Journal of Innovative Optical Health Sciences
Vol. 2, No. 1 (2009) 73–92

World Scientific
www.worldscientific.com

PHOTODYNAMIC THERAPY — AN UPDATE ON CLINICAL APPLICATIONS

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Photodynamic therapy (PDT) has received increased attention since the regulatory approvals of several photosensitizers and light applicators in numerous countries and regions around the world. In recent years, much progress has been seen in basic research as well as clinical application. PDT clinical application has now extended from treating malignant diseases to nonmalignant diseases. This review article will present recent clinical data published in English journals. The data will be organized according to their clinical specialties. The new development and future direction in clinical applications of PDT for the management of both malignant and nonmalignant diseases will be discussed.

Keywords: Photodynamic therapy; clinical application; malignant disease; non-malignant disease.

1. Introduction

Photodynamic therapy (PDT) is a relatively new treatment modality. It involves the local or systemic administration of a photosensitizer followed by illumination of the disease site with non-thermal visible light of specific wavelength(s). In the presence of the oxygen molecule, the light illumination of the photosensitizer can lead to a series of photochemical reactions and consequently generate a variety of cytotoxic oxygen species (e.g., singlet oxygen). The nature, location, and quantity of PDT-induced cytotoxic species and the

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Table 1. Recent special journal issues dedicated to PDT.

Journal Name	Year; Volume(Issue)	Guest Editor(s)	Focus
Journal of Photochemistry and Photobiology B: Biology	2005; 79(3)	Dominic Robinson	Monitoring PDT
Journal of Environmental Pathology, Toxicology and Oncology	2006; 25(1–2)	Qian Peng	Basic science
Lasers in Surgery and Medicine	2006; 38(5)	Thomas J. Dougherty and Charles J. Gomer	Clinical application and basic science
Dermatologic Clinics	2007; 25(1)	Michael H. Gold	Dermatology
Journal of Photochemistry and Photobiology B: Biology	2007; 86(1)	Klaus D. Winckler	Anti-microbial PDT
Photochemistry and Photobiology	2007; 83(5)	David Kessel and Thomas H. Foster	Clinical application and basic science
Photochemical & Photobiological Sciences	2007; 6(12)*	Qian Peng and Kristian Berg	PDT and photodetection

*Special issue on selected presentations from the 11th World Congress of the International Photodynamic Association (IPA) (Shanghai, China, March 28–31, 2007).

sensitivity of the targeted cells and tissues determine the outcome of PDT treatment.

The phenomena of cell death being induced by the interaction of light and chemicals were recognized and the term of "photodynamic action" was introduced about a hundred years ago. The modern PDT development in oncology dated back to the early 1970s when Thomas Dougherty (Roswell Park Cancer Institute) re-discovered hematoporphyrin derivatives (HpD) and began investigating the mechanism and clinical application of HpD for cancer detection and treatment.

Since the first regulatory approval of Photofrin® (a purified form of HpD) was granted for the treatment of bladder cancer in Canada in 1993, the applications of PDT in the treatment of malignant and non-malignant diseases have increased dramatically due to the improvement in photosensitizers and light applicators. Recently, there were several journal issues focused on recent progress in basic science and clinical application (Table 1). In May 2004, a new international journal *Photodiagnosis and Photodynamic Therapy* (Editor-in-Chief: Keyvan Moghissi, http://www.sciencedirect.com/science/journal/15721000) was launched with a goal for dissemination of scientific knowledge and clinical developments of photodiagnosis and PDT in all medical specialities.

To promote the appropriate use of new or emerging innovative PDT technologies and applications that have a potential impact on clinical practice, a PubMed (a database provided by U.S. National Library of Medicine, http://www.ncbi.nlm.nih.gov / sites / entrez?db = pubmed) literature search is performed to identify recent progress. This manuscript will summarize literature search results by revisiting some early pioneer work, reviewing new clinical data published in English journals, and updating our previous review articles on the same topic.[1,2] Selected original and review articles will be provided in the reference section.

2. PDT Applications for Treatment of Malignant Diseases

2.1. *Skin premalignant and malignant disease*

The feasibility and efficacy of PDT for skin diseases were among the first to be studied due to the easy accessibility of the skin to the topical application of photosensitizer and light.[3] Because of good cosmetic outcome, PDT is particularly suitable for lesions in the face and neck area. In the late 1970s, the combination of xenon arc lamp and systemic application of HpD was used to treat skin cancers. Early studies demonstrated a 20%–80% complete response (CR) for primary skin cancers (e.g., squamous cell carcinomas (SCCs), basal cell carcinomas (BCCs), and malignant melanomas) and secondary cancers originating from breast cancer, colon cancer, and endometrium cancer.[4,5] The use of Photofrin® and its optimal dose and drug-light interval could achieve a higher CR for multiple BCCs.[6]

Since the discovery of endogenous protoporphyrin IX (PpIX) photosensitization induced by exogenous administration of prodrug 5-aminolevulinic acid (ALA), pre-malignant and malignant skin lesions also became a favorite target of ALA-PDT.[7] Accumulated clinical data show that topical ALA-PDT is effective in the treatment of actinic keratoses (AK), SCC *in situ* (Bowen's disease) and superficial BCC.[8–12] Early multicenter clinical studies showed that ALA-PDT (e.g., Levulan® and Blu-U blue light system) resulted in a high CR and disease-free rate in AK patients. AK became the first approved dermatologic indication of ALA-PDT in the United States in 2000. Recently, methyl aminolevulinate (MLA, Metvix® — a methyl ester of ALA) was also approved for AK, Bowen's disease, and BCCs in Europe. Comparison studies show similar effectiveness of ALA and MLA for the treatment of AK and BCC.[13,14] In general, the treatment of AK using PDT shows the advantages of better cosmesis and higher patient preference than cryotherapy and other options.[15,16] Several case reports indicate actinic cheilitis (a type of AK occurring on the lips) responses well to ALA-PDT.[17]

A noticeable side effect of topical PDT during light irradiation is pain. Using variable pulsed light (VPL) can significantly reduce pain compared to using LED.[18] For a large area and multiple sessions, the local application of Lidocaine cream prior to light irradiation is effective for pain relief.[11]

Because of the improvement in efficacy, tolerability, cosmetic outcome, and recurrence rate, PDT might be considered for selected cases of nodular BCC although long-term follow-up indicates superior efficacy of surgery to PDT. For nodular and elevated lesions, in addition to interstitial light irradiation, the systemic administration of a photosensitizer following a debulking procedure might be considered.[19–21]

Organ transplant recipients (OTRs) on long-term immunosuppressive therapy are at a high risk of developing non-melanoma skin lesions. Repeated field PDT can be used to treat post-transplant premalignant skin diseases.[22,23]

Clinical investigations of dermatological PDT have also been extended into many other skin neoplasia, for instance, cutaneous T-cell lymphoma, cutaneous verrucous carcinoma, and extramammary Paget's disease.[11,24–27] PDT may also be useful for both Mediterranean and HIV-related Kaposi's sarcomas since it can be repeated and will not cause significant immunosuppression.[28]

While constantly optimizing the current protocols (e.g., drug formulation, drug delivery, drug-light interval, light fractionation, and combination modalities), the usefulness of other photosensitizers (e.g., mTHPC, hypericins) for non-melanoma skin cancers has also been explored around the world.[29–31]

2.2. *Ophthalmic tumor*

Although the transcorneal PDT of the surface of pigmented lesions such as choroidal melanoma has little thearapeutic effect, in the absence of pigment, PDT is a feasible modality for the treatment of intraocular tumors such as retinoblastoma or amelanotic melanoma of the iris or choroid.[32]

Several recent case studies demonstrated that PDT could be used to treat choroidal neovascularization secondary to choroidal osteoma — a rare intraocular tumor composed of mature calcified bone. A recent report shows the regression of extrafoveal choroidal osteoma after a single session of verteporfin-PDT although the authors caution that their results should not be extrapolated to subfoveal choroidal osteoma.[33–35]

Verteporfin-PDT can be used for the treatment of choroidal metastasis that is unresponsive to chemotherapy and radiation therapy and for such patients who require ocular treatment only.[36–38]

2.3. *Head and neck cancer*

Hematoporphyrin derivatives-medicated PDT has been tested for recurrent and metastatic cancers of head and neck regions since the early 1980s.[39,40] Later clinical data suggested that PDT was particularly suitable for head and neck cancers because it had little effect on underlying functional structures and had an excellent cosmetic outcome with greatly reduced morbidity and disfigurement. PDT has been employed in the treatment of malignancies of the oral mucosa, particularly multifocal squamous cell carcinoma.[41,42] The treated sites characteristically show erythema and edema, followed by necrosis and frank ulceration. The ulcerated lesions typically take up to 8 weeks to heal fully, and supportive analgesia is required in the first few weeks.

An early Photofrin-PDT study of 107 patients showed that cure for T1 and *in situ* cancer of the vocal cords could be achieved with a single treatment. There was only one recurrence in 25 patients in 79 months of follow-up. All patients responded initially and the cure rate for early oral cavity tumors was 80% after 70 months.[43]

Our pilot study of Photofrin-PDT versus cisplatin and 5-fluorouracil (DDP/5-FU) remedy suggests that PDT is effective and safe for the treatment of advanced nasopharyngeal cancer and relief of nasal obstruction.[44]

For early carcinomas of the oral cavity and larynx, PDT is an effective primary and alternative treatment modality since it can preserve normal tissue and vital functions of speech and swallowing. A recent study of 276 patients showed that the cure rates with a single treatment using Photofrin-PDT for early laryngeal and oral cancers were 91% and 94%, respectively.[45,46]

Foscan® was approved in Europe in 2001 for the palliative treatment of patients with advanced head and neck cancer who have exhausted other treatment options. Foscan-PDT can have significant clinical benefits and improve quality of life.[47–49] Several clinical trials are currently undertaken to evaluate the efficacy of other promising photosensitizers including ALA and Photosens. For patients with advanced disease, the combination of PDT and radiotherapy or surgery could also improve cure rates.

2.4. *Brain tumor*

The potentials of PDT for the treatment of brain tumor were proposed in the early 1970s.[50] The first interoperational PDT of human gliomas was reported in 1980 and the first trial in 1981.[51,52] More advanced cavitary PDT technique was introduced in the 1990s, which utilizes an optical fiber or LED array in a light-diffusing medium to irradiate residual tumors following surgical resection.[53–55]

Several multicenter studies have been carried out to evaluate the efficacy of Photofrin, ALA, BPD-MA, and Foscan for the treatment of nonresectable tumors.[56–58] A long-term evaluation of Photofrin-PDT has shown a prolongation of survival in patients with malignant gliomas.[59]

Optimizing photosensitizer uptake, elevating light dose, combined with interstitial chemotherapy and fluorescence-guided resection, might further improve the efficacy of intraoperative PDT.[60]

2.5. *Pulmonary and pleural mesothelial cancer*

Photodynamic therapy has been proposed for the treatment of bronchogenic carcinoma since the 1980s.[61] The worldwide data now show that bronchoscopic PDT appears to be effective as a curative therapy for superficial and early stage non-small cell lung cancer (NSCLC) and as a palliative therapy for obstructive cancers of the tracheobronchial tree.[62–64]

In addition to bronchoscopic Photofrin, Laserphyrin® (mono-L-aspartyl chlorin e6, NPe6 or talaporfin sodium) has also become a part of the standard PDT protocol for centrally located early-stage lung cancer in Japan.[65]

Photodynamic therapy can be used also to downstage obstructing endobronchial NSCLC and thereby enabling a complete resection.[66,67] PDT of symptomatic endobronchial metastatic tumors can effectively decrease the amount of endobronchial obstruction and improve quality of life.[68,69]

A new protocol using percutaneous insertion and intra-tumor illumination has been developed for the curative treatment of localized peripheral lung cancer (<1 cm) unsuitable for surgery or radiotherapy. Preliminary results have shown a partial response in majority of patients.[70]

Malignant pleural mesothelioma, often related to asbestos exposure, is an aggressive malignancy and responds poorly to conventional therapies. Intraoperative and transthoracic endoscopic PDT were proposed in the early 1990s.[71–73] Recently, Photofrin and Foscan PDT were tested as an adjuvant intraoperative modality in several countries. Clinical data demonstrate the safety and feasibility of intrapleural PDT which offers good survival results for stage I or II patients. However, for stage III or IV, PDT could not significantly prolong survival or improve local control.[74,75]

In recent years, the improvement in photosensitizers and PDT techniques has led to a renewed interest in intrapleural PDT as an adjunct to surgery. Refinements of PDT for mesothelioma will depend on a more detailed understanding of the pathways for preferential photosensitizer accumulation within the tumor as well as the synergistic effects between PDT and other modalities. Hyperoxygenation is an effective means to enhance PDT-induced cytotoxicity. Therefore, it is expected that it might further enhance the PDT efficacy to carry out the intrapleural PDT under hyperoxygenation conditions.[76,77]

2.6. *Breast cancer*

Locally recurrent breast carcinomas on the chest wall (i.e., cutaneous metastases) occur in 5%–20% of breast cancer patients after failure of salvage

surgery, radiation, and chemohormonal therapy. PDT has been proposed for the treatment of recurrent breast carcinoma since the 1970s.[5] Several reports suggest that Photofrin or Foscan PDT can offer 14%–73% CR and 14%–45% partial response (PR), but the duration of response can be variable (6 weeks–8 months).[78,79] It is expected that the photosensitizer acting at longer wavelengths could achieve deeper tissue penetration thereby greatly expanding the patient population for which this modality would become more acceptable and useful.[80] The intratumoral injection of photosensitizer has been proposed in order to minimize skin photosensitization — a main drawback of photodynamic therapy with systemic administration of photosensitizers.[81]

As breast cancer is diagnosed in over millions of patients a year globally, it is a significant health issue. Treatment paradigms have shifted to emphasize breast preservation protocols. PDT may play a role in the treatment of primary localized breast cancer to allow for greater breast conservation based in part on the emerging success of partial breast radiation.[82]

2.7. *Gastroenterological cancer*

Endoscopically accessible premalignant or malignant lesions located within the esophagus, the stomach, the bile duct or the colorectum with a high surgical risk are favorable targets of endoscopic PDT.[83–87] Photofrin-PDT has now been approved for obstructive esophageal cancer, early-stage esophageal cancer, and Barrett's esophagus with high-grade dysplasia in several countries. The usefulness of ALA-PDT for ablation of high-grade dysplasia in Barrett's esophagus is currently under investigation.[88]

A longer diffuser tip and the light centering balloon (e.g., Xcell PDT Balloon) are able to treat a long segment and large area of esophageal mucosa during a single treatment. It is suggested that optimizing light dose and re-treating small areas of residual or untreated Barrett's mucosamay reduce the post-PDT stricture formation and improve the overall efficacy.[89–91] However, some patients do not respond to PDT or progress to carcinoma despite PDT. To identify the role of biomarkers in predicting response to PDT might help the selection of appropriate therapy for patients and improve treatment outcomes.[92]

Cholangiocarcinoma is a rare tumor and even after seemingly curative resection, recurrence frequently occurs. Therefore, it continues to present formidable challenges in diagnosis and treatment. In recent clinical investigational studies of small numbers of patients with unresectable cholangiocarcinoma, PDT induced a decrease in bilirubin levels, improved quality of life for an extended period, and led to a slightly better survival. Endoscopic-guided illumination of the biliary tract is safe and effective for unresectable cholangiocarcinoma. Patients with unresectable cholangiocarcinoma without a visible mass may also benefit from an early treatment with PDT. Limited clinical data support that the combination of palliative PDT and subsequent stenting results in longer survival than stenting alone although these improvements in palliative treatment by PDT will unlikely change the concept of an aggressive resectional approach. For the time being, PDT is recommended for patients with nonresectable disease. The role of PDT before and after surgical resection merits to be assessed.[93–97]

In patients with malignant biliary obstruction associated with "ingrowth" and/or "overgrowth" of tumor mass over a metal stent, PDT can cause efficient tumor necrosis and recanalization of blocked stent. The PDT light dose might be adjusted to compensate for the reduction of trans-stent light transmittance caused by the stent materials during treatment.[98,99]

Due to advances in light applicators, the interstitial PDT is now becoming a practical option for solid lesions, including those in parenchymal organs such as the pancreas and liver.[100] The first pilot study of Foscan-PDT on inoperable pancreatic cancer was carried out in the United Kingdom. The percutaneous interstitial protocol, of multiple diffuser fiber illumination, could produce significant necrosis and prolong survival time. In most cases, the necrotic area of the treated tumor healed safely. There was no sign of a pseudocyst, abscess, or pancreatic duct leak.[101] These promising results encourage larger scale trials to further assess the feasibility of PDT and implementation of evolving techniques in the treatment of pancreatic cancer (e.g., vascular-targeted approach).

A pilot study of ultrasound-guided percutaneous interstitial PDT for the treatment of advanced liver cancer was reported by Chinese clinicians in 1996.[102] The study included 63 hepatocellular carcinomas, 2 cholangiocarcinoma, 1 hepatoblastoma, 1 tubular adenocarcinoma and 3 poorly differentiated adenocarcinoma. Fifty-six were newly diagnosed and the other 14 patients had either failed chemotherapy or post-resection recurrence.

Thirty-three patients had local or distance metastasis at the time of treatment. Tumor sizes ranged from 5 cm to 15 cm. Thirty patients received one-session treatments and 40 multisession treatments. At one-month post-PDT, the sonographic scan showed a slight signal enhancement in treated areas and tumor boundaries remained visible, and the size became smaller. CT scans confirmed tumor necrosis and a reduction of tumor mass. The histopathologic examination indicated a mix of necrosis, inflammation, and fibrosis in the treated areas. No damage was detected in the surrounding normal tissue. One patient underwent resection one-month post-PDT. Histopathologic examination showed larger areas of tumor necrosis. The preliminary results of this study suggested that PDT was effective and safe for the treatment of inoperable large primary and recurrent liver cancers. Multiple treatments could enhance both short-term and long-term survival.[103]

A recent multicenter trial of using talaporfin sodium and thin catheter-like array of LEDs in 27 patients with refractory liver metastases from colorectal cancer indicated that treatment-related adverse events were minimal and tumor response rate justified further evaluation in a larger trial.[104]

2.8. *Urological cancer*

The feasibility of PDT for ablation of superficial transitional cell carcinoma (TCC) of the bladder was among the first indications to be studied using HpD and white light in the early 1970s.[105] Photofrin obtained its first Canadian regulatory approval for recurrent papillary tumors in 1993. Intravenous Photofrin administration followed by intravesical illumination became an option for patients with refractory tumors. The initial response to a single treatment of the whole bladder tends to be good, but side effects such as bladder contraction and irritation are noticeable and the incidence of relapse within a year is high. Since the side effects are dose-dependent, fractionating drug and light doses in a sequential PDT mode might subside cancerous cells and meanwhile reduce local toxicity.

A long-term follow-up study (mean follow-up length of 52 months on 34 patients, more than half of them were refractory to traditional intravesical therapy) showed that refractory lesions can benefit from a single PDT session involving light irradiation through an intravesical diffusion medium. Although patients with extensive flat papillary lesions did not respond well, patients who achieve initial CR showed a longer time interval before needing cystectomy for progressive diseases.[106]

Bladder cancer tends to be a superficial condition; so a superficial treatment mediated with ALA or its ester derivatives may be a better option. Nonetheless, the intravesical instillation of ALA can eliminate cutaneous phototoxicity associated with systemic administration. Several clinical investigations show that ALA-PDT is an effective treatment option for patients with superficial bladder cancer who have failed transurethral resection and/or intravesical BCG immunotherapy. It has been shown that by repeating PDT treatments, it is possible to further inhibit the progression of bladder cancer.[107,108]

Hypericin (a substance extracted from *Hypericum perforatum*, commonly known as St. John's Wort) is also a potential PDT agent for the treatment of superficial TCC.[109]

Hexvix (hexaminolevulinate, hexyl ester of ALA, hexyl ALA, or HAL) is approved in Europe for photodynamic diagnosis (PDD) of early bladder cancer and visualization of flat lesions. PDD-guided transurethral resection has been reported to enhance tumor detection, reduce recurrences, and prolong tumor-free survival. Because of its superior pharmacokinetics and selectivity, this prodrug also has potentials for PDT of bladder cancers.[110]

Prostate cancer is still a significant health problem in the Western world. Recent clinical trials of Foscan-PDT and ALA-PDA on patients who had early cancer or failed radiotherapy showed a post-PDT decrease in prostate specific antigen (PSA) levels.[111–113] The preliminary results from two ongoing clinical trials of motexafin lutetium-PDT and Tookad-PDT designed to treat primary and recurrant lesions are also encouraging.[114,115]

The total ablation approach involves the implantation of multiple diffuser fibers into the prostate gland through a transperineal brachytherapy template. It should be fully recognized that characterization of light penetration and distribution in prostate is important due to the significant inter- and intra-prostatic differences in the tissue optical properties. Several recent studies suggest that a real-time drug/light dosimetry measurement and feedback system for monitoring drug concentrations and light fluences during interstitial PDT should be considered.[116,117] Protection of the pelvic nerve also becomes an inevitable challenge during

total ablation procedures since the light irradiation might reach the pelvic plexus.[118,119]

The epidemiologic and pathologic features of prostate cancer have given rise to an interest in focal treatment for localized primary cancer of a small size. Focal therapy might offer an effective alternative to a patient faced with a choice between aggressive local intervention (radiation or surgery) and watchful waiting. Pre-clinical studies demonstrate a clear correlation between lesion volume and drug/light dose in vascular-targeted PDT of canine prostate.[120] The potentials of vascular-targeted PDT in focal therapy of prostate cancer should be further explored.[121]

2.9. *Gynecological cancer*

Prior to and after its regulatory approval in Japan in 1994, Photofrin has been used successfully to treat carcinomas *in situ* and dysplasia of the uterine cervix. Several Japanese studies have shown that colposcopic-assisted cervical canal illumination after intravenous Photofrin administration can achieve a high CR ($< 94\%$) and preserve fertility.

A modified protocol that combined topical administration of photosensitizer and superficial illumination demonstrated that CR was light dose dependent for cervical intraepithelial neoplasia (CIN). Several *in vivo* studies demonstrate a selective absorption of ALA by dysplastic cervical cells. This leads to the presumption that ALA and its ester derivatives therefore represent a promising photosensitizing prodrug for the treatment of CIN.[123] However, several randomized, double-blind, placebo-controlled clinical trials showed that ALA-PDT was well tolerated by patients but the general consensus is that ALA-PDT has a minimal effect in the treatment of CIN 2 and CIN 3.[124]

Recent pilot studies of topical application of ALA or its ester derivatives or systemic administration of Foscan and superficial illumination for the treatment of vulvar and vaginal intraepithelial neoplasia (VIN, VAIN) showed that PDT was as effective as conventional treatments though not equally efficacious for all subgroups, but with shorter healing time and excellent cosmetic results. PDT is also an effective alternative in the treatment of penile intraepithelial neoplasia.[125–127]

Several case reports suggest that palliative PDT using systemic administration of photosensitizer might be considered for recurrences of ovary, vaginal, and vault cervix carcinomas.[128,130] PDT has also been employed to treat ovarian cancer and both benign and malignant lesions of the endometrium but no reliable clinical results have yet to been shown in the limited clinical trials.[129]

2.10. *Peritoneal carcinomatosis and sarcomatosis*

Peritoneal carcinomatosis and sarcomatosis are advanced diseases in which multiple tiny tumors develop in the abdominal cavity and linings. They are impossible to be completely removed by surgery and often recur after chemotherapy. The first attempts of using intraperitoneal PDT to treat disseminated peritoneal tumors were made in the late 1980s.[131] Previous U.S. trials of Photofrin-mediated intraperitoneal PDT established the maximally tolerated dose and showed encouraging efficacy although some patients developed a capillary-leak syndrome.[132–134]

Clinical data also indicate that peritoneal carcinomatosis and sarcomatosis may exhibit severe tumor hypoxia and intrapatient and interpatient variation of photosensitizer accumulation in tumors. Moreover, although some selectivity is found in Photofrin uptake between tumor and normal tissues of the peritoneal cavity, the absolute differences in drug accumulation between tumors and normal tissues (e.g., intestine) are small. This narrow differential in drug selectivity likely contributes to a narrow window in therapeutic application.[135]

3. PDT Applications for Treatment of Non-Malignant Diseases

3.1. *Dermatological disease*

Photodynamic inactivation of viruses was a hot topic in the 1970s.[136] Later, many attempts have been made to treat viral warts using topical PDT.[137,138] Recently, several Chinese groups also studied the feasibility of ALA-PDT for the treatment of genital warts (condylomata acuminate) associated with human papillomavirus (HPV) infection. Initial results showed a high CR rate and low recurrence rate.[139,140] A pharmacokinetic study of ALA-induced protoporphyrin IX (PpIX) in lesions of urethral condylomata acuminata demonstrates that PpIX is dominantly distributed in the HPV-infected epidermis.[141]

The importance of antibiotic resistance in dermatological practice is increasing. An alternative

approach may be to use PDT. One of the unlikely advantages of the broad spectra of antimicrobial PDT is the development of resistance to photodynamically induced direct killing.[142–145] Although the bactericidal effect of PDT against methicillin-resistant *Staphylococcus aureus* (MRSA) strains using different porphyrin has been demonstrated, somehow routine ALA-PDT does not affect the bacterial flora of the skin in a clinically significant manner.[146,147]

Leishmaniasis is a widespread arthropod-borne protozoan zoonosis caused by more than 21 *Leishmania* species. Old World cutaneous leishmaniasis is the result of leishmanial infection of dermal macrophages. Several clinical reports have shown promising results from ALA-PDT.[148,149] The clinical outcome observed with ALA-PDT is likely the result of unspecific tissue destruction accompanied by depopulation of macrophages rather than direct killing of parasites.[150]

The benefit of PDT for treatment of a number of inflammatory and immune disorders, such as acne vulgaris, folliculitis, psoriasis, cutaneous sarcoidosis, granuloma annulare, and morphoea, is currently under clinical investigation worldwide.[151–158]

Another potential application is the treatment of port-wine stain birthmarks (PWS), a capillary vascular malformation, with vascular-targeted PDT to induce selective injury of only the abnormal blood vessels in the dermis while sparing the normal overlying epidermis.[159] Several Chinese studies demonstrate that PDT is an effective and safe modality for treating various types of PWS.[102,160–162] A retrospective analysis of 1358 patients (6 months to 65 years old) treated with domestically made HpD at one hospital in Beijing, China between 1991 and 2003 showed that among 1949 lesions (pink = 110, purple = 1369, thicker or nodular lesion = 470), good-to-excellent responses (i.e., $> 75\%$ clearance) were achieved in 45% of patients. Interestingly, pink lesions show a better response than purple lesions. The latter often require multiple treatments.[163] A recent study compared clinical outcomes of PDT versus conventional pulsed dye laser (PDL) in Chinese patients. Results suggested that PDT was as effective as PDL for pink flat lesions and more effective than PDL for purple flat lesions. The true value of PDT deserves further investigation.[164]

There is an increased interest in skin photorejuvenation. Topical PDT might improve fine lines, tactile roughness, and skin tightness in patients with moderate photoaging.[165,166]

3.2. *Ophthalmic diseases*

Liposome-encapsulated BPD-MA (benzoporphyrin derivative monoacid ring A) under the generic name of Verteporfin or Visudyne® was synthesized in the mid-1980s with an intention for cancer treatment. However, it has been used primarily for ocular PDT. Several well-designed clinical studies in North America and Europe showed that neovascular forms of age-related macular degeneration (AMD) treated with Verteporfin PDT were more likely to experience stabilized vision than a control group. Therefore, Verteporfin-PDT, approved for AMD worldwide since 2000, should be considered as a first-line therapy in those difficult-to-manage conditions such as sub-foveal choroidal neovascularization (CNV) secondary to AMD, pathological myopia, or presumed ocular histoplasmosis syndrome.[167,168]

Besides those standard applications, there are many extended applications (e.g., CNV secondary to choroiditis and retinochoroiditis, angioid streaks, central serous chorioretinopathy, retinal angiomatous proliferation, parafoveal telangiectasia or CNV associated with macular dystrophy and idiopathic CNV, etc.) which have been summarized in recent reviews.[169,170]

Eyes with choroidal neovascularization condition often show the histopathologic evidence of inflammation and other immunological changes. Examination of CNV complexes has shown the presence of inflammatory cells. The inflammatory cells may play a role in neovascularization in the subretinal space. There is a body of clinical evidences suggesting that the intravitreal injection of steroids may have a beneficial effect on CNV patients.[171,172] Nonetheless, PDT-induced inflammatory reactions are two sides of the same coin. The acute inflammatory response might cause a transient visual disturbance and the proliferation of vessels might cause treatment failure.[173] Anti-inflammatory adjuvant therapy might have the potential to counteract some of these adverse effects.[174,175]

Several case studies have also demonstrated that Verteporfin-PDT could resolve the exudative retinal detachment associated with a diffuse choroidal haemangioma. An investigational study of circumscribed choroidal haemangioma showed evidence of tumor flattening, reducing sub-retinal fluid and choroidal vasculature.[176]

3.3. *Oral and dental disease*

The technical challenges of conventional therapeutic procedures extend from the continued struggle against two of the most common infectious diseases — dental caries and periodontal diseases — to eliminate life-threatening oral and pharyngeal malignancies and other conditions that compromise oral health and the quality of life. The implementation of PDT for the treatment of oral infection and malignancy faces similar or even greater challenges due to the need of delivering sufficient photosensitizer and light to a complex structure.[177]

It has been shown that PDT mediated with a topical application of phenothiazinium dyes is effective for killing bacteria in complex biofilms, such as sub-gingival plaque, which are typically resistant to the action of antibiotics. Several clinical trials indicate that in patients with chronic periodontitis, clinical outcomes of conventional sub-gingival debridement can be improved by adjunctive antimicrobial PDT.[178–180]

Systems using tolonium chloride (toluidine blue O, TBO) and low power 635 nm laser for the treatment of endodontics and caries are now available commercially under the trademark of PAD (photoactivated disinfection). Since 635 nm laser light transmits well across dentine, locally applied TBO can be used effectively in carious lesions. In dental caries, the use of PAD can eliminate residual bacteria in softened dentine and provide an environment which encourages rapid healing. This means that less tissue is removed and thus cavity repair is more conservative. In addition, endodontic PAD might lead to accelerated postoperative bone regrowth. Other possible clinical applications include disinfection of root canals, periodontal pockets, deep carious lesions and sites of peri-implantitis, and prevention of alveolar ostitis and post-extraction pain.[181]

Due to the highly colored nature of TBO and the potential for staining of teeth, lips, and buccal mucosa when used as a liquid mouthwash, a mucoadhesive patch containing TBO has been tested as a potential delivery system for use in oropharyngeal applications.[182]

3.4. *Cardiovascular disease*

Pre-clinical studies showed that motexafin lutetium could be taken up by atherosclerotic plaque and concentrated within macrophages and vascular smooth muscle cells. This led to several Phase I trials in the United States and Japan to develop endovascular photoangioplastic modality for cardiovascular diseases such as intimal hyperplasia, and atherosclerosis or vulnerable plaque, and prevention of restenosis after coronary-stent placement. Preliminary results suggested that PDT might be useful for the treatment of flow-limiting coronary atherosclerosis or vulnerable plaque while sparing normal surrounding vascular tissues.[183–187]

3.5. *Gastroenterological disease*

In 1997, a Japanese group reported that the PDT treatment of esophageal cancer could meanwhile eliminate esophageal varices coexisting with esophageal cancer.[188] This group further tested their hypothesis using rabbit auricular veins as model vessels. Their results suggested that vascular-targeted PDT delivered at a short drug-light interval (5 minutes) could induce marked thrombosis.[189]

Recently, a Chinese group conducted a small-scale pilot study and demonstrated that endoscopic PDT seemed to be effective in eliminating newly visible esophageal vessels and therefore preventing recurrent bleeding after endoscopic injection sclerotherapy.[190]

3.6. *Urological disease*

Benign prostatic hyperplasia (BPH) is a common condition for aging men. There has been a renewed interest in transurethral PDT in recent years and there are several ongoing preclinical and clinical studies to assess the feasibility of transurethral PDT for the management of BPH with lemuteporfin (also known as QLT0074) and talaporfin sodium. Vascular-targeted transurethral PDT shows minimal effects on the prostatical urethra. The potentials of vascular-targeted PDT in management of BPH should be further investigated.[119]

4. Extracorporeal PDT

Extracorporeal PDT, also known as extracorporeal photophoresis, is an *ex vivo* approach which involves a short incubation of the whole blood or blood products with a photosensitizer (e.g., Riboflavin®, TH9402) and *ex vivo* light irradiation at a shorter wavelength (e.g., 285 nm–514 nm). This process may or may not require a photosensitizer extrusion step before and after light

irradiation. Extracorporeal PDT has been used for the pathogen inactivation in blood transfusion and selective cell purging in graft-versus-host disease (GvHD) prevention.[191–193] Noticeably, cross-linking anti-Fas antibody combined with PDT could have an additive impact against the survival of $CD41^+CD81^+$ thymocytes through proapoptotic pathways.[194] The safety of extracorporeal PDT in the treatment of steroid refractory or intolerant GvHD is currently undergoing investigations.

5. Future Prospects

The number of scientific articles on PDT clinical applications as well as basic science steadily increases in English language and other language literatures. Review articles on past work, new aspects, and future applications have been published on a regular basis while new technology and promising applications continue to be discovered. The literature survey indicates there is still a strong and increasing interest and research effort focused on developing new photosensitizers,[195] exploring PDT mechanisms at molecular and tissue levels,[100,175,196] enhancing PDT efficacy with combined modality,[175,197] dosimetry,[100,198,199] and evaluating potential clinical indications. Some new strategies currently under development might break in some fundamental way from conventional conditions.[200]

One new strategy is the use of nanoparticles (NPs) in PDT. NPs themselves might be photodynamically active or serve as an "energy transducer" to absorb the light and transfer photon energy to a nearby photosensitizer molecule. Some NPs can also act as carriers for photosensitizer delivery.[201,202] The utility of the target-specific photosensitizers in developing multimodality agents (i.e., tumor-imaging, and therapy) represents another new strategy.[203] Two-photon excitation (TPE) has received increasing attention due to its potential application in high resolution two-photon fluorescent microscopy and imaging. There are several advantages when using femtosecond laser as a light source for two-photon PDT. TPE offers a high peak power with a comparatively low average power. Since the wavelength used for TPE is roughly twice that of one-photon excitation, the influence of tissue absorbing or scattering on the beam intensity can be greatly reduced, therefore two-photon PDT could minimize collateral damage to healthy tissue and deliver light energy more precisely to the target tissue or cell with a high degree of spatial specificity.[204]

Although regulatory approvals for the clinical use of PDT photosensitizers and light applicators now exist in many countries, the total number of approved clinical indications is still limited. There is still a need for involvement from pharmaceutical industries and research institutes to continue to launch clinical trials, and evaluate applications of PDT in conjunction with, or as a replacement for, conventional approaches. It is expected that combined modality and individualized treatment planning will become an essential component of clinical PDT in the near future.

Acknowledgments

This work is supported in part by a NIH grant CA43892. The content of this review does not necessarily reflect the position of NIH and the authors' institutes, and no official endorsement should be inferred. We thank Sue Huang for editorial assistance.

References

1. Huang, Z., "A review of progress in clinical photodynamic therapy," *Tech. Cancer Res. Treat.* **4**, 283–293 (2005).
2. Qiang, Y. G., Zhang, X. P., Li, J. and Huang, Z., "Photodynamic therapy for malignant and non-malignant diseases: Clinical investigation and application," *Chin. Med. J. (Engl.).* **119**, 845–857 (2006).
3. Veien, N. K., Genner, J., Brodthagen, H. and Wettermark, G., "Photodynamic inactivation of verrucae vulgares. II," *Acta Derm. Venereol.* **57**, 445–447 (1977).
4. Dougherty, T. J., Kaufman, J. E., Goldfarb, A., Weishaupt, K. R., Boyle, D. and Mittleman, A., "Photoradiation therapy for the treatment of malignant tumors," *Cancer Res.* **38**, 2628–2635 (1978).
5. Dougherty, T. J., Lawrence, G., Kaufman, J. H., Boyle, D., Weishaupt, K. R. and Goldfarb, A., "Photoradiation in the treatment of recurrent breast carcinoma," *J. Natl. Cancer Inst.* **62**, 231–237 (1979).
6. Oseroff, A. R., Blumenson, L. R., Wilson, B. D., Mang, T. S., Bellnier, D. A., Parsons, J. C., Frawley, N., Cooper, M., Zeitouni, N. and Dougherty, T. J., "A dose ranging study of photodynamic therapy with porfimer sodium (Photofrin) for treatment of basal cell carcinoma," *Lasers Surg. Med.* **38**, 417–426 (2006).

7. Kennedy, J. C., Pottier, R. H. and Pross, D. C., "Photodynamic therapy with endogenous protoporphyrin IX: Basic principles and present clinical experience," *J. Photochem. Photobiol. B.* **6**, 143–148 (1990).
8. Tschen, E. H., Wong, D. S., Pariser, D. M., Dunlap, F. E., Houlihan, A., Ferdon, M. B. and Phase IV ALA-PDT Actinic Keratosis Study Group, "Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: Phase IV multicentre clinical trial with 12-month follow up," *Br. J. Dermatol.* **155**, 1262–1269 (2006).
9. Stables, G. I., Stringer, M. R., Robinson, D. J. and Ash, D. V., "Large patches of Bowen's disease treated by topical aminolaevulinic acid photodynamic therapy," *Br. J. Dermatol.* **136**, 957–960 (1997).
10. Wang, X. L., Xu, S. Z., Zhang, C. R. and Zheng, W., "Photodynamic therapy of Bowen's disease using 5-aminolevulinic acid," *Chin. J. Med. Surg.* **8**, 9–11 (1999) (in Chinese)
11. Wang, X. L., Wang, H. W., Guo, M. X. and Xu, S. Z., "Treatment of skin cancer and pre-cancer using topical ALA-PDT — A single hospital experience," *Photodiag. Photodyn. Ther.* **5**, 127–133 (2008).
12. Braathen, L. R., Szeimies, R. M., Basset-Seguin, N., Bissonnette, R., Foley, P., Pariser, D., Roelandts, R., Wennberg, A. M. and Morton, C. A., "International Society for Photodynamic Therapy in Dermatology, Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. International Society for Photodynamic Therapy in Dermatology, 2005," *J. Am. Acad. Dermatol.* **56**, 125–143 (2007).
13. Moloney, F. J. and Collins, P., "Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis," *Br. J. Dermatol.* **157**, 87–91 (2007).
14. Schleier, P., Berndt, A., Kolossa, S., Zenk, W., Hyckel, P. and Schultze-Mosgau, S., "Comparison of aminolevulinic acid (ALA)-thermogel-PDT with methyl-ALA-thermogel-PDT in basal cell carcinoma," *Photodiag. Photodyn. Ther.* **4**, 197–201 (2007).
15. Kaufmann, R., Spelman, L., Weightman, W., Reifenberger, J., Szeimies, R. M., Verhaeghe, E., Kerrouche, N., Sorba, V., Villemagne, H. and Rhodes, L. E., "Multicentre intraindividual randomized trial of topical methyl aminolaevulinate-photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities," *Br. J. Dermatol.* **158**, 994–999 (2008).
16. Tierney, E. P., Eide, M. J., Jacobsen, G. and Ozog, D., "Photodynamic therapy for actinic keratoses: Survey of patient perceptions of treatment satisfaction and outcomes," *J. Cosmet. Laser Ther.* **10**, 81–86 (2008).
17. Sotiriou, E., Apalla, Z., Koussidou-Erremonti, T. and Ioannides, D., "Actinic cheilitis treated with one cycle of 5-aminolaevulinic acid-based photodynamic therapy: Report of 10 cases," *Br. J. Dermatol.* **159**, 261–262 (2008).
18. Babilas, P., Knobler, R., Hummel, S., Gottschaller, C., Maisch, T., Koller, M., Landthaler, M. and Szeimies, R. M., "Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: A prospective randomized controlled trial," *Br. J. Dermatol.* **157**, 111–117 (2007).
19. Rhodes, L. E., de Rie, M. A., Leifsdottir, R., Yu, R. C., Bachmann, I., Goulden, V., Wong, G. A., Richard, M. A., Anstey, A. and Wolf, P., "Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs. surgery for nodular basal cell carcinoma," *Arch. Dermatol.* **143**, 1131–1136 (2007).
20. Souza, C. S., Neves, A. B., Felício, L. A., Ferreira, J., Kurachi, C. and Bagnato, V. S., "Optimized photodynamic therapy with systemic photosensitizer following debulking technique for nonmelanoma skin cancers," *Dermatol. Surg.* **33**, 194–198 (2007).
21. Mosterd, K., Thissen, M. R., Nelemans, P., Kelleners-Smeets, N. W., Janssen, R. L., Broekhof, K. G., Neumann, H. A., Steijlen, P. M. and Kuijpers, D. I., "Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial," *Br. J. Dermatol.* **159**, 864–870 (2008).
22. Piaserico, S., Belloni Fortina, A., Rigotti, P., Rossi, B., Baldan, N., Alaibac, M. and Marchini, F., "Topical photodynamic therapy of actinic keratosis in renal transplant recipients," *Transplant. Proc.* **39**, 1847–1850 (2007).
23. Perrett, C. M., McGregor, J. M., Warwick, J., Karran, P., Leigh, I. M., Proby, C. M. and Harwood, C. A., "Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy," *Br. J. Dermatol.* **156**, 320–328 (2007).
24. Leman, J. A., Dick, D. C. and Morton, C. A., "Topical 5-ALA photodynamic therapy for the treatment of cutaneous T-cell lymphoma," *Clin. Exp. Dermatol.* **27**, 516–518 (2002).
25. Edström, D. W. and Hedblad, M. A., "Long-term follow-up of photodynamic therapy for mycosis fungoides," *Acta. Derm. Venereol.* **88**, 288–290 (2008).

26. Nikkels, A. F., Thirion, L., Quatresooz, P. and Piérard, G. E., "Photodynamic therapy for cutaneous verrucous carcinoma," *J. Am. Acad. Dermatol.* **57**, 516–519 (2007).
27. Raspagliesi, F., Fontanelli, R., Rossi, G., Ditto, A., Solima, E., Hanozet, F. and Kusamura, S., "Photodynamic therapy using a methyl ester of 5-aminolevulinic acid in recurrent Paget's disease of the vulva: A pilot study," *Gynecol. Oncol.* **103**, 581–586 (2006).
28. Calzavara-Pinton, P. G., Szeimies, R. M., Ortel, B. and Zane, C., "Photodynamic therapy with systemic administration of photosensitizers in dermatology," *J. Photochem. Photobiol. B: Biol.* **36**, 225–231 (1996).
29. Kacerovská, D., Pizinger, K., Majer, F. and Smíd, F., "Photodynamic therapy of nonmelanoma skin cancer with topical hypericum perforatum extract — a pilot study," *Photochem. Photobiol.* **84**, 779–785 (2008).
30. Betz, C. S., Rauschning, W., Stranadko, E. P., Riabov, M. V., Albrecht, V., Nifantiev, N. E. and Hopper, C., "Optimization of treatment parameters for Foscan-PDT of basal cell carcinomas," *Lasers Surg. Med.* **40**, 300–311 (2008).
31. Taub, A. F., "Photodynamic therapy: Other uses," *Dermatol. Clin.* **25**, 101–109 (2007).
32. Murphree, A. L., Cote, M. and Gomer, C. J., "The evolution of photodynamic therapy techniques in the treatment of intraocular tumors," *Photochem. Photobiol.* **46**, 919–923 (1987).
33. Battaglia Parodi, M., Da Pozzo, S., Toto, L., Saviano, S. and Ravalico, G., "Photodynamic therapy for choroidal neovascularization associated with choroidal osteoma," *Retina* **21**, 660–661 (2001).
34. Blaise, P., Duchateau, E., Comhaire, Y. and Rakic, J. M., "Improvement of visual acuity after photodynamic therapy for choroidal neovascularization in choroidal osteoma," *Acta Ophthalmol. Scand.* **83**, 515–516 (2005).
35. Shields, C. L., Materin, M. A., Mehta, S., Foxman, B. T. and Shields, J. A., "Regression of extrafoveal choroidal osteoma following photodynamic therapy," *Arch. Ophthalmol.* **126**, 135–137 (2008).
36. Harbour, J. W., "Photodynamic therapy for choroidal metastasis from carcinoid tumor," *Am. J. Ophthalmol.* **137**, 1143–1145 (2004).
37. Mauget-Faÿsse, M., Gambrelle, J., Quaranta-El Maftouhi, M. and Moullet, I., "Photodynamic therapy for choroidal metastasis from lung adenocarcinoma," *Acta Ophthalmol. Scand.* **84**, 552–554 (2006).
38. Isola, V., Pece, A. and Pierro, L., "Photodynamic therapy with verteporfin of choroidal malignancy from breast cancer," *Am. J. Ophthalmol.* **142**, 885–887 (2006).
39. Schuller, D. E., McCaughan Jr, J. S. and Rock, R. P., "Photodynamic therapy in head and neck cancer," *Arch. Otolaryngol.* **111**, 351–355 (1985).
40. Zhao, S. P., Tao, Z. D., Xiao, J. Y., Peng, Y. Y., Yang, Y. H., Zeng, Q. S. and Liu, Z. W., "Photoradiation therapy of animal tumors and nasopharyngeal carcinoma," *Ann. Otol. Rhinol. Laryngol.* **99**, 454–460 (1990).
41. Copper, M. P., Triesscheijn, M., Tan, I. B., Ruevekamp, M. C. and Stewart, F. A., "Photodynamic therapy in the treatment of multiple primary tumours in the head and neck, located to the oral cavity and oropharynx," *Clin. Otolaryngol.* **32**, 185–189 (2007).
42. Chen, H. M., Yu, C. H., Tsai, T. M., Hsu, Y. C., Kuo, R. C. and Chiang, C. P., "Topical 5- aminolevulinic acid-mediated photodynamic therapy for oral verrucous hyperplasia, oral leukoplakia and oral erythroleukoplakia," *Photodiag. Photodyn. Ther.* **4**, 44–52 (2007).
43. Biel, M. A., "Photodynamic therapy and the treatment of head and neck neoplasia," *Laryngoscope* **108**, 1259–1268 (1998).
44. Li, L. B., Luo, R. C., Liao, W. J., Zhang, M. J., Luo, Y. L. and Miao, J. X., "Clinical study of Photofrin photodynamic therapy for the treatment of relapse nasopharyngeal carcinoma," *Photodiag. Photodyn. Ther.* **3**, 266–271 (2006).
45. Biel, M. A., "Photodynamic therapy treatment of early oral and laryngeal cancers," *Photochem. Photobiol.* **83**, 1063–1068 (2007).
46. Biel, M., "Advances in photodynamic therapy for the treatment of head and neck cancers," *Lasers Surg. Med.* **38**, 349–355 (2006).
47. Copper, M. P., Tan, I. B., Oppelaar, H., Ruevekamp, M. C. and Stewart, F. A., "Metatetra(hydroxyphenyl) chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck," *Arch. Otolaryngol. Head Neck Surg.* **129**, 709–711 (2003).
48. Hopper, C., Kubler, A., Lewis, H., Tan, I., B., Putnam, G. and the Foscan 01 Study Group, "mTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma," *Int. J. Cancer.* **111**, 138–146 (2004).
49. D'Cruz, A. K., Robinson, M. H. and Biel, M. A., "mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: A multicenter study of 128 patients," *Head Neck.* **26**, 232–240 (2004).
50. Diamond, I., Granelli, S. G., McDonagh, A. F., Nielsen, S., Wilson, C. B. and Jaenicke, R., "Photodynamic therapy of malignant tumours," *Lancet* **2**, 1175–1177 (1972).

51. Perria, C., Capuzzo, T., Cavagnaro, G., Datti, R., Francaviglia, N., Rivano, C. and Tercero, V. E., "Fast attempts at the photodynamic treatment of human gliomas," *J. Neurosurg. Sci.* **24**, 119–129 (1980).
52. Laws Jr, E. R., Cortese, D. A., Kinsey, J. H., Eagan, R. T. and Anderson, R. E., "Photoradiation therapy in the treatment of malignant brain tumors: A phase I (feasibility) study," *Neurosurgery* **9**, 672–678 (1981).
53. Kostron, H., Plangger, C., Fritsch, E. and Maier, H., "Photodynamic treatment of malignant brain tumors," *Wien Klin. Wochenschr.* **102**, 531–535 (1990).
54. Muller, P. J. and Wilson, B. C., "Photodynamic therapy for recurrent supratentorial gliomas," *Semin. Surg. Oncol.* **11**, 346–354 (1995).
55. Schmidt, M. H., Bajic, D. M., Reichert II, K. W., Martin, T. S., Meyer, G. A. and Whelan, H. T., "Light-emitting diodes as a light source for intraoperative photodynamic therapy," *Neurosurgery* **38**, 552–556 (1996).
56. Zimmermann, A., Ritsch-Marte, M. and Kostron, H., "mTHPC-mediated photodynamic diagnosis of malignant brain tumors," *Photochem. Photobiol.* **74**, 611–616 (2001).
57. Muller, P. J. and Wilson, B. C., "Photodynamic therapy of brain tumors — a work in progress," *Lasers Surg. Med.* **38**, 384–389 (2006).
58. Beck, T. J., Kreth, F. W., Beyer, W., Mehrkens, J. H., Obermeier, A., Stepp, H., Stummer, W. and Baumgartner, R., "Interstitial photodynamic therapy of nonresectable malignant glioma recurrences using 5-aminolevulinic acid induced protoporphyrin IX," *Lasers Surg. Med.* **39**, 386–393 (2007).
59. Stylli, S. S., Kaye, A. H., Macgregor, L., Howes, M. and Rajendra, P., "Photodynamic therapy of high-grade glioma — long term survival," *J. Clin. Neurosci.* **12**, 389–398 (2005).
60. Moseley, H., Mclean, C., Hockaday, S. and Eljamel, S., "In vitro light distributions from intracranial PDT balloons," *Photodiag. Photodyn. Ther.* **4**, 213–220 (2007).
61. Dougherty, T. J., "Photoradiation therapy for bronchogenic cancer," *Chest.* **81**, 265–266 (1982).
62. Usuda, J., Kato, H., Okunaka, T., Furukawa, K., Tsutsui, H., Yamada, K., Suga, Y., Honda, H., Nagatsuka, Y., Ohira, T., Tsuboi, M. and Hirano, T., "Photodynamic therapy (PDT) for lung cancers," *J. Thorac. Oncol.* **1**, 489–493 (2006).
63. Corti, L., Toniolo, L., Boso, C., Colaut, F., Fiore, D., Muzzio, P. C., Koukourakis, M. I., Mazzarotto, R., Pignataro, M., Loreggian, L. and Sotti, G., "Long-term survival of patients treated with photodynamic therapy for carcinoma *in situ* and early non-small-cell lung carcinoma," *Lasers Surg. Med.* **39**, 394–402 (2007).
64. Moghissi, K. and Dixon, K., "Update on the current indications, practice and results of photodynamic therapy (PDT) in early central lung cancer (ECLC)," *Photodiag. Photodyn. Ther.* **5**, 10–18 (2008).
65. Usuda, J., Tsutsui, H., Honda, H., Ichinose, S., Ishizumi, T., Hirata, T., Inoue, T., Ohtani, K., Maehara, S., Imai, K., Tsunoda, Y., Kubota, M., Ikeda, N., Furukawa, K., Okunaka, T. and Kato, H., "Photodynamic therapy for lung cancers based on novel photodynamic diagnosis using talaporfin sodium (NPe6) and autofluorescence bronchoscopy," *Lung Cancer* **58**, 317–323 (2007).
66. Kato, H., Konaka, C., Ono, J., Kawate, N., Nishimiya, K., Shinohara, H., Saito, M., Sakai, H., Noguchi, M. and Kito, T., "Preoperative laser photodynamic therapy in combination with operation in lung cancer," *J. Thorac. Cardiovasc. Surg.* **90**, 420–429 (1985).
67. Mortman, K. D. and Frankel, K. M., "Pulmonary resection after successful downstaging with photodynamic therapy," *Ann. Thorac. Surg.* **82**, 722–724 (2006).
68. Litle, V. R., Christie, N. A., Fernando, H. C., Buenaventura, P. O., Ferson, P. F. and Luketich, J. D., "Photodynamic therapy for endobronchial metastases from nonbronchogenic primaries," *Ann. Thorac. Surg.* **76**, 370–375 (2003).
69. Magro, C. M., Abbas, A. E. and Ross Jr, P., "The application of photodynamic therapy in the treatment of metastatic endobronchial disease," *Lasers Surg. Med.* **38**, 376–383 (2006).
70. Okunaka, T., Kato, H., Tsutsui, H., Ishizumi, T., Ichinose, S. and Kuroiwa, Y., "Photodynamic therapy for peripheral lung cancer," *Lung Cancer* **43**, 77–82 (2004).
71. Pass, H. I., Tochner, Z., DeLaney, T., Smith, P., Friauf, W., Glatstein, E. and Travis, W., "Intraoperative photodynamic therapy for malignant mesothelioma," *Ann. Thorac. Surg.* **50**, 687–688 (1990).
72. Lofgren, L., Larsson, M., Thaning, L. and Hallgren, S., "Transthoracic endoscopic photodynamic treatment of malignant mesothelioma," *Lancet* **337**, 359 (1991).
73. Ris, H. B., Altermatt, H. J., Inderbitzi, R., Hess, R., Nachbur, B., Stewart, J. C., Wang, Q., Lim, C. K., Bonnett, R. and Berenbaum, M. C., "Photodynamic therapy with chlorins for diffuse malignant mesothelioma: Initial clinical results," *Br. J. Cancer* **64**, 1116–1120 (1991).
74. Hahn, S. M., Smith, R. P. and Friedberg, J., "Photodynamic therapy for mesothelioma," *Curr. Treat. Options Oncol.* **2**, 375–383 (2001).

75. Friedberg, J. S., Mick, R., Stevenson, J., Metz, J., Zhu, T., Buyske, J., Sterman, D. H., Pass, H. I., Glatstein, E. and Hahn, S. M., "A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma," *Ann. Thorac. Surg.* **75**, 952–959 (2003).
76. Huang, Z., Chen, Q., Shakil, A., Chen, H., Beckers, J., Shapiro, H. and Hetzel, F. W., "Hyperoxygenation enhances the tumor cell killing of Photofrin-mediated photodynamic therapy," *Photochem. Photobiol.* **78**, 496–502 (2003).
77. Matzi, V., Maier, A., Sankin, O., Lindenmann, J., Woltsche, M., Smolle, J. and F. Smolle-Jüttner, "Photodynamic therapy enhanced by hyperbaric oxygenation in palliation of malignant pleural mesothelioma: Clinical experience," *Photodiag. Photodyn. Ther.* **1**, 57–64 (2004).
78. Sperduto, P. W., DeLaney, T. F., Thomas, G., Smith, P., Dachowski, L. J., Russo, A., Bonner, R. and Glatstein, E., "Photodynamic therapy for chest wall recurrence in breast cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **21**, 441–446 (1991).
79. Wyss, P., Schwarz, V., Dobler-Girdziunaite, D., Hornung, R., Walt, H., Degen, A. and Fehr, M., "Photodynamic therapy of locoregional breast cancer recurrences using a chlorin-type photosensitizer," *Int. J. Cancer* **93**, 720–724 (2001).
80. Cuenca, R. E., Allison, R. R., Sibata, C. and Downie, G. H., "Breast cancer with chest wall progression: Treatment with photodynamic therapy," *Ann. Surg. Oncol.* **11**, 322–327 (2004).
81. D'Hallewin, M. A., Kochetkov, D., Viry-Babel, Y., Leroux, A., Werkmeister, E., Dumas, D., Gräfe, S., Zorin, V., Guillemin, F. and Bezdetnaya, L., "Photodynamic therapy with intratumoral administration of Lipid-Based mTHPC in a model of breast cancer recurrence," *Lasers Surg. Med.* **40**, 543–549 (2008).
82. Allison, R. R., Sibata, C., Downie, G. H. and Cuenca, R. E., "Photodynamic therapy of the intact breast," *Photodiag. Photodyn. Ther.* **3**, 139–146 (2006).
83. Hayata, Y., Kato, H., Okitsu, H., Kawaguchi, M. and Konaka, C., "Photodynamic therapy with hematoporphyrin derivative in cancer of the upper gastrointestinal tract," *Semin. Surg. Oncol.* **1**, 1–11 (1985).
84. McCaughan Jr, J. S., "Overview of experiences with photodynamic therapy for malignancy in 192 patients," *Photochem. Photobiol.* **46**, 903–909 (1987).
85. Barr, H., Krasner, N., Boulos, P. B., Chatlani, P. and Bown, S. G., "Photodynamic therapy for colorectal cancer: A quantitative pilot study," *Br. J. Surg.* **77**, 93–96 (1990).
86. Jin, M. L., Yang, B. Q., Zhang, W. and Ren, P., "Review of photodynamic therapy for gastrointestinal tumours in the past 6 years in China," *J. Photochem. Photobiol. B: Biol.* **7**, 87–92 (1990).
87. Patrice, T., Foultier, M. T., Yactayo, S., Adam, F., Galmiche, J. P., Douet, M. C. and Le Bodic, L., "Endoscopic photodynamic therapy with hematoporphyrin derivative for primary treatment of gastrointestinal neoplasms in inoperable patients," *Dig. Dis. Sci.* **35**, 545–552 (1990).
88. Mackenzie, G. D., Jamieson, N. F., Novelli, M. R., Mosse, C. A., Clark, B. R., Thorpe, S. M., Bown, S. G. and Lovat, L. B., "How light dosimetry influences the efficacy of photodynamic therapy with 5-aminolaevulinic acid for ablation of high-grade dysplasia in Barrett's esophagus," *Lasers Med. Sci.* **23**, 203–210 (2008).
89. Panjehpour, M., Overholt, B. F., Phan, M. N. and Haydek, J. M., "Optimization of light dosimetry for photodynamic therapy of Barrett's esophagus: Efficacy vs. incidence of stricture after treatment," *Gastrointest. Endosc.* **61**, 13–18 (2005).
90. Prasad, G. A., Wang, K. K., Buttar, N. S., Wongkeesong, L. M., Lutzke, L. S. and Borkenhagen, L. S., "Predictors of stricture formation after photodynamic therapy for high-grade dysplasia in Barrett's esophagus," *Gastrointest. Endosc.* **65**, 60–66 (2007).
91. Yachimski, P., Puricelli, W. P. and Nishioka, N. S., "Patient predictors of esophageal stricture development after photodynamic therapy," *Clin. Gastroenterol. Hepatol.* **6**, 302–308 (2008).
92. Prasad, G. A., Wang, K. K., Halling, K. C., Buttar, N. S., Wongkeesong, L. M., Zinsmeister, A. R., Brankley, S. M., Fritcher, E. G., Westra, W. M., Krishnadath, K. K., Lutzke, L. S. and Borkenhagen, L. S., "Utility of biomarkers in prediction of response to ablative therapy in Barrett's esophagus," *Gastroenterology* **135**, 370–379 (2008).
93. Ortner, M. A., "Photodynamic therapy in cholangiocarcinoma: An overview," *Photodiag. Photodyn. Ther.* **1**, 85–92 (2004).
94. Prasad, G. A., Wang, K. K., Baron, T. H., Buttar, N. S., Wongkeesong, L. M., Roberts, L. R., LeRoy, A. J., Lutzke, L. S. and Borkenhagen, L. S., "Factors associated with increased survival after photodynamic therapy for cholangiocarcinoma," *Clin. Gastroenterol. Hepatol.* **5**, 743–748 (2007).
95. Kahaleh, M., Mishra, R., Shami, V. M., Northup, P. G., Berg, C. L., Bashlor, P., Jones, P., Ellen, K., Weiss, G. R., Brenin, C. M., Kurth, B. E., Rich, T. A., Adams, R. B. and Yeaton, P., "Unresectable cholangiocarcinoma: Comparison of survival in biliary stenting alone versus stenting with photodynamic therapy," *Clin. Gastroenterol. Hepatol.* **6**, 290–297 (2008).

96. Saito, H., Takada, T., Miyazaki, M., Miyakawa, S., Tsukada, K., Nagino, M., Kondo, S., Furuse, J., Tsuyuguchi, T., Kimura, F., Yoshitomi, H., Nozawa, S., Yoshida, M., Wada, K., Amano, H., Miura, F., Japanese Association of Biliary Surgery, Japanese Society of Hepato- Biliary-Pancreatic Surgery and Japan Society of Clinical Oncology, "Radiation therapy and photodynamic therapy for biliary tract and ampullary carcinomas," *J. Hepatobiliary Pancreat. Surg.* **15**, 63–68 (2008).
97. Witzigmann, H., Berr, F., Ringel, U., Caca, K., Uhlmann, D., Schoppmeyer, K., Tannapfel, A., Wittekind, C., Mossner, J., Hauss, J. and Wiedmann, M., "Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: Palliative photodynamic therapy plus stenting is comparable to r1/r2 resection," *Ann. Surg.* **244**, 230–239 (2006).
98. Pereira, S. P., Ayaru, L., Rogowska, A., Mosse, A., Hatfield, A. R. and Bown, S. G., "Photodynamic therapy of malignant biliary structures using mesotetrahydroxyphenylchlorin," *Eur. J. Gastroenterol. Hepatol.* **19**, 479–485 (2007).
99. Wang, L. W., Li, L. B., Li, Z. S., Chen, Y. K., Hetzel, F. W. and Huang, Z., "Self-expandable metal stents and trans-stent light delivery: Are stents and PDT compatible?" *Lasers Surg. Med.* **40**, 651–659 (2008).
100. Huang, Z., Xu, H., Meyers, A. D., Musani, A. I., Wang, L., Tagg, R., Barqawi, A. B. and Chen, Y. K., "Photodynamic therapy for treatment of solid tumors — potential and technical challenges," *Tech. Cancer Res. Treat.* **7**, 309–320 (2008).
101. Bown, S. G., Rogowska, A. Z., Whitelaw, D. E., Lees, W. R., Lovat, L. B., Ripley, P., Jones, L., Wyld, P., Gillams, A. and Hatfield, A. W., "Photodynamic therapy for cancer of the pancreas," *Gut.* **50**, 549–557 (2002).
102. Huang, Z., "Photodynamic therapy in China: over 25 years of unique clinical experience: part two — Clinical experience," *Photodiag. Photodyn. Ther.* **3**, 71–84 (2006).
103. Zeng, C. Y., Yang, D., Huang, P., Zhang, J. H., Chen, J. and Lu, G. R., "Long-term follow-up results of 70 Liver cancer cases received ultrasound guided percutaneous PDT," *Chin. J. Laser Med. Surg.* **9**, 146–149 (2000) (in Chinese)
104. Kujundzić, M., Vogl, T. J., Stimac, D., Rustemović, N., Hsi, R. A., Roh, M., Katicić, M., Cuenca, R., Lustig, R. A. and Wang, S., "A phase II safety and effect on time to tumor progression study of intratumoral light infusion technology using talaporfin sodium in patients with metastatic colorectal cancer," *J. Surg. Oncol.* **96**, 518–524 (2007).
105. Kelly, J. F., Snell, M. E. and Berenbaum, M. C., "Photodynamic destruction of human bladder carcinoma," *Br. J. Cancer* **31**, 237–244 (1975).
106. Manyak, M. J. and Ogan, K., "Photodynamic therapy for refractory superficial bladder cancer: Long-term clinical outcomes of single treatment using intravesical diffusion medium," *J. Endourol.* **17**, 633–639 (2003).
107. Waidelich, R., Stepp, H., Baumgartner, R., Weninger, E., Hofstetter, A. and Kriegmair, M., "Clinical experience with 5-aminolevulinic acid and photodynamic therapy for refractory superficial bladder cancer," *J. Urol.* **165**, 1904–1907 (2001).
108. Berger, A. P., Steiner, H., Stenzl, A., Akkad, T., Bartsch, G. and Holtl, L., "Photodynamic therapy with intravesical instillation of 5-aminolevulinic acid for patients with recurrent superficial bladder cancer: A single-center study," *Urology* **61**, 338–341 (2003).
109. Kamuhabwa, A., Agostinis, P., Ahmed, B., Landuyt, W., van Cleynenbreugel, B., van Poppel, H. and de Witte, P., "Hypericin as a potential phototherapeutic agent in superficial transitional cell carcinoma of the bladder," *Photochem. Photobiol. Sci.* **3**, 772–780 (2004).
110. Marti, A., Jichlinski, P., Lange, N., Ballini, J. P., Guillou, L., Leisinger, H. J. and Kucera, P., "Comparison of aminolevulinic acid and hexylester aminolevulinate induced protoporphyrin IX distribution in human bladder cancer," *J. Urol.* **170**, 428–432 (2003).
111. Nathan, T. R., Whitelaw, D. E., Chang, S. C., Lees, W. R., Ripley, P. M., Payne, H., Jones, L., Parkinson, M. C., Emberton, M., Gillams, A. R., Mundy, A. R. and Bown, S. G., "Photodynamic therapy for prostate cancer recurrence after radiotherapy: A phase I study," *J. Urol.* **168**, 1427–1432 (2002).
112. Zaak, D., Sroka, R., Höppner, M., Khoder, W., Reich, O., Tritschler, St., Muschter, R., Knüchel, R. and Hofstetter, A., "Photodynamic therapy by means of 5-ALA induced PPIX in human prostate cancer — preliminary results," *Med. Laser Appl.* **18**, 91–95 (2003).
113. Moore, C. M., Nathan, T. R., Lees, W. R., Mosse, C. A., Freeman, A., Emberton, M. and Bown, S. G., "Photodynamic therapy using meso tetra hydroxy phenyl chlorin (mTHPC) in early prostate cancer," *Laser Surg. Med.* **38**, 356–363 (2006).
114. Du, K. L., Mick, R., Busch, T. M., Zhu, T. C., Finlay, J. C., Yu, G., Yodh, A. G., Malkowicz, S. B., Smith, D., Whittington, R., Stripp, D. and Hahn, S. M., "Preliminary results of interstitial motexafin lutetium-mediated PDT for prostate cancer," *Laser Surg. Med.* **38**, 427–434 (2006).
115. Trachtenberg, J., Bogaards, A., Weersink, R. A., Haider, M. A., Evans, A., McCluskey, S. A.,

Scherz, A., Gertner, M. R., Yue, C., Appu, S., Aprikian, A., Savard, J., Wilson, B. C. and Elhilali, M., "Vascular targeted photodynamic therapy with palladium-bacteriopheophorbide photosensitizer for recurrent prostate cancer following definitive radiation therapy: Assessment of safety and treatment response," *J. Urol.* **178**, 1974–1979 (2007).

116. Weersink, R. A., Bogaards, A., Gertner, M., Davidson, S. R. H., Zhang, K., Netchev, G., Trachtenberg, J. and Wilson, B. C., "Techniques for delivery and monitoring of TOOKAD (WST09)-mediated photodynamic therapy of the prostate: Clinical experience and practicalities," *J. Photochem. Photobiol. B. Biol.* **79**, 211–222 (2005).
117. Zhu, T. C. and Finlay, J. C., "Prostate PDT dosimetry," *Photodiag. Photodyn. Ther.* **3**, 234–246 (2006).
118. Dole, K. C., Chen, Q., Hetzel, F. W., Whalen, L. R., Blanc, D. and Huang, Z., "Effects of photodynamic therapy on peripheral nerve: *in situ* compound-action potentials study in a canine model," *Photomed. Laser Surg.* **23**, 172–176 (2005).
119. Huang, Z., Chen, Q., Dole, K. C., Barqawi, A. B., Chen, Y. K., Blanc, D., Wilson, B. C. and Hetzel, F. W., "The effect of Tookad-mediated photodynamic ablation of the prostate gland on adjacent tissues — *in vivo* study in a canine model," *Photochem. Photobiol. Sci.* **6**, 1318–1324 (2007).
120. Huang, Z., Chen, Q., Luck, D., Beckers, J., Wilson, B. C., Trncic, N., LaRue, S. M., Blanc, D. and Hetzel, F. W., "Studies of a vascular-acting photosensitizer, Pdbacteriopheophorbide (Tookad), in normal canine prostate and spontaneous canine prostate cancer," *Laser Surg. Med.* **36**, 390–397 (2005).
121. Eggener, S. E. and Coleman, J. A., "Focal treatment of prostate cancer with vasculartargeted photodynamic therapy," *Scientific World J.* **3**, 963–973 (2008).
122. Muroya, T., Suehiro, Y., Umayahara, K., Akiya, T., Iwabuchi, H., Sakunaga, H., Sakamoto, M., Sugishita, T. and Tenjin, Y., "Photodynamic therapy (PDT) for early cervical cancer," *Cancer Chemother. [Gan To Kagaku Ryoho]* **23**, 47–56 (1996) (in Japanese).
123. Allison, R. R., Cuenca, R., Downie, G. H., Randall, M., Bagnato, V. and Sibata, C., "PD/PDT for gynecological disease: A clinical review," *Photodiag. Photodyn. Ther.* **2**, 51–63 (2005).
124. Barnett, A. A., Haller, J. C., Cairnduff, F., Lane, G., Brown, S. B. and Roberts, D. J. H., "A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia," *Int. J. Cancer* **103**, 829–832 (2003).
125. Fehr, M. K., Hornung, R., Degen, A., Schwarz, V. A., Fink, D., Haller, U. and Wyss, P., "Photodynamic therapy of vulvar and vaginal condyloma and intraepithelial neoplasia using topically applied 5-aminolevulinic acid," *Laser Surg. Med.* **30**, 273–279 (2002).
126. Campbell, S. M. and Curnow, A., "Extensive vulval intraepithelial neoplasia treated with a new regime of systemic photodynamic therapy using meta-tetrahydroxychlorin (Foscan)," *J. Eur. Acad. Dermatol. Venereol.* **22**, 502–503 (2008).
127. Paoli, J., Ternesten Bratel, A., Löwhagen, G. B., Stenquist, B., Forslund, O. and Wennberg, A. M., "Penile intraepithelial neoplasia: Results of photodynamic therapy," *Acta Derm. Venereol.* **86**, 418–421 (2006).
128. Corti, L., Tomio, L., Maluta, S., Minucci, D., Fontana, M., Cittar, H. and Calzavara, F., "Recurring gynaecologic cancer treated with photodynamic therapy," *Photochem. Photobiol.* **46**, 949–952 (1987).
129. Koren, H. and Alth, G., "Photodynamic therapy in gynaecologic cancer," *J. Photochem. Photobiol. B* **36**, 189–191 (1996).
130. Wierrani, F., Fiedler, D., Grin, W., Henry, M., Dienes, E., Gharehbaghi, K., Krammer, B. and Grünberger, W., "Clinical effect of meso-tetrahydroxyphenylchlorine based photodynamic therapy in recurrent carcinoma of the ovary: Preliminary results," *Br. J. Obstet. Gynaecol.* **104**, 376–378 (1997).
131. Tochner, Z., Mitchell, J. B., Smith, P., Harrington, F., Glatstein, E., Russo, D. and Russo, A., "Photodynamic therapy of ascites tumours within the peritoneal cavity," *Br. J. Cancer* **53**, 733–736 (1986).
132. DeLaney, T. F., Sindelar, W. F., Tochner, Z., Smith, P. D., Friauf, W. S., Thomas, G., Dachowski, L., Cole, J. W., Steinberg, S. M. and Glatstein, E., "Phase I study of debulking surgery and photodynamic therapy for disseminated intraperitoneal tumors," *Int. J. Radiat. Oncol. Biol. Phys.* **25**, 445–457 (1993).
133. Hendren, S. K., Hahn, S. M., Spitz, F. R., Bauer, T. W., Rubin, S. C., Zhu, T., Glatstein, E. and Fraker, D. L., "Phase II trial of debulking surgery and photodynamic therapy for disseminated intraperitoneal tumors," *Ann. Surg. Oncol.* **8**, 65–71 (2001).
134. Hahn, S. M., Fraker, D. L., Mick, R., Metz, J., Busch, T. M., Smith, D., Zhu, T., Rodriguez, C., Dimofte, A., Spitz, F., Putt, M., Rubin, S. C., Menon, C., Wang, H. W., Shin, D., Yodh, A. and Glatstein, E., "A phase II trial of intraperitoneal photodynamic therapy for patients with peritoneal carcinomatosis and sarcomatosis," *Clin. Cancer Res.* **12**, 2517–2525 (2006).

135. Hahn, S. M., Putt, M. E., Metz, J., Shin, D. B., Rickter, E., Menon, C., Smith, D., Glatstein, E., Fraker, D. L. and Busch, T. M., "Photofrin uptake in the tumor and normal tissues of patients receiving intraperitoneal photodynamic therapy," *Clin. Cancer Res.* **12**, 5464–5470 (2006).
136. Bockstahler, L. E., Coohill, T. P., Hellman, K. B., Lytle, C. D. and Roberts, J. E., "Photodynamic therapy for herpes simplex: A critical review," *Pharmacol. Ther.* **4**, 473–499 (1979).
137. Stahl, D., Veien, N. K. and Wulf, H. C., "Photodynamic inactivation of virus warts: A controlled clinical trial," *Clin. Exp. Dermatol.* **4**, 81–85 (1979).
138. Wang, Y. S., Tay, Y. K., Kwok, C. and Tan, E., "Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population," *Int. J. Dermatol.* **46**, 1180–1184 (2007).
139. Wang, X. L., Wang, H. W., Wang, H. S., Xu, S. Z., Liao, K. H. and Hillemanns, P., "Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminate," *Br. J. Dermatol.* **151**, 880–885 (2004).
140. Chen, K., Chang, B. Z., Ju, M., Zhang, X. H. and Gu, H., "Comparative study of photodynamic therapy vs. CO_2 laser vaporization in treatment of condylomata acuminata: A randomized clinical trial," *Br. J. Dermatol.* **156**, 516–520 (2007).
141. Wang, X. L., Wang, H. W., Huang, Z., Stepp, H., Baumgartner, R., Dannecker, C. and Hillemanns, P., "Study of protoporphyrin IX (PpIX) pharmacokinetics after topical application of 5-aminolevulinic acid in urethral condylomata acuminate," *Photochem. Photobiol.* **83**, 1069–1073 (2007).
142. Wainwright, M., "Photodynamic antimicrobial chemotherapy (PACT)," *J. Antimicrob. Chemother.* **42**, 13–28 (1998).
143. Jori, G. and Brown, S. B., "Photosensitized inactivation of microorganisms," *Photochem. Photobiol. Sci.* **3**, 403–405 (2004).
144. Hamblin, M. R. and Hasan, T., "Photodynamic therapy: A new antimicrobial approach to infectious disease?" *Photochem. Photobiol. Sci.* **3**, 436–450 (2004).
145. Donnelly, R. F., McCarron, P. A. and Tunney, M. M., "Antifungal photodynamic therapy," *Microbiol. Res.* **163**, 1–12 (2008).
146. Grinholc, M., Szramka, B., Olender, K. and Graczyk, A., "Bactericidal effect of photodynamic therapy against methicillin-resistant *Staphylococcus aureus* strain with the use of various porphyrin photosensitizers," *Acta Biochim. Pol.* **54**, 665–670 (2007).
147. Bryld, L. E. and Jemec, G. B., "The bacterial flora of the skin surface following routine MAL-PDT," *J. Dermatolog. Treat.* **17**, 222–223 (2006).
148. Enk, C. D., Fritsch, C., Jonas, F., Nasereddin, A., Ingber, A., Jaffe, C. L. and Ruzicka, T., "Treatment of cutaneous leishmaniasis with photodynamic therapy," *Arch. Dermatol.* **139**, 432–434 (2003).
149. Asilian, A. and Davami, M., "Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: A placebocontrolled, randomized clinical trial," *Clin. Exp. Dermatol.* **31**, 634–637 (2006).
150. Akilov, O. E., Kosaka, S., O'Riordan, K. and Hasan, T., "Parasiticidal effect of deltaaminolevulinic acid-based photodynamic therapy for cutaneous leishmaniasis is indirect and mediated through the killing of the host cells," *Exp. Dermatol.* **16**, 651–660 (2007).
151. Wiegell, S. R. and H.C. Wulf. "Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: A blinded, randomized, controlled trial," *Br. J. Dermatol.* **154**, 969–976 (2006).
152. C. Hörfelt, Stenquist, B., Larkö, O., Faergemann, J. and Wennberg, A. M., "Photodynamic therapy for acne vulgaris: A pilot study of the dose–response and mechanism of action," *Acta Derm. Venereol.* **87**, 325–329 (2007).
153. Horn, M. and Wolf, P., "Topical methyl aminolevulinate photodynamic therapy for the treatment of folliculitis," *Photodermatol. Photoimmunol. Photomed.* **23**, 145–147 (2007).
154. Smits, T., Kleinpenning, M. M., van Erp, P. E., van de Kerkhof, P. C. and Gerritsen, M. J., "A placebo-controlled randomized study on the clinical effectiveness, immunohistochemical changes and protoporphyrin IX accumulation in fractionated 5-aminolaevulinic acidphotodynamic therapy in patients with psoriasis," *Br. J. Dermatol.* **155**, 429–436 (2006).
155. Schleyer, V., Radakovic-Fijan, S., Karrer, S., Zwingers, T., Tanew, A., Landthaler, M. and Szeimies, R. M., "Disappointing results and low tolerability of photodynamic therapy with topical 5-aminolaevulinic acid in psoriasis. A randomized, double-blind phase I/II study," *J. Eur. Acad. Dermatol. Venereol.* **20**, 823–828 (2006).
156. Wilsmann-Theis, D., Bieber, T. and Novak, N., "Photodynamic therapy as an alternative treatment for cutaneous sarcoidosis," *Dermatology* **217**, 343–346 (2008).
157. Weisenseel, P., Kuznetsov, A. V., Molin, S., Ruzicka, T., Berking, C. and Prinz, J. C., "Photodynamic therapy for granuloma annulare: More

than a Shot in the Dark," *Dermatology* **217**, 329–332 (2008).
158. Batchelor, R., "Photodynamic therapy for the treatment of morphoea," *Clin. Exp. Dermatol.* **33**, 661–663 (2008).
159. Orenstein, A., Nelson, J. S., Liaw, L. H., Kaplan, R., Kimel, S. and Berns, M. W., "Photochemotherapy of hypervascular dermal lesions: A possible alternative to photothermal therapy?" *Laser Surg. Med.* **10**, 334–343 (1990).
160. Gu, Y., Li, J. H. and Guo, Z. H., "Photodynamic therapy for treating port wine stain," *Beijing Med. J.* **13,** 317 (1991) (in Chinese).
161. Lin, X. X., Wang, W., Wu, S. F., Yang, C. and Chang, T. S., "Treatment of capillary vascular malformation (port-wine stains) with photochemotherapy," *Plast. Reconstr. Surg.* **99**, 1826–1830 (1997).
162. Qin, Z. P., Li, K. L., Ren, L. and Liu, X. J., "Photodynamic therapy of port wine stains — a report of 238 cases," *Photodiag. Photodyn. Ther.* **4**, 53–59 (2007).
163. Gu, Y., Huang, N. Y., Liang, J., Pan, Y. M., Liu, F. G., "Clinical study of 1949 cases of port wine stains treated with vascular photodynamic therapy (Gu's PDT)," *Ann. Dermatol. Venereol.* **134**, 241–244 (2007) (in French).
164. Yuan, K. H., Li, Q., Yu, W. L., Zeng, D., Zhang, C. and Huang, Z., "Comparison of photodynamic therapy and pulsed dye laser in patients with port wine stain birthmarks: A retrospective analysis," *Photodiag. Photodyn. Ther.* **5**, 50–57 (2008).
165. Gold, M. H., Bradshaw, V. L., Boring, M. M., Bridges, T. M. and Biron, J. A., "Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage," *Dermatol. Surg.* **32**, 795–801 (2006).
166. Ruiz-Rodríguez, R., López, L., Candelas, D. and Pedraz, J., "Photorejuvenation using topical 5-methyl aminolevulinate and red light," *J. Drugs Dermatol.* **7**, 633–637 (2008).
167. Pieramici, D. J., Bressler, S. B., Koester, J. M. and Bressler, N. M., "Occult with no classic sub-foveal choroidal neovascular lesions in age-related macular degeneration: Clinically relevant natural history information in larger lesions with good vision from the Verteporfin in Photodynamic Therapy (VIP) Trial: VIP Report No. 4," *Arch. Ophthalmol.* **124**, 660–664 (2006).
168. Kaiser, P. K., "Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group. Verteporfin therapy of sub-foveal choroidal neovascularization in age-related macular degeneration: 5-year results of two randomized clinical trials with an open-label extension: TAP report no. 8," *Graefes Arch. Clin. Exp. Ophthalmol.* **244**, 1132–1142 (2006).
169. Mennel, S., Barbazetto, I., Meyer, C. H., Peter, S. and Stur, M., "Ocular photodynamic therapy — standard applications and new indications (part 1). Review of the literature and personal experience," *Ophthalmologica* **221**, 216–226 (2007).
170. Mennel, S., Barbazetto, I., Meyer, C. H., Peter, S. and Stur, M., "Ocular photodynamic therapy — standard applications and new indications. Part 2. Review of the literature and personal experience," *Ophthalmologica* **221**, 282–291 (2007).
171. Kijlstra, A., La Heij, E. and Hendrikse, F., "Immunological factors in the pathogenesis and treatment of age-related macular degeneration," *Ocul. Immunol. Inflamm.* **13**, 3–11 (2005).
172. Schmidt-Erfurth, U., Niemeyer, M., Geitzenauer, W. and Michels, S., "Time course and morphology of vascular effects associated with photodynamic therapy," *Ophthalmology* **112,** 2061–2069 (2005).
173. Michels, S. and Schmidt-Erfurth, U., "Sequence of early vascular events after photodynamic therapy," *Invest. Ophthalmol. Vis. Sci.* **44**, 2147–254 (2003).
174. Ergun, E., Maár, N., Ansari-Shahrezaei, S., Wimpissinger, B., Krepler, K., Wedrich, A. and Stur, M., "Photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide in the treatment of neovascular age-related macular degeneration," *Am. J. Ophthalmol.* **142,** 10–16 (2006).
175. Qiang, Y. G., Yow, C. M. and Huang, Z., "Combination of photodynamic therapy and immunomodulation: Current status and future trends," *Med. Res. Rev.* **28**, 632–644 (2008).
176. Singh, A. D., Kaiser, P. K., Sears, J. E., Gupta, M., Rundle, P. A. and Rennie, I. G., "Photodynamic therapy of circumscribed choroidal haemangioma," *Br. J. Ophthalmol.* **88**, 1414–1418 (2004).
177. Huang, Z., Liu, H. and Chen, W. R., "Mechanisms and applications of photodynamic therapy," in *Series on Biomaterials and Bioengineering, Vol. 4 Fundamentals & Applications of Biophotonics in Dentistry*, Eds., Kishen, A. and Asundi, A., (World Scientific Publishing Co., Singapore, 2006), pp. 175–176.
178. Wilson, M., "Lethal photosensitisation of oral bacteria and its potential application in the photodynamic therapy of oral infections," *Photochem. Photobiol. Sci.* **3**, 412–418 (2004).
179. Christodoulides, N., Nikolidakis, D., Chondros, P., Becker, J., Schwarz, F., Rössler, R. and Sculean, A., "Photodynamic therapy as an adjunct to non-surgical periodontal treatment: A randomized, controlled clinical trial," *J. Periodontol.* **79**, 1638–1644 (2008).
180. Braun, A., Dehn, C., Krause, F. and Jepsen, S., "Short-term clinical effects of adjunctive

antimicrobial photodynamic therapy in periodontal treatment: A randomized clinical trial," *J. Clin. Periodontol.* **35**, 877–884 (2008).
181. Bonsor, S. J. and Pearson, G. J., "Current clinical applications of photo-activated disinfection in restorative dentistry," *Dent. Update.* **33**, 143–144, 147–150, 153 (2006).
182. Donnelly, R. F., McCarron, P. A., Tunney, M. M. and Woolfson, A. D., "Potential of photodynamic therapy in treatment of fungal infections of the mouth. Design and characterisation of a mucoadhesive patch containing toluidine blue O," *J. Photochem. Photobiol. B.* **86**, 59–69 (2007).
183. Rockson, S. G., Kramer, P., Razavi, M., Szuba, A., Filardo, S., Fitzgerald, P., Cooke, J. P., Yousuf, S., DeVault, A. R., Renschler, M. F. and Adelman, D. C., "Photoangioplasty for human peripheral atherosclerosis: Results of a phase I trial of photodynamic therapy with motexafin lutetium (Antrin)," *Circulation* **102**, 2322–2324 (2000).
184. Kereiakes, D. J., Szyniszewski, A. M., Wahr, D., Herrmann, H. C., Simon, D. I., Rogers, C., Kramer, P., Shear, W., Yeung, A. C., Shunk, K. A., Chou, T. M., Popma, J., Fitzgerald, P., Carroll, T. E., Forer, D. and Adelman, D. C., "Phase I drug and light dose-escalation trial of motexafin lutetium and far red light activation (phototherapy) in subjects with coronary artery disease undergoing percutaneous coronary intervention and stent deployment: Procedural and long-term results," *Circulation* **108**, 1310–1315 (2003).
185. Cheung, J., Todd, M., Turnbull, R., Allison, B., Mornin, L., Carvalho, A. M., Spurr, G. and Hsiang, Y., "Longer term assessment of photodynamic therapy for intimal hyperplasia: A pilot study," *J. Photochem. Photobiol. B. Biol.* **73**, 141–147 (2004).
186. Waksman, R., Leitch, I. M., Roessler, J., Yazdi, H., Seabron, R., Tio, F., Scott, R. W., Grove, R. I., Rychnovsky, S., Robinson, B., Pakala, R. and Cheneau, E., "Intracoronary photodynamic therapy reduces neointimal growth without suppressing re-endothelialisation in a porcine model," *Heart* **92**, 1138–1144 (2006).
187. Heckenkamp, J., Mellander, S., Fogelstrand, P., Breuer, S., Brunkwall, J. and Mattsson, E., "Photodynamic therapy reduces intimal hyperplasia in prosthetic vascular bypass grafts in a pig model," *Eur. J. Vasc. Endovasc. Surg.* **34**, 333–339 (2007).
188. Ido, K., Yamamoto, H., Kawamoto, C., Koiwai, H., Yoshida, Y. and Kimura, K., "Esophageal varices obliterated by photodynamic therapy for coexisting early esophageal carcinoma," *Gastrointest. Endosc.* **45**, 420–423 (1997).
189. Nagamine, N., Ido, K., Saihuku, K., Higashizawa, T., Ono, K., Hirasawa, T., Sugano, K. and Chong, J. M., "Photodynamic effects on rabbit auricular veins after photosensitization with porfimer sodium: Implications of the results with respect to the treatment of esophageal varices with photodynamic therapy," *Gastrointest. Endosc.* **55**, 420–424 (2002).
190. Li, C. Z., Cheng, L. F., Wang, Z. Q. and Gu, Y., "Photodynamic therapy of esophageal varices: Experimental studies in animal veins, and first clinical cases," *Endoscopy* **35**, 1043–1048 (2003).
191. Seghatchian, J. and de Sousa, G., "Pathogen-reduction systems for blood components: The current position and future trends," *Transfus. Apher. Sci.* **35**, 189–196 (2006).
192. Boumedine, R. S. and Roy, C. D., "Elimination of alloreactive T cells using photodynamic therapy," *Cytotherapy* **7**, 134–143 (2005).
193. Bladon, J. and Taylor, P., "Extracorporeal photopheresis normalizes some lymphocyte subsets (including T regulatory cells) in chronic graft-versus-host-disease," *Ther. Apher. Dial.* **12**, 311–318 (2008).
194. Jiang, H., Granville, D. J., McManus, B. M., Levy, J. G. and Hunt, D. W., "Selective depletion of a thymocyte subset *in vitro* with an immunomodulatory photosensitizer," *Clin. Immunol.* **91**, 178–187 (1999).
195. Wainwright, M., "Photodynamic therapy: The development of new photosensitisers," *Anticancer Agents Med. Chem.* **8**, 280–291 (2008).
196. Chen, B., Pogue, B. W., Hoopes, P. J., Hasan, T., "Vascular and cellular targeting for photodynamic therapy," *Crit. Rev. Eukaryot. Gene. Expr.* **16**, 279–305 (2006).
197. Zuluaga, M. F. and Lange, N., "Combination of photodynamic therapy with anti-cancer agents," *Curr. Med. Chem.* **15**, 1655–1673 (2008).
198. Wilson, B. C. and Patterson, M. S., "The physics, biophysics and technology of photodynamic therapy," *Phys. Med. Biol.* **53**, R61–109 (2008).
199. Zhu, T. C. and Finlay, J. C., "The role of photodynamic therapy (PDT) physics," *Med. Phys.* **35**, 3127–3136 (2008).
200. Wilson, B. C., "Emerging strategies in photodynamic therapy," in *Advances in Photodynamic Therapy: Basic, Translational, and Clinical*, Eds., Hamblin, M. R. and Mroz, P., (Artech House Inc., Book News, Inc., Portland, OR 2008), pp. 235–254.
201. Allison, R. R., Mota, H. C., Bagnato, V. S. and Sibata, C. H., "Bio-nanotechnology and photodynamic therapy — state of the art review," *Photodiag. Photodyn. Ther.* **5**, 19–28 (2008).
202. Josefsen, L. B. and Boyle, R. W., "Photodynamic therapy: Novel third-generation photosensitizers

one step closer?" *Br. J. Pharmacol.* **154**, 1–3 (2008).

203. Pandey, R. K., Goswami, L. N., Chen, Y., Gryshuk, A., Missert, J. R., Oseroff, A. and Dougherty, T. J., "Nature: A rich source for developing multifunctional agents. Tumor-imaging and photodynamic therapy," *Laser Surg. Med.* **38**, 445–467 (2006).
204. Collins, H. A., Khurana, M., Moriyama, E. H., Mariampillai, A., Dahlstedt, E., Balaz, M., Kuimova, M. K., Drobizhev, M., Yang, V. X. D., Phillips, D., Rebane, A., Wilson, B. C. and Anderson, H. L., "Blood vessel closure using photosensitizers engineered for two-photon excitation," *Nat. Photonics* **2**, 420–424 (2008).