

REVIEW

Photodynamic Therapy in the Treatment of Cancer: A Review

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ABSTRACT

The search for non-invasive or minimally invasive approaches for the treatment of cancer has led to the development of different therapeutic regimes and one such regime is photodynamic therapy (PDT). PDT is a non-thermal treatment based on the synergy of three elements: the administration of a photosensitizer drug; light at a precise wavelength; and the presence of oxygen. When these three components are combined, they lead to the formation of reactive oxygen species (ROS), resulting in a complex cascade of events and subsequent cell death. Studies revealed that PDT can prolong survival in patients with inoperable cancers and significantly improve the quality of life. With a number of recent technological improvements, PDT has the potential to become integrated into the mainstream strategy for cancer treatment. In this review, we have addressed the most important biological and physicochemical aspects of PDT, summarized its clinical status and provided an outlook for its potential future development. We also discussed the factors that hamper the exploration of this effective therapy and what should be changed to render it a more effective and more widely available option for patients.

1. Introduction

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body^[1,2]. Not all tumors are cancerous; benign tumors do not spread to other parts of the body^[2]. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements^[3]. While these symptoms may indicate cancer, they may have other causes^[3]. Cancer can be detected by certain signs and

symptoms or screening tests^[1]. It is then typically further investigated by medical imaging and confirmed by biopsy^[4]. Cancer has been one of the major threats to the lives of human beings for centuries^[5]. Current cancer therapies mainly include surgery, chemotherapies, radiotherapies, hormonal therapy, targeted therapy and palliative care. Which treatments are used depends on the type, location and grade of the cancer as well as the patient's health and preferences. The treatment intent may or may not be curative. While surgery in many occasions is not able to com-

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pletely remove all cancer cells in the human body, chemotherapy and radiotherapy all suffer from their severe toxic side effects to normal tissues and limited specificities to cancer cells [6]. Despite progress in basic research that has given us a better understanding of tumor biology and led to the design of new generations of targeted drugs, recent large clinical trials for cancer, with some notable exceptions, have been able to detect only small differences in treatment outcomes [7,8]. Moreover, the number of new clinically approved drugs is disappointingly low [9]. These sobering facts indicate that to make further progress, it is necessary to put an emphasis on other existing but still underappreciated therapeutic approaches. Research has been focused on developing alternate treatment modalities that are safe, potent, and cost-effective. Photodynamic therapy (PDT) is an alternative tumor-ablative and function-sparing oncologic intervention. Since its inception in early 1900s and its first modern demonstration by Dougherty *et al.* in 1975 [10], PDT has undergone extensive investigations and has emerged as a disease site specific treatment modality. Photodynamic therapy (PDT) has the potential to meet many currently unmet medical needs. Although still emerging, it is already a successful and clinically approved therapeutic modality used for the management of neoplastic and non-malignant diseases. PDT was the first drug-device combination approved by the US Food and Drug Administration (FDA) almost 2 decades ago, but even so remains underutilized clinically. PDT is a laser treatment that requires the selective incorporation of a drug, i.e., a photosensitizer (PS), into the targeted cells/tissues, followed by the subsequent exposure of the target region to light of appropriate wavelengths, visible/near infrared (NIR) light, to produce reactive oxygen species (ROS) such as singlet oxygen (1O_2) for sequential cancer eradication, leading to cellular death, vascular shutdown, and immune activation [11]. Hence, PDT employs 3 non-toxic components that by its own do not have any toxic effects on the biological systems, unlike chemotherapy drugs that induce systemic toxicity and ionizing light of radiation therapy that damages neighbouring normal tissues. Clearly, PDT has its own merits compared to the conventional treatment methods due to its minimal invasiveness, repeatability without cumulative toxicity, excellent functional and cosmetic results, reduced long-term morbidity and improved quality of life of the patients [12]. Since its regulatory approval as a cancer therapy, PDT has been subject of numerous studies and has proven to be an effective form of cancer therapy. This article would comprehensively review the recent advances regarding the development of PDT for cancer treatment. Herein a variety of inorganic and organic NIR-absorbing compounds ex-

plored for PDT cancer treatment have been summarized. The combination of PDT with other therapeutic approaches such as chemotherapy has also been discussed. Finally, examples from the most recent studies has been given to show in which directions PDT is headed, both in the near and distant future. The future prospects and challenges in this rapidly growing field have also been addressed. The aim of this review is therefore to analyze the current state of PDT and to give insights as to how the future of PDT will look like as a (first-line) treatment for cancer.

2. Principles of Photodynamic Therapy

PDT consists of 3 essential components: photosensitizer (PS), light and oxygen [13]. None of these is individually toxic, but together they initiate a photochemical reaction that culminates in the generation of a highly reactive product termed singlet oxygen (1O_2). The latter can rapidly cause significant toxicity leading to cell death *via* apoptosis or necrosis [13]. A photosensitizer (PS) is administered systemically or topically. After a period of systemic PS distribution, it selectively accumulates in the tumor. Irradiation activates the PS and in the presence of molecular oxygen triggers a photochemical reaction that culminates in the production of singlet oxygen (1O_2).

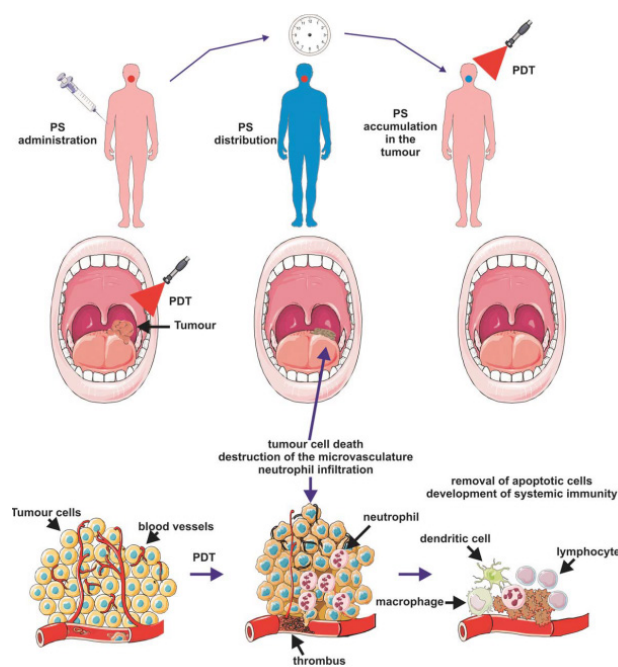


Figure 1. The Principles of Photodynamic Therapy (PDT) [14]

Irreparable damage to cellular macromolecules leads to tumor cell death *via* an apoptotic, necrotic or autophagic mechanism, accompanied by induction of an acute local inflammatory reaction that participates in the removal of dead

cells, restoration of normal tissue homeostasis and sometimes, in the development of systemic immunity (Figure 1).

3. Photodynamic Therapy for Treatment of Different Kinds of Cancers

PDT has been used clinically in the treatment of human carcinomas since it was introduced by Dougherty *et al.* in 1978^[15], and the clinical significance of PDT in the treatment of digestive tract carcinomas, such as in the oesophagus, stomach, and bile duct, were reported in a Japanese series^[16]. The first clinically approved photosensitizer was a hemato-porphyrin derivative, such as porfimer sodium. Moreover, many clinical trials are currently under way to study the potential of PDT in the treatment of various other types of cancers^[17].

3.1 Photodynamic Therapy of Breast Cancer

Breast cancer is the most frequently diagnosed and one of the leading causes of death among women worldwide^[18]. Although breast cancer mortality is falling, particularly in developed countries, its incidence is raising^[19-21]. With the advent of breast screening more cancers are being diagnosed early and therefore often require less extensive surgical treatment when combined with adjuvant therapies. The use of novel technologies to treat all stages of breast cancer is desirable because they allow more options to be available for all patients, including those who are not eligible for standard management. However, in order to be successful they need to offer additional benefits or fewer side-effects when compared to the standard of care. Here, photodynamic therapy (PDT) is reviewed with regard to the components that make it a successful. The first clinical application for this technology in breast cancer treatment was in the treatment of skin metastases in chest wall recurrence^[22,23]. The initial series of 37 patients with breast carcinoma chest wall recurrence treated with PDT by Khan *et al.*, in 1993^[24] and that was an effective treatment in selected patients, although there was some variation in the extent of the response. Photofrin was used as the photosensitizer in this light-dose-escalation study to determine the minimal light dose at which an effective response could be achieved. The results showed that five patients achieved a complete response, 13 demonstrated partial responses, and 19 showed no benefit^[24]. The extent and type of the recurrent disease were strong determinants of the likelihood of response. Minimal and nodular disease responded well to PDT; partial responses were seen in patients with disease of moderate extent.

Polymeric micelles composed of vitamin E derivatives arise as promising candidates for the treatment of breast can-

cer^[25]. Among them, D- α -tocopheryl succinate (TOS) and D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) may be used to prepare micelles for cancer therapy and these are already approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) as pharmaceutical solubilizers^[26,27]. Pais-Silva *et al.* produced and characterized IR780-loaded TPGS-TOS micelles (IR780-TTM) to evaluate their application in breast cancer phototherapy. IR780 was chosen due to its versatility as a light-responsive compound and TPGS and TOS due to their ability to form micelles and to their intrinsic anticancer activity. Their results demonstrated that IR780-loaded micelles with suitable properties were obtained by using specific TPGS and TOS weight feed ratios during micelles formulation^[28]. *Via* assays demonstrated that the IR780-loaded micelles induce a cytotoxic effect on cancer cells upon exposure to NIR irradiation through the generation of ROS (PDT). This effective ablation of cancer cells was achieved by using the lowest IR780 concentration reported until now and it was suggested that TPGS and TOS might have an important role in such effect through their intrinsic capacity to generate ROS. Moreover the capability of the IR780-loaded micelles to act as PTT and imaging agents, was also demonstrated which widens their therapeutic and diagnostic potential. Wyss *et al.* treated breast cancer chest wall recurrence in seven patients with complete response^[29]. In this short series the photosensitizer *meta*-tetra (hydroxyphenyl) chlorin (*m*-THPC) was injected intravenously. Response to treatment did not differ with use of the two different drug dose protocols. Healing time depended mainly on the size of the illumination field but not on the light dose. Similarly Cuenca *et al.* found that PDT was an effective treatment for the palliation of chest wall recurrence using Photofrin^[30]; 500 separate cutaneous truncal lesions were treated in 14 patients^[30]. The follow-up period ranged from 6 to 24 months. While all patients demonstrated tumor necrosis, and 9 out of 14 had complete responses and several had regression of untreated lesions, there was no effect on disease progression. Li *et al.*, in 2011 combined PDT with immune therapy in a trial assessing safety and efficacy of laser immunotherapy (LIT) for the treatment of metastatic breast cancer^[31]. All 10 patients who were enrolled had either stage 3 or 4 diseases, and 8 patients were suitable for final evaluation^[31]. Only 1 patient had complete response; 4 patients had partial responses, 2 maintained stable disease, and 2 patients had disease progression^[31]. There was transient thermal injury, the prolonged duration of which was strongly associated with previous radiotherapy. However, there were no serious adverse effects or deaths due to this treatment. While the application of immunotherapy to treat cancers is not new, this study demonstrated that adjuvant treatment with immunotherapy following PDT may improve its effec-

tiveness and represents a *viabile* future treatment of tumors at distant sites.

Further clinical research may perhaps lead to PDT being considered as a method of vaccination against tumors^[32]. This clearly would be of great advantage as PDT treatment in patients treated for primary breast cancer could also result in acquired immunity against the cancer at distant sites for all metastases of the same tumor clone. Under these circumstances, PDT's current position as a potential complementary adjuvant therapy could be extended to become a standard of care in breast cancer treatment. Further research is required if PDT is to be used successfully in primary breast cancer.

3.2 Photodynamic Therapy in Colorectal Cancer Treatment

Colorectal cancer (CRC) is the third most common cancer in men (10.0% of the total incidences) and the second in women (9.2%, respectively) worldwide. About 750,000 deaths from CRC are predicted in 2015 globally, accounting for 8.5% of all cancer deaths predicted in this year, which makes CRC the fourth most common cause of death from cancer^[33-35]. According to the data from 2011, approximately 20-25% of patients with CRC already have metastases at the time of diagnosis and 50-60% of the remainder will develop metastases^[36]. The treatment options and prognosis for patients with CRC have improved through the development of novel drugs and treatment regimens^[37]. However, the increasing resistance of tumor cells toward chemotherapeutic and biologic drugs used in CRC^[38] as well as non-specific toxicity of these drugs on healthy tissues^[39] creates a necessity to find other methods of CRC therapy. One of these methods is photodynamic therapy (PDT)^[40] involving interaction between light, photosensitizer and oxygen to destruct tumor tissue through direct oxidative damage, vascular shutdown and activation of immune response against cancer cells^[41,42]. The advantages of PDT over conventional chemotherapy are: higher tumor selectivity, lack of cross-resistance which enables the use of PDT in cases of recurrent tumors, wide range of total light and drug dose, allowing multiple application of PDT toward the same tumor as well as very good cosmetic effect with small or no scarring^[43]. The majority of preclinical studies concerning possibility of PDT application in colon and rectal cancer are focused on phototoxic action of photosensitizers towards cultured colorectal tumor cells *via*. The *via* research simplifies the system under study comparing to living organism so that investigator can focus on the limited number of cell components and interactions between them^[44].

3.3 Digestive Tract Carcinomas

PDT has been approved as a curative treatment in the digestive tract for superficial carcinoma of the oesophagus and stomach under the national health insurance system by Japan's Ministry of Health and Welfare since 1994. Oesophageal cancer accounted for 3.2% of the newly diagnosed cancers in 2012. With a very poor mortality to incidence ratio, it is the sixth most common cause of cancer related death (4.9% of total)^[45]. Oesophageal cancer histology differs by location: oesophageal squamous cell carcinoma (ESCC) is located in the upper and middle part of the oesophagus while adenocarcinoma (ADC) is mostly located in the lower part. Locally advanced oesophageal cancer can be surgically removed by esophagectomy in operable patients but postoperative morbidity and mortality occur regularly and long-term outcome is poor^[46]. Only small advantages of neoadjuvant CT and CRT to improve treatment outcome have been observed^[46,47]. Peri-operative chemo-therapy (PCT) or chemo-radiation therapy (CRT) appears beneficial but the advantage was more pronounced for younger patients as no survival advantage was seen for the elderly patients^[48]. CRT is used as definitive treatment option for ESCC but residual or recurrent lesions remain a major obstacle showing need of improved therapies. Moreover, reducing morbidity associated with CT would also improve current treatment strategies, which is why PDT has great potential. Clinical studies showed the curative potential of Photofrin®-PDT for BE and early esophageal cancer. In a retrospective study, Photofrin®-PDT applied with curative intend proved successful in Barretts esophagus (BE) patients with high grade dysplasia (HGD), an indication with a higher chance of progression to cancer. It was less effective in patients who had ADC or ESCC, especially with larger lesions^[49]. A similar study supports this data by stating PDT proved effective in treating smaller BE or ADC lesions but complete ablation was less likely with lesions over 3 cm in length^[50]. May be even more important than BE length is oesophageal wall thickness, as thicker walls have a lower chance of achieving successful results with Photofrin®-PDT^[51]. Photofrin®-PDT is indeed effective but it appears that taking lesion length, thickness and possibly several genetic biomarker levels into account when establishing PDT dosage, can still improve Photofrin®-PDT efficacy. It is considered an effective component of adjuvant therapy for patients with dysphagia that are unfit for, or refuse, surgery. As part of a multimodal approach, Photofrin®-PDT has shown good results with improving the patients' quality of life by effectively and immediately palliating dysphagia^[52]. A randomised controlled, dose-finding

study showed comparable or even better efficacy using 5-ALA compared to Photofrin® in patients with high grade dysplasia (HGD). Moreover, PDT using 5-ALA was carried out without the complications seen with Photofrin® due to improved localisation^[53]. Studies with second generation PSs show better efficacy and lower morbidity but additional trials are needed to potentially implement them as first-line treatment of oesophageal cancer.

Photofrin-PDT is clinically applied for unresectable bile duct carcinomas worldwide; however, PDT for unresectable bile duct carcinoma was used in clinical research trials at a small number of institutes, but was not approved by the national health insurance system in Japan. Between 1998 and 2006, cancer institutes in Europe showed improved patient status and survival benefits of photofrin-PDT for unresectable bile duct carcinomas in randomized or phase II prospective trials^[54,55]. Thus, PDT has become a promising modality for local treatment of bile duct carcinoma and PDT using the new photosensitizer, temoporfin, recently showed a decrease of phototoxicity and treatment efficacy^[56]. Thus, PDT has been found to be potentially safe and effective treatment for digestive tract carcinomas, which lead to increased quality of life, prolonged tumor progression-free period and related increased overall survival accompanied by other therapy modalities.

3.4 Head and Neck Tumors

PDT has been successfully employed to treat early carcinomas of the oral cavity, pharynx, and larynx, preserving normal tissue and vital functions of speech and swallowing^[57]. Biel reported the largest series of over 300 patients accrued over a 15- year clinical time period and treated with porfimer sodium-mediated PDT^[58]. The treated lesions, there were predominantly squamous cell carcinoma (SCCs) of the oral cavity, pharynx, or larynx, Kaposi sarcoma, melanoma, and SCC in the head and neck area^[59]. Among the reported group, 133 patients presented with recurrent or primary CIS, T1N0 and T2N0 laryngeal carcinomas and were treated with PDT with curative intent. After a single PDT procedure, the patients were followed on average for 96 months and at 5 years demonstrated a 90% cure rate. The second group of patients who underwent PDT consisted of 138 patients with CIS and T1N0 SCCs of the oral cavity. Similarly, one PDT treatment was delivered and the patients were followed for up to 211 months. All patients were reported to achieve complete pathological and clinical responses and the cure rate at 5 years remained at 100%. PDT was also used for patients with more advanced stages of oral cavity lesions. Fifty-two patients with T2N0 as well as T3N0 SCC also received a single PDT treatment that led to complete

pathological and clinical response, affording a 100% cure rate at 3 years. Overall, over 500 patients with early stage oral cavity, larynx, pharynx, and nasopharynx lesions were treated with porfimer sodium-based PDT worldwide with similar success^[60-62]. The intense development of a second generation of PSs has led to their entering clinical application in head and neck lesions as well^[63]. Several series have reported on the use of the second-generation PSs such as ALA and temoporfin^[64,65]. The study by Hopper *et al.*^[64] of patients with early oral cancer, in whom the tumors measured up to 2.5 cm in diameter, reported a complete response rate of 85% (97 of 114 patients) at 12 weeks and a disease-free survival rate of 75% at 2 years. In another study by Copper *et al.*^[66] PDT was used in the treatment of a total of 27 patients with 42 second or multiple primary head and neck tumors. Perhaps the most interesting study reported the application of temoporfin-mediated PDT for advanced disease. A total of 128 patients with advanced head and neck cancer were treated with a single PDT session.^[67] The patients included in this study had failed conventional therapy or were unsuitable for such treatment. PDT delivered 96 hours after temoporfin administration allowed for 100% tumor mass reduction in 43% of lesions and the remaining lesions were reduced by at least 50%. In this trial, tumor mass reduction was measured for each lesion by multiplying the lesion's length by its width. The 100% tumor mass reduction represented a complete local tumor clearance. A relatively limited study that has been conducted with ALA for head and neck lesions reported results that were slightly inferior to those observed with porfimer sodium and temoporfin^[68,69]. Taken together, the data from phase 1/2 trials strongly suggested that PDT could be an effective primary and alternative treatment modality for patients presenting with early head and neck tumors and that further research in this area, including randomized trials, is needed.

3.5 Urinary System Tumors

3.5.1 Prostate Cancer

Patients with prostate cancer who elect to undergo definitive radiotherapy have limited options for salvage therapy for isolated local failure. Unlike chemotherapy or radiotherapy, the mechanism of cell killing by PDT is not dependent on DNA damage or cell cycle effects, decreasing the chances of therapy cross-resistance and eliminating late normal tissue effects such as second malignancy. All of these factors combine to make prostate cancer an attractive target for clinical trial development. Several groups have published clinical trial results for prostate PDT using second-generation PSs. In a pilot study of temoporfin-me-

diated PDT, 14 patients who experienced biopsy confirmed local failure after definitive radiotherapy for early stage prostate cancer were treated using up to 8 implanted, interstitial, cylindrically diffusing optical fibers^[70]. Another group has studied motexafin lutetium (MLu) as a PS for PDT of the prostate^[71,72]. In the phase 1 trial, 17 patients with biopsy confirmed, locally recurrent prostate cancer after definitive radiotherapy were treated with increasing doses of 732 nm (red) light using interstitial fibers. The primary goal of this trial was to determine the maximally tolerated dose and dose-limiting toxicities of MLu-mediated prostate PDT, and one important secondary goal was to begin to develop the capability to perform real-time measurements of tissue optical properties, tissue levels of oxygen, and PS to eventually allow real-time light fluence modulation that would provide a more homogenous dose of PDT to the entire prostate gland. As in the temoporfin study, one patient developed a urorectal fistula that was attributed to inhomogeneity of the light dose. The remainder of toxicities observed in these patients were mild to moderate and consisted of urinary toxicities, including stress incontinence. Although not designed to measure efficacy, a significant difference was found in time to biochemical failure (prostate-specific antigen recurrence between the low and high PDT dose cohorts, providing some evidence of biochemical and pathologic disease response to PDT. Another group has investigated vascular targeted PDT using palladium (Pd)-bacteriopheophorbide (padoporfin)-mediated PDT and a short drug-light interval^[73]. In the phase 1 trial, 24 patients with biopsy confirmed local failure after definitive radiotherapy for prostate adenocarcinoma were treated with padoporfin-mediated PDT using 2 interstitial fibers.^[74] This study demonstrated that vascular-targeted PDT could be safely performed in this patient population. In the follow-up phase 2 study, 28 patients were treated with increasing light doses^[75]. After 6 months of follow-up, less residual cancer was noted on biopsy as the light dose increased. All had negative biopsies at follow-up if greater than 60% of the prostate was determined to be avascular by post-PDT magnetic resonance imaging (MRI). Toxicities were significant, with 2 patients developing urethrorectal fistulas. This study demonstrated the potential for pathologic complete response over a short-term follow-up. Together, these studies suggested that although PDT to the prostate is feasible, comprehensive treatment of the entire gland will be necessary and improved techniques and dosimetry will be critical in providing an acceptable toxicity profile.

3.5.2 Bladder Cancer

Bladder cancers, which are often superficial and multi-

focal, can be assessed and debulked endoscopically. In addition, the geometry of the bladder should allow for improved and homogeneous delivery of light. These factors make superficial bladder cancer an attractive target for PDT. In one study, focal HPD-mediated PDT was used to treat 50 superficial bladder transitional cell carcinomas (TCCs) in 37 patients and achieved a 74% complete response rate^[76]. Another study used HPD-mediated PDT to treat the entire bladder wall for 34 patients with refractory CIS of the bladder and achieved a 73.5% complete response rate at 3 months^[77]. However, by 2 years, 77.8% of these patients experienced disease recurrence. In these studies, treatment of superficial bladder cancer with PDT is generally well tolerated, with dysuria, hematuria and skin photosensitivity being the most common acute toxicities. However, bladder wall fibrosis/ diminished bladder capacity has been and continues to be a problem in some treated patients. With improved dosimetry and the use of porfimer sodium as a PS, other investigators have achieved durable complete response rates as high as 60% for patients with refractory bladder CIS or superficial TCC^[78,79]. Studies of locally applied (intravesical) ALA demonstrate that similar durable complete response rates of 52% to 60% at 2 to 3 years can be achieved for patients with treatment-refractory bladder CIS without the prolonged skin photosensitivity experienced when using systemic porfimer sodium^[80,81].

Although most of the patients treated with bladder PDT are refractory to BCG, one randomized controlled study has compared a single porfimer sodium-mediated PDT with multiple BCG treatments (induction plus maintenance) and found that these therapies are equivalent in durable treatment response^[82]. Studies combining intravesical immunotherapies such as BCG or chemotherapies such as mitomycin C with PDT showed that these therapies might significantly enhance the PDT responsiveness of bladder tumors^[83,84]. Despite these promising results, PDT for bladder cancer remains largely investigational with limited use. PDT for bladder cancer is approved in Canada and in some EU nations but has not been approved by the US FDA.

3.6 Non-Small Cell Lung Cancer and Mesothelioma

PDT for non-small cell lung cancer (NSCLC) was first used in 1982 by Hayata *et al.* to achieve tumor necrosis and reopening of the airway^[85]. PDT for lung cancer is particularly useful for (1) patients with advanced disease in whom PDT is used as a palliation strategy^[86] and (2) patients with early central lung cancer when patients are unable to undergo surgery^[87]. PDT is considered to be more specific and lesion-oriented compared with other

available modalities and produces less collateral damage, and therefore fewer complications. Indeed, a randomized trial of PDT versus Nd:YAG laser therapy for obstructing NSCLC lesions showed equal initial efficacy for these 2 treatments, with a longer duration of response noted for PDT^[88]. PDT plus palliative radiation also appears to increase the time to bronchus reocclusion when combined compared with radiation alone^[89]. In patients with early stage lung cancer, PDT has been used to successfully treat patients for whom surgery is not feasible. In one phase 2 study, 54 patients with 64 lung carcinoma lesions underwent porfimer sodium-mediated PDT and showed an 85% complete response rate with a 6.5% local failure rate at 20.2 months^[90]. Other studies have supported these excellent results, with complete response rates averaging 73% in studies totaling 359 patients^[91]. Recently, Usuda et al^[92] reported a series of 70 cancer lesions measuring 1.0 cm or less in diameter and 21 lesions measuring greater than 1.0 cm in diameter treated with PDT with talaporfin. The complete response rates were 94.3% (66 of 70 patients) and 90.4% (19 of 21 patients), respectively. PDT with talaporfin was capable of destroying the residual cancer lesions observed after the mass of large tumors had been reduced by electrocautery. Another report^[93] described the results of 529 PDT procedures performed on 133 patients who presented with NSCLC (89 patients), metastatic airway lesions (31 patients), small cell lung cancer (4 patients), benign tumors (7 patients), and other (unspecified) lung conditions (2 patients). The lesions were most commonly located in the main stem bronchi (71 patients). Most patients received 2 treatments during a 3-day hospitalization and returned in 2 weeks for 2 additional PDTs. The authors concluded that PDT can be safely and effectively used in the described setting, leading to improved dyspnea in selected patients. Malignant pleural mesothelioma (MPM) is a cancer of the pleura that, similar to NSCLC with pleural spread, has no currently available curative options. In a phase 2 study of porfimer sodium mediated PDT after extrapleural pneumonectomy for MPM, patients with stage I and II disease experienced a median survival of 36 months with a 2-year survival rate of 61%, whereas patients with stage III and IV disease experienced a median survival time of 10 months^[94]. Both of these rates were significantly improved compared with historical series of surgery alone. One important finding in these studies of resection with PDT for MPM is that a lung-sparing, tumor debulking surgery can be combined with PDT to achieve local control rates similar to those observed with extrapleural pneumonectomy. Indeed, a more recent study of macroscopically complete, lung-sparing surgical debulking followed by intraoperative porfimer sodium-mediated

PDT for patients with locally advanced MPM found a median survival that had not been reached with a 2.1-year median follow-up in patients after radical pleurectomy with PDT^[95]. Thus, PDT for MPM needs to be further evaluated in clinical trials of lung-sparing surgery.

3.7 Brain Tumors

PDT is currently undergoing intensive clinical investigation as an adjunctive treatment for brain tumors^[96]. The major tumor lesions particularly suitable for PDT treatment are newly diagnosed and recurrent brain tumors due to their high uptake of PSs. Since the early 1980s, close to 1000 patients worldwide have received PDT for brain lesions. Perria *et al.*^[97] reported one of the earliest attempts to use PDT to treat the postresection glioma cavity in humans, and Kaye et al^[98] reported a phase 1/2 trial involving 23 patients with glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA). Other brain lesions treated with PDT included malignant ependymomas,^[99,100] malignant meningiomas,^[101] melanoma and lung cancer brain metastasis,^[98,101] and recurrent pituitary adenomas^[102]. The initial trials provided encouraging results, and the authors concluded that PDT can be used as an adjuvant therapy in patients with brain tumors. The PSs used to date were various formulations of HPDs (porfimer sodium) and ALA as well as temoporfin. The light sources used to activate those PSs included lamps, dye lasers, gold vapor potassium titanyl phosphate dye lasers, and diode lasers. Currently, PSs are being evaluated both as intraoperative diagnostic tools by means of photodetection (PD) and fluorescence-guided resection (FGR) as well as during PDT as an adjunctive therapeutic modality^[101,103-105]. All 3 approaches take advantage of the higher uptake of PS by the malignant cells and are used intraoperatively. The most recently published trials that employed PD, FGR, and PDT provided additional encouraging results, but the initial delay in tumor progression did not translate to extended overall survival^[106]. Muller and Wilson reported the results of a prospective randomized controlled trial using adjuvant porfimer sodium-mediated PDT in the study group^[107]. The 96 patients treated for supratentorial gliomas with PDT with porfimer sodium at St. Michael's Hospital in Toronto, Ontario, Canada were randomized to 2 groups that received either 40 J/cm² or 120 J/cm². The patients who received the higher dose (48 patients) survived on average for 10 months, whereas the 49 patients in the low-dose group survived on average 9 months; the difference between both groups was not statistically significant ($P = .05$). Stummer *et al.* reported the results of the ALA study group, a multicenter prospective randomized controlled trial in Germany^[108]. This trial compared

the effectiveness of ALA-based FGR with conventional surgery. The 322 patients with suspected malignant gliomas were followed for 35.4 months. Patients randomized to the FGR group demonstrated much better time to progression (5.1 months) compared with the controls (3.6 months), which translated into a greater survival of 16.7 months versus 11.8 months, respectively. However, the difference in overall survival was not statistically significant. The current standard therapies that include surgery, radiotherapy, and chemotherapy afford a median survival of approximately 15 months and although there are limited data comparing PD, FGR, and photodiagnosis with those standard therapies, the initial results from randomized trials are encouraging. It remains to be seen whether PDT for brain tumors remains a palliative or, at most, an alternative treatment modality. The new classes of PSs, the better understanding of dosimetry, and further improvement in technology may significantly change the currently achieved clinical outcome. In addition, preclinical data indicating that protracted light delivery may increase the therapeutic index of PDT in the brain combined with newer technologies such as implantable LED-based light delivery systems could lead to significant improvements in treatment outcomes^[96].

4. X-Ray-Induced Photodynamic Therapy

Achieving effective treatment of deep-seated tumors is a major challenge for traditional photodynamic therapy (PDT) due to difficulties in delivering light into the subsurface. Lasers and light-emitting diodes (LEDs) are light sources that are commonly used in PDT, halogen and arc lamps can also be used in some cases. However, most photosensitizers (PSs), such as porphyrin derivatives, absorb in the ultraviolet or visible regions that overlap with the tissue absorption spectrum^[109,110]. This makes it difficult to apply PDT in the clinic due to the short penetration depth of illumination light, which leads to ineffective treatment of tumors located deep under the skin. A potential solution to the limitation of PDT for deep tumor treatment is developing near-infrared (NIR) photosensitizers. Due to the weak scattering and absorption of most tissue chromophores, including oxyhemoglobin, deoxyhemoglobin, melanin, and fat in the NIR window, only light in the range of 700–1100 nm can penetrate deep into the tissue^[111]. However, for practical applications, NIR light can still only penetrate 5 mm into the tissue because enough energy needs to be reserved for PS activation^[112]. Moreover, reduced $^1\text{O}_2$ generation efficiency has been reported by using NIR-activated PSs due to the narrow energy gaps and the faster non-radiative transition rate (when compared with that of wide-band photosensitizers)^[113,114].

Another methodology used to achieve deeper tissue penetration is through utilizing an NIR laser as the light source. Even with this advancement, there is still room for further improvement of the penetration depth and the generation efficacy of $^1\text{O}_2$ ^[115]. To work on overcoming these problems, researchers introduced X-rays as an energy source to initiate PDT^[116]. The utilization of X-rays as a PDT light source makes it feasible to integrate diagnosis, radiotherapy, and PDT for the next generation of tumor theranostic applications. In order to use X-rays in this technology, scintillator materials are used to convert the X-rays to UV/visible light since there is no PS that can directly absorb X-ray energy^[117]. The scintillation process can be divided into three parts: (1) conversion of incoming radiation into a large number of electron-hole pairs, (2) transfer of the electron-hole pairs' energy to the luminescent ions, and (3) emission of the luminescent ions that radiatively return from an excited state to the ground state^[117,118]. Low energy beams (40–100 kV or “superficial” X-rays) are useful only for skin cancers because the beams can only penetrate <5 mm deep. Subsurface tumors require medium energies (200 kV to 1 MV orthovoltage and supervoltage X-rays). Presently, high-energy beams (4–25 megavoltage [MV] or “deep” X-rays) are commonly used to treat deep tumors (>2 cm deep). The derived unit for absorbed dose is the gray (Gy), according to International System of Units, and is equivalent to 1 J of energy deposited by ionizing radiation per kilogram of matter ($1 \text{ Gy} = 1 \text{ J/kg} = 1 \text{ m}^2/\text{s}^2$)^[119]. The Figure 2 shows principle of X-ray-activatable nanoparticles for PDT. The PS's electrons from the ground state (S_0) will absorb energy and move to singlet-excited states (S_1). Some of the absorbed energy will be released *via* intersystem crossing, and the promoted electron will move to a triplet excited state (T_1). This triplet state has a relatively long half-life, allowing energy to be transferred to nearby oxygen molecules. This generates $^1\text{O}_2$ in most cases *via* the type II pathway, which can damage the cells in the surrounding area.

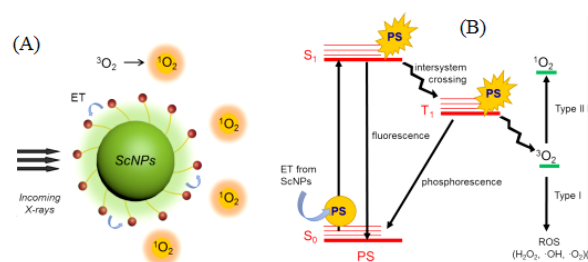


Figure 2. Principle of X-ray-Activatable Nanoparticles for PDT. (A) Scintillating nanoparticles act as an X-ray transducer to generate $^1\text{O}_2$ through the energy transfer process. (B) diagram of the PDT mechanism that occurs when energy is transferred from ScNPs to activate the PS^[120]

5. Nanotechnology in PDT

Despite the widespread and rapidly growing applications, PDT has yet to gain clinical acceptance as a first-line oncological intervention due to certain limitations including lack of an ideal PS, challenges in formulating PS, choosing the right light dosimetry for a complete and effective treatment, difficulties in planning the treatment and monitoring the treatment response. The application of nanoparticles in PDT has been a major stride forward in resolving some of the challenges associated with classic PS. With the rapid development of nanoscience and technology in the past decade, phototherapies based on nanomaterials and nanotechnologies have attracted tremendously increasing interest^[121]. Over the past decade, nanoparticle-based PDT has emerged as an alternative to conventional PDT to effectively target cancer. PS-carrying nanoparticles could increase the water solubility of PS molecules, enhance their tumor accumulation, and thus improve the therapeutic efficacy and specificity of PDT. In addition, nanotechnology provides a platform for the integration of multiple functionalities in a single construct. Various nanomaterials such as liposomes^[122], polymeric nanoparticles^[123], magnetic nanoparticles^[124-126], quantum dots^[127], carbon-based nanomaterials^[128], mesoporous silica nanoparticles^[129] as well as a number of other functional nanoparticles with interesting chemical and physical properties^[130] have been developed for the delivery of PDT, showing encouraging results *via* and *in vivo*. The potential advantage of NPs is that a high “payload” can be delivered and they can be “decorated” with multiple targeting moieties such as antibodies or peptides. Other approaches^[131] include biodegradable polymers and ceramic (silica) and metallic (gold, iron oxide) NPs; magnetic NPs, in which an applied magnetic field enhances localization to the tumor; and hybrid NPs that allow both PDT and either another therapeutic strategy such as hyperthermia or an imaging technique such as MRI. NP delivery of 2-photon PSs has also been reported, because these typically have very poor water solubility^[132]. Moreover, in recent years, another unique class of optical nanomaterials, Upconverting NPs have been investigated, in which relatively long wavelength light (NIR) is absorbed and converted to shorter wavelength light that activates the attached PS^[133]. “Upconversion Nanoparticles” (UCNs), a multifaceted tool that due to its recent accelerated progress shows great potential in augmenting the scope of PDT in the treatment of solid tumors. These concepts illustrate a general advantage of NP based PDT in that the photophysical and photochemical properties of the PS can be uncoupled from the delivery and activation

processes. A final recent approach is the encapsulation of a PS inside polymeric NPs that in turn are incorporated into liposomes containing a second drug such as an antiangiogenic agent (or vice versa)^[134]. This co-delivery increases the therapeutic synergy of the 2 modalities.

6. Combinations of PDT with Other Therapies

Combinations of various therapeutic modalities with non-overlapping toxicities are among the commonly used strategies to improve the therapeutic index of treatments in modern oncology. Two general approaches may increase the antitumor effectiveness of PDT: (1) sensitization of tumor cells to PDT and (2) interference with cytoprotective molecular responses triggered by PDT in surviving tumor or stromal cells. Any interactions between PDT and PDT-sensitizing agents will be confined to the illuminated area. Therefore, the potentiated toxicity of the combinations is not systemic. This should be of special importance in elderly or debilitated patients who tolerate more intensive therapeutic regimes poorly. Moreover, considering its unique $^1\text{O}_2$ -dependent cytotoxic effects, PDT can be safely combined with other antitumor treatments without the risk of inducing cross-resistance^[135]. There have been few studies on combinations of PDT with standard antitumor regimens published to date^[136]. PDT can be used in combination with surgery as a neoadjuvant, adjuvant, or repetitive adjuvant treatment, preferably fluorescence image guided to confine illumination to the most suspicious lesions. PDT has also been successfully combined with radiotherapy (RT) and chemotherapy^[137-139]. The promising emerging approach of using nanoparticles to enable the combination of PDT with RT for deep cancer treatment was proposed by Chen and Zhang in 2006^[140]. Under this concept, luminescent nanoparticles were utilized for the delivery of PS such as porphyrin. Upon simulation by X-rays, the nanoparticles emit scintillation or persistent luminescence to activate the PS to generate singlet oxygen. The novel strategy described in this study involves the use of *in vivo* luminescent nanoparticles so that an external light source is not necessary to activate the photosensitizing agent within tumors. Moreover, Figure 3 shows high energy beams such as X-rays can penetrate deep tissue easily; therefore, after the PDT activation by X-ray, it will be feasible for deep cancer treatment^[141].

The development of novel target-specific antitumor drugs has enabled examination of a number of concept-based combinations that in various molecular mechanisms sensitize tumor cells to the cytotoxic effects of PDT. Proteins are major targets for oxidative reactions because

they constitute nearly 70% of the dry weight of cells. Oxidized proteins can be refolded by molecular chaperones such as HSPs. Inefficient restoration of their structure leads to accumulation of misfolded proteins and their aggregation, which precipitates cell death. Accumulation of damaged or misfolded proteins within ER triggers a process called ER stress, which can be ameliorated by unfolded protein response or can lead to cell death^[142]. Therapeutic approaches that interfere with refolding or removal of oxidized proteins can be used to sensitize tumor cells to PDT. For example, modulation of HSP function with geldanamycin, a HSP90 inhibitor, sensitizes tumor cells to PDT^[143]. Bortezomib, a proteasome inhibitor successfully used in the treatment of haematological disorders, potentiates the cytotoxic effects of PDT by aggravation of ER stress^[144]. Moreover, several apoptosis-modulating factors such as rapamycin, Bcl-2 antagonists, ursodeoxycholic acid, or ceramide analogues have been shown to increase PDT-mediated cancer cell death. Transformed cells deeply seated within the tumor mass receive suboptimal light doses and survive due to induction of numerous cytoprotective mechanisms. Targeting enzymes participating in ROS scavenging (such as superoxide dismutase, HO-1, or nitric oxide synthase) with selective inhibitors has been shown to improve the antitumor activity of PDT^[145,146,147]. Antivascular effects of PDT can be further potentiated by cyclooxygenase (COX) inhibitors,^[148] antiangiogenic or

antivascular drugs,^[149] or monoclonal antibodies targeting factors promoting neovascularization (such as vascular endothelial growth factor),^[150] significantly improving tumor growth control after PDT. Finally, combining PDT with agents that target signal transduction pathways such as the anti-epidermal growth factor receptor agent cetuximab may also improve the efficacy of PDT.^[151] Moreover, combining 2 different PSs in one treatment regimen leads to simultaneous targeting of tumor as well as vascular cells^[152]. The use of agents that enhance the efficacy without increasing the normal tissue effects of PDT, thereby improving the therapeutic index, will represent a major focus of clinical research going forward.

7. Current Limitations of PDT

In spite of solving so many problems and resolving restrictions regarding PDT, there are still limitations of PDT treatment. Although it delivers site-specific therapy, its acceptance in clinical practice as a mainstream cancer treatment modality is hindered, for the most part, by accumulation of sensitizers in skin. As discussed in the previous sections, PDT proves to be effective in inducing tumor responses as well as improving patient survival and quality of life. Efficacy is seen when PDT is part of a multimodal approach, is used as a first-line treatment for premalignant or early disease and as standalone palliative treatment. Even though PDT shows great potential, there are still some limitations that prevent a firm position for PDT in standard care regimen of cancer. When reviewing the clinical trials and studies done over the last few years, some general problems become evident. A major problem is related to the adverse events (AEs) associated with PDT. With systemically administered PSs, especially of the first generation, skin photosensitivity is one of the most common AEs. Patients have to avoid sunlight and strong artificial light for weeks, which is highly undesirable when they are nearing the end of life. Another AE often reported is pain. The main mechanism in PDT induced pain has yet to be elucidated, but several studies have found some predictors of pain. The biggest predictors appear to be the size of the treated area while location, PS type, lesion type, gender, age and light protocol have also been mentioned^[153]. Several strategies of pain management have been tested but none fully relieved PDT induced pain^[153]. The occurrence of AEs like inflammation, fever and nausea are typically location dependent but are often successfully managed with medication. Another drawback is the decreasing efficacy of PDT for larger lesions, especially with first generation PSs. Due to inadequate tissue penetration of light or PS, bulky or deep seated tumors are difficult to treat with PDT. Especially

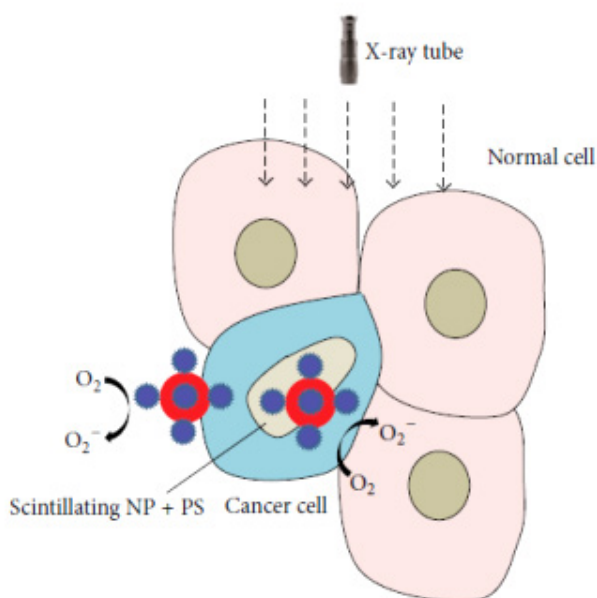


Figure 3. Schematic of combination therapy of radiotherapy and photodynamic therapy. Ionizing radiation is used to excite scintillating nanoparticles, which may be located deep within tissue. The nanoparticles transfer energy to the attached photosensitizer molecules, killing cells by the same mechanism as photodynamic therapy^[141]

evident with Photofrin® and 5-ALA, the limited penetration of the appropriate light prevents sufficient depth of tumoricidal action^[154]. Even second generation PSs perform less in larger lesions in which case surgery is more effective^[155,156]. The most effective PSs tend to be hard to dissolve due to hydrophobicity and can form aggregates that have trouble penetrating tumor tissue^[157]. Besides larger lesions, PDT is also not indicated for metastasizing tumors. Almost all clinical studies exclude patients with tumor metastasis as it is almost impossible to reach those tumors with light. Metastasis remains one of the largest challenges in cancer therapy and PDT is no exception. Tumor recurrence is often reported in clinical trials, probably due to inadequate tumor eradication. Not only insufficient penetration, but also the presence of PDT resistant tumor tissues due to hypoxia probably adds to the chance of recurrence. Although the reason for recurrence often lies beyond the scope of clinical trials, the importance of pre-existing hypoxia in cancer therapy outcome is well known^[158,159]. It is believed, however, that with improved technology, dosimetry and new PSs the above limitations could be overcome in the future.

8. PDT in the Future

Researchers continue to study ways to improve the effectiveness of PDT and expand it to other cancers. Clinical trials (research studies) are under way to improve/evaluate the use of PDT for cancers of the brain, skin, prostate, cervix, and peritoneal cavity (the space in the abdomen that contains the intestines, stomach, and liver). Other research is focused on the development of photosensitizers that are more powerful, more specifically target cancer cells^[160] and are activated by light that can penetrate tissue and treat deep or large tumors. Recently the addition of other photo-activated therapeutics that improves the anti-tumor potential of PS based theranostics has often been investigated. The use of light activated photothermal therapeutic (PTT) agents can increase the overall cell killing effect compared to PDT alone, while the nanocarrier also hinders efficient imaging modalities for image-guided PTT/PDT^[161,162]. These multifunctional nanoplateforms can become even more complex by incorporation of chemotherapeutics^[163,164]. The interest in combining diagnostics and therapeutics in the field of PDT is illustrated by the vast body of literature from the last couple of years, describing the ideas and endless possibilities to create multi-layered PDT-based theranostics. These multifunctional modalities will improve the applicability of PDT and possibly strengthen its position in the clinic. Not only will nanomaterials provide a scaffold for both PS and targeting moieties, they will also enable the incorporation of imaging

agents and other therapeutics to improve PDT efficacy and applicability^[165]. Nevertheless, with the monoclonal antibodies conjugated PSs, the increased size of such complex theranostic platforms might negatively affect PS circulation times and tissue penetration. Further studies are needed to show the applicability of such compounds.

One of the hallmarks of PDT is the inflammatory response following treatment-induced tumor cell death. This response is also crucial for the development of anti-tumor immunity^[166]. Few pre-clinical studies have shown the occurrence of tumor immunogenicity, control of distant disease and protection for further tumor challenges^[167]. Considerable effort is put into understanding the mechanisms underlying tumor immune response and systemic anti-tumor immunity and exploring how to exploit them to improve PDT efficacy^[168]. Earlier work mentions several ways of stimulating the immune system to improve anti-tumor immune-reactions after PDT. Administration of inflammatory cytokines such as tumor necrosis factor (TNF)- α or macrophage colony stimulating factor or the local administration of pathogen-associated molecular patterns (PAMPs) such as bacterial or fungal components stimulated the immune-system and improved PDT efficacy^[169,170]. The application of PAMPs to improve PDT induced tumor immunity is still being investigated. Peritumoral injection of CpG oligodeoxynucleotides, a TLR-9 agonist used in clinical trials to improve immunotherapy, resulted in tumor directed migration of primed DCs that show enhanced phagocytosis, maturation and antigen presentation to T-cells. When combined with PDT, this ultimately results in prolonged host survival in a metastatic murine breast cancer model compared to PDT alone^[171]. Modulating gene expression by epigenetic reversal can also aid in enhancing PDT anti-tumor effect. Essential components in eliciting an immune response such as MHC I or tumor associated antigens (TAA) are often downregulated in cancers^[172]. The importance of TAA in anti-tumor responses was elucidated when PDT treatment of P1A positive tumors elicited an epitope-specific immune response while treatment of P1A negative tumors did not^[173]. Additionally, PDT is used to generate therapeutic or prophylactic anti-tumor vaccines based on tumor cells or lysates obtained after ex vivo PDT^[174]. PDT generated cell lysates proved more effective than lysates generated by UV or ionizing irradiation or freeze thaw cycles in inducing an immune response^[175]. Following cell lysate vaccination, several studies reported stimulated DC migration and maturation, enhanced T-cell activation and tumor specific immune recognition leading to tumor growth inhibition, prolonged survival time and acquisition of resistance against rechallenge in mice^[175,176]. Similar

results were seen after administration of PDT treated whole tumor cells as a cancer vaccine^[177].

9. Conclusion

Photodynamic therapy (PDT) is an emerging cancer treatment that takes advantage of the interaction between light and a photosensitizing agent to initiate apoptosis of cancer cells. Photodynamic therapy (PDT) offers a minimally invasive, effective and highly controllable therapeutic strategy, and has become popular as an alternative or additional approach to conventional cancer treatments, such as chemotherapy and surgery. The increasing popularity of this treatment method is largely due to its selectivity: only tissues that are simultaneously exposed to the photosensitizer and light, in the presence of oxygen, are the ones subjected to the cytotoxic reactions during PDT. Thus, under ideal circumstances only diseased tissues are eradicated, leaving the surrounding healthy cells undamaged. With several commercially available photosensitizing agents now on the market, numerous well designed clinical trials have demonstrated the efficacy of PDT on various cutaneous and deep tissue tumors. Moreover, PDT-induced immunogenic cell death associated with induction of a potent local inflammatory reaction offers the possibility to flourish into a therapeutic procedure with excellent local antitumor activity and the capability of boosting the immune response for effective destruction of metastases. However, current photosensitizers and light sources still suffer a number of challenges. Future PDT will build on those findings to allow development and refinement of more optimal therapeutic agents and illumination devices.

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