 (2022) 2521, https://doi.org/10.3390/biomedicines10102521.
[79] V.A. Ivanova, E.V. Verenikina, V.P. Nikitina, O.E. Zhenilo, A.Y. Ardzha, Photodynamic therapy for preinvasive vaginal cancer, J. Clin. Oncol. 39 (2021) 5592, https://doi.org/10.1200/JCO.2021.39.15_suppl.5592.
[80] X. Cai, B. Liu, Aggregation-induced emission: recent advances in materials and biomedical applications, Angew. Chem. Int. Ed. 59 (2020) 9868–9886, https://doi.org/10.1002/anie.202000845.
[81] N.M. Inada, C.A. de Castro, H.H. Buzzá, W. Lombardi, V.S. Bagnato, Long-term effectiveness and HPV clearance of low and high-grade cervical lesions treated with photodynamic therapy, in: T. Hasan (Ed.), Proceedings of the 17th International Photodynamic Association World Congress 11070, SPIE, 2019, p. 226.
[82] C.A. de Castro, W. Lombardi, M.D. Stringasci, V.S. Bagnato, N.M. Inada, High-risk HPV clearance and CIN 3 treated with MAL-PDT: a case report, Photodiag. Photodyn. Ther. 31 (2020) 101937, https://doi.org/10.1016/j.pdpdt.2020.101937.
[83] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.
[84] M. Gormley, G. Creaney, A. Schache, K. Ingarfield, D.I. Conway, Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors, Br. Dent. J. 233 (2022) 780–786, https://doi.org/10.1038/s41415-022-5166-x.
[85] J. Meulemans, P. Delaere, V. Vander Poorten, Photodynamic therapy in head and neck cancer: indications, outcomes, and future prospects, Curr. Opin. Otolaryngol. Head Neck Surg. 27 (2019) 136–141, https://doi.org/10.1097/MOO.0000000000000521.
[86] L.L. Santos, J. Oliveira, E. Monteiro, J. Santos, C. Sarmento, Treatment of head and neck cancer with photodynamic therapy with Redaporfin: a clinical case report, Case Rep. Oncol. 11 (2018) 769–776, https://doi.org/10.1159/000493423.
[87] T.E.M. van Doeveren, M.B. Karakullukçu, R.L.P. van Veen, M. Lopez-Yurda, W. H. Schreuder, I.B. Tan, Adjuvant photodynamic therapy in head and neck cancer after tumor-positive resection margins, Laryngoscope 128 (2018) 657–663, https://doi.org/10.1002/lary.26792.
[88] W. Jerjes, H. Stevenson, D. Ramsay, Z. Hamdoon, C. Hopper, Quality of life following photodynamic therapy for head and neck pathologies: an exploratory study, Photodiag. Photodyn. Ther. 38 (2022) 102800, https://doi.org/10.1016/j.pdpdt.2022.102800.
[89] A.L. Chan, M. Juarez, R. Allen, W. Volz, T. Albertson, Pharmacokinetics and clinical effects of mono- <scp>l</Scp>-aspartyl Chlorin E6 (NPe6) photodynamic therapy in adult patients with primary or secondary cancer of the skin and mucosal surfaces, Photodermatol. Photoimmunol. Photomed. 21 (2005) 72–78, https://doi.org/10.1111/j.1600-0781.2005.00138.x.
[90] Study details | safety study using photodynamic therapy light therapy for patients with chest wall progression of breast cancer and satellite metastases of melanoma | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT00862901 (accessed on 14 August 2024).
[91] Study details | treatment of primary breast cancer using PDT | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT02872064 (accessed on 14 August 2024).
[92] S.S. Taneja, J. Bennett, J. Coleman, R. Grubb, G. Andriole, R.E. Reiter, L. Marks, A.-R. Azzouzi, M. Emberton, Final results of a phase I/II multicenter trial of WST11 vascular targeted photodynamic therapy for hemi-ablation of the prostate in men with unilateral low risk prostate cancer performed in the United States, J. Urol. 196 (2016) 1096–1104, https://doi.org/10.1016/j.juro.2016.05.113.
[93] A. Azzouzi, E. Barret, C.M. Moore, A. Villers, C. Allen, A. Scherz, G. Muir, M. de Wildt, N.J. Barber, S. Lebdai, et al., <scp>TOOKAD</Scp>® <scp>S</Scp>Oluble Vascular-targeted Photodynamic (<scp>VTP</Scp>) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer, BJU Int. 112 (2013) 766–774, https://doi.org/10.1111/bju.12265.
[94] Study details | study of erectile dysfunction, urinary incontinence and related QoL after TOOKAD® VTP for low risk prostate cancer | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT03849365 (accessed on 14 August 2024).
[95] Study details | alteration of the immune microenvironment in basal cell carcinoma following photodynamic therapy | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT05020912 (accessed on 14 August 2024).
[96] Study details | photodynamic therapy in treating patients with skin cancer | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT00002975 (accessed on 14 August 2024).
[97] Study details | photodynamic therapy for prevention of nonmelanoma skin cancer in organ transplant recipients | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT02751151 (accessed on 14 August 2024).
[98] Study details | laser assisted drug delivery in the treatment of superficial non melanoma skin cancer: a randomized controlled trial | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT03012009 (accessed on 14 August 2024).
[99] E. Kohl, M. Koller, F. Zeman, R.-M. Szeimies, W.G. Philipp-Dormston, W. Prager, P.A. Gerber, S. Karrer, Daylight photodynamic therapy *versus* cryosurgery for the treatment and prophylaxis of actinic keratoses of the face – protocol of a multicenter, prospective, randomized, controlled, two-armed study, BMC Dermatol. 17 (2017) 12, https://doi.org/10.1186/s12895-017-0064-7.
[100] Study details | photodynamic therapy (PDT) effect on large surface photodamaged skin | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT00843323 (accessed on 14 August 2024).
[101] Study details | ALA-PDT versus vehicle PDT for treatment of AK and reduction of new NMSC in solid organ transplant recipients | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT00865878 (accessed on 14 August 2024).
[102] Study details | potential impact of patient vitamin D status in AK response to MAL-PDT | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT02878382 (accessed on 14 August 2024).
[103] P. Hillemanns, F. Garcia, K.U. Petry, V. Dvorak, O. Sadovsky, O.-E. Iversen, M. H. Einstein, A randomized study of hexaminolevulinate photodynamic therapy in patients with cervical intraepithelial neoplasia 1/2, Am. J. Obstet. Gynecol. 212 (2015), https://doi.org/10.1016/j.ajog.2014.10.1107, 465.e1-465.e7.
[104] P.-J. Lou, H.R. Jäger, L. Jones, T. Theodossy, S.G. Bown, C. Hopper, Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer, Br. J. Cancer 91 (2004) 441–446, https://doi.org/10.1038/sj.bjc.6601993.
[105] N.R. Rigual, K. Thankappan, M. Cooper, M.A. Sullivan, T. Dougherty, S.R. Popat, T.R. Loree, M.A. Biel, B. Henderson, Photodynamic therapy for head and neck

dysplasia and cancer, Arch. Otolaryngol. Head Neck Surg. 135 (2009) 784, https://doi.org/10.1001/archoto.2009.98.
[106] Study details | photodynamic therapy (PDT) for recurrent high grade gliomas | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT01966809 (accessed on 14 August 2024).
[107] Study details | photodynamic therapy (PDT) for recurrent pediatric brain tumors | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT01682746 (accessed on 14 August 2024).
[108] Study details | photodynamic therapy with HPPH compared to standard of care surgery in treating patients with oral cavity cancer | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT03090412 (accessed on 14 August 2024).
[109] Study details | endoscopic therapy of early cancer in Barretts Esophagus | ClinicalTrials.Gov Available online: https://clinicaltrials.gov/study/NCT00217087 (accessed on 14 August 2024).
[110] Study details | safety of PDT-Photofrin® prior to lung surgery | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT03344861 (accessed on 14 August 2024).
[111] Study details | intravesical photodynamic therapy (PDT) in BCG refractory high-risk non-muscle invasive bladder cancer (NMIBC) patients | clinicaltrials.Gov Available online: https://clinicaltrials.gov/study/NCT03053635 (accessed on 14 August 2024).
[112] Study details | sequential whole bladder photodynamic therapy (WBPDT) in the management of superficial bladder cancer | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT00322699 (accessed on 14 August 2024).
[113] Study details | vascular targeted photodynamic therapy T1a renal tumours | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT01573156 (accessed on 14 August 2024).
[114] Study details | efficacy and safety study of PDT using photofrin in unresectable advanced perihilar cholangiocarcinoma (OPUS) | clinicaltrials.*Gov Available online*: https://clinicaltrials.gov/study/NCT02082522 (accessed on 14 August 2024).
[115] T. Zoepf, R. Jakobs, J.C. Arnold, D. Apel, J.F. Riemann, Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy, Am. J. Gastroenterol. 100 (2005) 2426–2430, https://doi.org/10.1111/j.1572-0241.2005.00318.x.
[116] C. Shim, Y. Cheon, S. Cha, S. Bhandari, J. Moon, Y. Cho, Y. Kim, L. Lee, M. Lee, B. Kim, Prospective study of the effectiveness of percutaneous transhepatic photodynamic therapy for advanced bile duct cancer and the role of intraductal ultrasonography in response assessment, Endoscopy 37 (2005) 425–433, https://doi.org/10.1055/s-2005-861294.
[117] J.-Y. Kim, W.I. Choi, M. Kim, G. Tae, Tumor-targeting nanogel that can function independently for both photodynamic and photothermal therapy and its synergy from the procedure of PDT followed by PTT, J. Controll. Release 171 (2013) 113–121, https://doi.org/10.1016/j.jconrel.2013.07.006.
[118] N. Yang, C. Cao, H. Li, Y. Hong, Y. Cai, X. Song, W. Wang, X. Mou, X. Dong, Polymer-based therapeutic nanoagents for photothermal-enhanced combination cancer therapy, Small Struct. 2 (2021) 2100110, https://doi.org/10.1002/sstr.202100110.
[119] Z. Guo, Y. Liu, X. Cheng, D. Wang, S. Guo, M. Jia, K. Ma, C. Cui, L. Wang, H. Zhou, Versatile biomimetic cantharidin-tellurium nanoparticles enhance photothermal therapy by inhibiting the heat shock response for combined tumor therapy, Acta Biomater. 110 (2020) 208–220, https://doi.org/10.1016/j.actbio.2020.03.028.
[120] C. Kong, B. Xu, G. Qiu, M. Wei, M. Zhang, S. Bao, J. Tang, L. Li, J. Liu, Multifunctional nanoparticles-mediated PTT/PDT synergistic immune activation and antitumor activity combined with anti-PD-L1 immunotherapy for breast cancer treatment, Int. J. Nanomed. 17 (2022) 5391–5411, https://doi.org/10.2147/IJN.S373282.
[121] D. Fan, Y. Cao, M. Cao, Y. Wang, Y. Cao, T. Gong, Nanomedicine in cancer therapy, Signal Transduct. Target. Ther. 8 (2023) 293, https://doi.org/10.1038/s41392-023-01536-y.
[122] M. Chehelgerdi, M. Chehelgerdi, O.Q.B. Allela, R.D.C. Pecho, N. Jayasankar, D. P. Rao, T. Thamaraikani, M. Vasanthan, P. Viktor, N. Lakshmaiya, et al., Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation, Mol. Cancer 22 (2023) 169, https://doi.org/10.1186/s12943-023-01865-0.
[123] D.K. Chatterjee, L.S. Fong, Y. Zhang, Nanoparticles in photodynamic therapy: an emerging paradigm, Adv. Drug Deliv. Rev. 60 (2008) 1627–1637, https://doi.org/10.1016/j.addr.2008.08.003.
[124] J.B. Vines, J.-H. Yoon, N.-E. Ryu, D.-J. Lim, H. Park, Gold nanoparticles for photothermal cancer therapy, Front. Chem. 7 (2019), https://doi.org/10.3389/fchem.2019.00167.
[125] M.F. Naief, S.N. Mohammed, H.J. Mayouf, A.M. Mohammed, A review of the role of carbon nanotubes for cancer treatment based on photothermal and photodynamic therapy techniques, J. Organomet. Chem. 999 (2023) 122819, https://doi.org/10.1016/j.jorganchem.2023.122819.
[126] A.C. Anselmo, S. Mitragotri, Nanoparticles in the clinic: an update, Bioeng. Transl. Med. 4 (2019), https://doi.org/10.1002/btm2.10143.
[127] D. Bobo, K.J. Robinson, J. Islam, K.J. Thurecht, S.R. Corrie, Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date, Pharm. Res. 33 (2016) 2373–2387, https://doi.org/10.1007/s11095-016-1958-5.
[128] J. Estelrich, M.A. Busquets, Iron oxide nanoparticles in photothermal therapy, Molecules 23 (2018) 1567, https://doi.org/10.3390/molecules23071567.
[129] H. Zhu, P. Cheng, P. Chen, K. Pu, Recent progress in the development of near-infrared organic photothermal and photodynamic nanotherapeutics, Biomater. Sci. 6 (2018) 746–765, https://doi.org/10.1039/C7BM01210A.
[130] T.-K. Ryu, S.-W. Baek, R.-H. Kang, K.-Y. Jeong, D.-R. Jun, S.-W. Choi, Photodynamic and photothermal tumor therapy using phase-change material nanoparticles containing chlorin E6 and nanodiamonds, J. Controll. Release 270 (2018) 237–245, https://doi.org/10.1016/j.jconrel.2017.12.008.
[131] J.K. Patra, G. Das, L.F. Fraceto, E.V.R. Campos, M. Rodriguez-Torres, P. del, L. S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, et al., Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnol. 16 (2018) 71, https://doi.org/10.1186/s12951-018-0392-8.
[132] Z. Yin, D. Chen, J. Zou, J. Shao, H. Tang, H. Xu, W. Si, X. Dong, Tumor microenvironment responsive oxygen-self-generating nanoplatform for dual-imaging guided photodynamic and photothermal therapy, ChemistrySelect 3 (2018) 4366–4373, https://doi.org/10.1002/slct.201800498.
[133] P. He, G. Yang, D. Zhu, H. Kong, Y.R. Corrales-Ureña, L. Colombi Ciacchi, G. Wei, Biomolecule-mimetic nanomaterials for photothermal and photodynamic therapy of cancers: bridging nanobiotechnology and biomedicine, J. Nanobiotechnol. 20 (2022) 483, https://doi.org/10.1186/s12951-022-01691-4.
[134] J. Yang, M. Hou, W. Sun, Q. Wu, J. Xu, L. Xiong, Y. Chai, Y. Liu, M. Yu, H. Wang, et al., Sequential PDT and PTT using dual-modal single-walled carbon nanohorns synergistically promote systemic immune responses against tumor metastasis and relapse, Adv. Sci. 7 (2020) 2001088, https://doi.org/10.1002/advs.202001088.
[135] Z.K. Lyles, M. Tarannum, C. Mena, N.M. Inada, V.S. Bagnato, J.L. Vivero-Escoto, Biodegradable silica-based nanoparticles with improved and safe delivery of protoporphyrin IX for the in vivo photodynamic therapy of breast cancer, Adv. Ther. (Weinh) (2020) 3, https://doi.org/10.1002/adtp.202000022.
[136] P. Li, L. Liu, Q. Lu, S. Yang, L. Yang, Y. Cheng, Y. Wang, S. Wang, Y. Song, F. Tan, et al., Ultrasmall MoS_2 nanodots-doped biodegradable SiO_2 nanoparticles for clearable FL/CT/MSOT imaging-guided PTT/PDT combination tumor therapy, ACS Appl. Mater. Interfaces 11 (2019) 5771–5781, https://doi.org/10.1021/acsami.8b18924.
[137] M.P. Romero, H.H. Buzza, M.D. Stringasci, B.M. Estevão, C.C. Silva, M.A. Pereira-da-Silva, N.M. Inada, V.S. Bagnato, Graphene oxide theranostic effect: conjugation of photothermal and photodynamic therapies based on an in vivo demonstration, Int. J. Nanomed. 16 (2021) 1601–1616, https://doi.org/10.2147/IJN.S287415.
[138] C.-H. Kim, S.-Y. Lee, K.Y. Rhee, S.-J. Park, Carbon-based composites in biomedical applications: a comprehensive review of properties, applications, and future directions, Adv. Compos. Hybrid Mater. 7 (2024) 55, https://doi.org/10.1007/s42114-024-00846-1.
[139] L. Liu, H.-J. Xie, L.-M. Mu, R. Liu, Z.-B. Su, Y.-N. Cui, Y. Xie, W.-L. Lu, Functional chlorin gold nanorods enable to treat breast cancer by photothermal/photodynamic therapy, Int. J. Nanomed. 13 (2018) 8119–8135, https://doi.org/10.2147/IJN.S186974.
[140] W. Shao, C. Yang, F. Li, J. Wu, N. Wang, Q. Ding, J. Gao, D. Ling, Molecular design of conjugated small molecule nanoparticles for synergistically enhanced PTT/PDT, Nanomicro Lett. 12 (2020) 147, https://doi.org/10.1007/s40820-020-00474-6.
[141] K.-H. Choi, K.C. Nam, G. Cho, J.-S. Jung, B.J. Park, Enhanced photodynamic anticancer activities of multifunctional magnetic nanoparticles (Fe3O4) conjugated with chlorin E6 and folic acid in prostate and breast cancer cells, Nanomaterials 8 (2018) 722, https://doi.org/10.3390/nano8090722.
[142] P. Bhattarai, X. Liang, Y. Xu, Z. Dai, A novel cyanine and porphyrin based theranostic nanoagent for near-infrared fluorescence imaging guided synergistic phototherapy, J. Biomed. Nanotechnol. 13 (2017) 1468–1479, https://doi.org/10.1166/jbn.2017.2427.
[143] C. Ji, A. Yuan, L. Xu, F. Zhang, S. Zhang, X. Zhao, G. Liu, W. Chen, H. Guo, Activatable photodynamic therapy for prostate cancer by NIR dye/photosensitizer loaded albumin nanoparticles, J. Biomed. Nanotechnol. 15 (2019) 311–318, https://doi.org/10.1166/jbn.2019.2685.
[144] S. Shi, Y. Wang, B. Wang, Q. Chen, G. Wan, X. Yang, J. Zhang, L. Zhang, C. Li, Y. Wang, Homologous-targeting biomimetic nanoparticles for photothermal therapy and Nrf2-SiRNA amplified photodynamic therapy against oral tongue squamous cell carcinoma, Chem. Eng. J. 388 (2020) 124268, https://doi.org/10.1016/j.cej.2020.124268.