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# A Review of Progress in Clinical Photodynamic Therapy

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Photodynamic therapy (PDT) has received increased attention since the regulatory approvals have been granted to several photosensitizing drugs and light applicators worldwide. Much progress has been seen in basic sciences and clinical photodynamics in recent years. This review will focus on new developments of clinical investigation and discuss the usefulness of various forms of PDT techniques for curative or palliative treatment of malignant and non-malignant diseases.

Key words: Photodynamic therapy; Clinical application; Malignant disease; and Non-malignant disease.

## *Introduction*

Photosensitive agents and light have been used for medical purposes for a very long time. However, photodynamic therapy (PDT) only began to form in the 1960s after Lipson and Baldes reported that neoplastic tissues containing photosensitizer of porphyrin mixture could fluoresce under ultraviolet light irradiation (1). The porphyrin mixture, prepared by Schwartz, and formally named as hematoporphyrin derivative (HpD), was found to have a better affinity for tumor tissue and stronger phototoxicity than crude hematophorphyrin (2). Early studies were quickly expanded to investigate the phototherapeutic potentials of HpD in both preclinical and clinical studies in the 1970s (3-5). An effort led by Dougherty to prepare a drug grade HpD in large quantities following the US FDA regulations produced the first approved photosensitizing drug, Photofrin, for clinical use. The early clinical studies using Photofrin for tumor ablation of various malignant diseases quickly established a series of clinical protocols around the world in the 1980s. This laid an important milestone of modern phototodynamic therapy. Several light applicators were also developed to facilitate clinical protocols. This gradually progressed from noncoherent light sources

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**Abbreviations:** AK, Actinic keratosis; ALA, 5-aminolevulinic acid; AMD, Age-related macular degeneration; Antrin, Motexafin lutetium, MLu, Lutetium(III) texaphyrin, Lu-Tex; BCCs, Basal cell carcinomas; BCG, Bacille Calmette-Guerin; BPD-MA, Benzoporphyrin derivative monoacid ring A, verteporfin; BPH, Benign prostatic hyperplasia; CIN, Cervical intraepithelial neoplasia; CR, Complete response; FDA, Food and Drug Administration; Foscan, Temoporfin, meta-tetrahydroxyphenylchlorin, mTHPC; HBO, Hyperbaric oxygenation; HpD, Hematoporphyrin derivative; HPPH, 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a, Photochlor; KTP, Potassium-titanyl-phosphate; LED, Light emitting diode; MLA, Methyl aminolevulinate, M-ALA; mPDT, Metronomic PDT; MPM, Malignant pleural mesothelioma; NPe6, Mono-L-aspartyl chlorin e6, taporfin sodium, talaporfin sodium, LS11; NSCLC, Non-small cell lung cancer; PDD, Photodynamic diagnostics; PDT, Phototodynamic therapy; PpIX, Protoporphyrin IX; SCCs, Squamous cell carcinomas; SnET2, Tin ethyl etiopurpurin, Sn etiopurpurin, rostaporfin, purlytin, Photrex.

(*e.g.*, arc lamps) to laser/fiber optic systems that allow significant light fluxes of specific wavelength delivered into tumors. A standardization on photosensitizer preparation led to approvals of several PDT protocols for malignant and non-malignant indications in several countries in the 1990s.

Regulatory approvals for the clinical use of photosensitizers and PDT light applicators now exist in many countries around the world though the total number of approved clinical indications is still limited. The number of scientific articles on PDT, clinical application as well as basic science, steadily increases in both English language and non-English language literatures. Review articles on past work, new aspects and future applications have been published regularly while new technology and promising applications continue to be discovered (2, 6-14). This review article will focus on the clinical investigations published in English language journals and present the recent progress in PDT clinical applications.

### *Photosensitizing Drug*

The majority of PDT photosensitizers possess a heterocyclic ring structure similar to that of chlorophyll or heme in hemoglobin. Upon capturing light energy by the photosensitizer, a transfer and translation of light energy into chemical reaction in the presence of molecular oxygen produces singlet oxygen ($^1O_2$) or superoxide ($O_2^-$), and induces cell damage through direct and indirect cytotoxicity. Therefore, the photosensitizer is considered to be a critical element in PDT procedures. Many photosensitizers were introduced in the 1980s and 1990s. New ones are discovered and reported regularly. Photosensitizers can be categorized by their chemical structures and origins. In general, they can be divided into three broad families: (i) porphyrin-based photosensitizer (*e.g.*, Photofrin, ALA/PpIX, BPD-MA), (ii) chlorophyll-based photosensitizer (*e.g.*, chlorins, purpurins, bacteriochlorins), and (iii) dye (*e.g.*, phtalocyanine, napthalocyanine). Most of the currently approved clinical photosensitizers belong to the porphyrin family. Traditionally, the porphyrins and those photosensitizers developed in the 1970s and early 1980s are called first generation photosensitizers (*e.g.*, Photofrin). Porphyrin derivatives or synthetics made since the late 1980s are called second generation photosensitizers (*e.g.*, ALA). Third generation photosensitizers generally refer to the modifications such as biologic conjugates (*e.g.*, antibody conjugate, liposome conjugate) and built-in photo quenching or bleaching capability (15). These terms are still being used although not accepted unanimously and dividing photosensitizing drugs into such generations may be very confusing. In lot of cases, the claim that newer generation drugs are better than older ones is unjustified (16). The premature conclusions on novel or investigational photosensitizers may send a misleading message to researchers or clinicians by suggesting that the older drugs should be replaced by the newer ones or wrongly imply to patients that newer photosensitizing drugs are superior to older ones.

Clinicians and chemists have different views on what is the ideal photosensitizer (16, 17). For instance, chemists may emphasize more on a high extinction coefficient and a high quantum yield of singlet oxygen, whereas clinicians emphasize on low toxicity and high selectivity. Nonetheless, both sides are in agreement that for clinical PDT an ideal photosensitizer at least should meet some of the following criteria that are clinically relevant: a commercially available pure chemical, low dark toxicity but strong photocytotoxicity, good selectivity towards target cells, long-wavelength absorbing, rapid removal from the body, and ease of administration though various routes. These criteria provide a general guideline for comparison. Although some photosensitizers satisfy all of or some of these criteria, there are currently only a few PDT photosensitizers that have received official approval around the world. These include, but are not limited to, Photofrin® (Porfimer sodium; Axcan Pharma, Inc.), Foscan® (temoporfin, meta-tetrahydroxyphenylchlorin, mTHPC; Biolitec AG), Visudyne® (verteporfin, benzoporphyrin derivative monoacid ring A, BPD-MA; Novartis Pharmaceuticals), Levulan® (5-aminolevulinic acid, ALA; DUSA Pharmaceuticals, Inc.), and most recently Metvix® (methyl aminolevulinate, MLA or M-ALA; PhotoCure ASA.). Several promising photosensitizers are currently under clinical trials. These include HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a, Photochlor; Rosewell Park Cancer Institute), motexafin lutetium (MLu, lutetium(III) texaphyrin, Lu-Tex, Antrin; Pharmacyclics Inc.), NPe6 (mono-L-aspartyl chlorin e6, taporfin sodium, talaporfin, LS11; Light Science Corporation), SnET2 (tin ethyl etiopurpurin, Sn etiopurpurin, rostaporfin, Photrex; Miravant Medical Technologies).

### *Light Applicator and Light Delivery*

The first light sources used in PDT were noncoherent light sources (*e.g.*, conventional arc lamps). Noncoherent light sources are safer, easy to use, and less expensive. They can produce spectra of wavelengths to accommodate various photosensitizers. They can be used in conjunction with optical filers to output selective wavelength(s). The disadvantages of conventional lamps include significant thermal effect, low light intensity, and difficulty in controlling light dose. However, nowadays, most of these drawbacks can be overcome by a careful engineering design. For instance, the BLU-U light illuminator (DUSA Pharmaceuticals, Inc.), an illumination system for ALA-PDT of actinic keratosis (AK) of the face and scalp is a fairly simple timer-controlled switch on-off unit. The LumaCare™ lamp (MBG Technologies), a compact portable fiber optic delivery system provides interchangeable fiber optic probes containing a series of lenses

and optical filters. It can generate light of specific bandwidth between 350-800 nm in a variable power for a broad range of photosensitizers. Light emitting diode (LED) is another emerging PDT light applicator. LED can generate high energy light of desired wavelengths and can be assembled in a range of geometries and sizes. For intra-operative PDT of brain tumor, LED-probe may be arranged in a cylinder tip to fit into a balloon catheter (18), whereas, for minimally invasive interstitial PDT, the small and flexible light delivery LED catheter can be implanted into the tumor percutaneously (19, 20). Large LED array may be more suitable for flat surface illumination of wide-area superficial lesion (21, 22).

However, the most commonly used PDT light sources are lasers. They produce high energy monochromatic light of a specific wavelength with a narrow bandwidth for a specific photosensitizer. The laser light can be focused, passed down an optical fiber and directly delivered to the target site through a specially designed illuminator tip, for example a microlens or a cylindrical or spherical diffuser. Argon dye, potassium-titanyl-phosphate (KTP) dye, metal vapor lasers, and most recently diode lasers have been used for clinical PDT around the world. The KTP-dye modular combination system (Laserscope PDT Dye Module) was the most widely used PDT laser prior to the approval of the portable, lightweight, and less expensive diode lasers (*e.g.*, DIOMED 630 PDT; Diomed Inc.). One preferred advantage of the diode laser is that it can be engineered into a multi-channel unit to meet a highly sophisticated PDT procedure, which may require multi-channel diode lasers and each independent light output channel to simultaneously provide the light sources of variable power (*e.g.*, Ceralas PDT 762 nm; CeramOptec GmbH of Biolitec AG).

### *Clinical Application*

#### *Dermatological Disease*

Several types of skin conditions are among the first to be studied due to their accessibility to photosensitizer and external light. Dougherty's group pioneered skin cancer PDT in the 1970s using HpD and red light from a xenon arc lamp in patients who suffered primary or secondary skin cancers. This early study demonstrated that the primary skin cancers that showed a complete response (CR) included squamous cell carcinomas (SCCs, 20%), basal cell carcinomas (BCCs, 70-80%) and malignant melanomas (50%), and the secondary cancers originated from primary breast cancer, colon cancer, and endometrium cancer (80%) (5). Interstitial PDT might be an option for subcutaneous and cutaneous tumors of a larger volume (23).

Since the discovery of endogenous protoporphyrin IX (PpIX) photosensitization induced by exogenous administration of ALA (24) skin premalignant and malignant lesions also become a favorite target of ALA-PDT with the exception of the pigmented malignant melanomas due to a limited light penetration. AK, a premalignant lesion became the first approved dermatologic indication of PDT. Early multicenter clinical studies showed that a combination of Levulan and blue light resulted in 63-69% CR and approximately 5-fold higher than the control. With one or two treatments, 88% of patients had over 2/3 of lesions cleared. The long-term follow-up also showed ALA-PDT to be beneficial with a projected disease-free rate of 71% (25, 26). These studies demonstrated ALA-PDT to be effective, safe, and well tolerated by patients, and led to the US FDA approval in 2000 which marked another historic event for PDT. Recently, MLA-PDT has also been approved for AK in several countries. ALA-PDT was also approved for moderate inflammatory acne vulgaris in US in 2003. A number of other nonmalignant conditions (*e.g.*, psoriasis, viral warts, and hair removal) are currently under clinical investigation worldwide (27-30). Clinical investigational studies of ALA-PDT have also extended to BCCs, basaloid follicular hamartomas, SCC *in situ* (Bowen's disease), cutaneous T-cell lymphoma, and sebaceous gland hyperplasia in recent years (31-38). PDT may be a promising treatment modality for both Mediterranean and HIV-related Kaposi's sarcomas since it can be repeated and will not cause immunosuppression (39). SnET2 (Miravant Medical Technologies, formerly PDT Inc.) was also underwent clinical trials for the potential treatment of basal cell carcinoma and HIV-related Kaposi's sarcoma in the late 1990s. But some of these studies have been discontinued because of business considerations (40).

Photofrin-PDT has also been used off-label to treat locally recurrent breast carcinoma on the chest wall. Such recurrence occurs in 5-20% of breast cancer patients. Several reports suggest that PDT can offer 14-73% complete response and 14-45% partial response, but the duration of response was variable (6 weeks - 8 months) (41-43). It is expected that the photosensitizer acting at longer wavelengths could achieve deeper tissue penetration and thereby greatly expand the patient population for which this modality is useful.

#### *Ophthalmic Disease*

Verteporfin (BPD-MA, benzoporphyrin derivative monoacid ring A) was synthesized in the mid-1980s with an intention of cancer treatment. However, it has been used primarily for ocular PDT and approved for age-related macular degeneration (AMD) worldwide since 2000. Verteporfin in photodynamic therapy involves intravenous administration of Visudyne® (verteporfin) followed by activation through an ophthalmoscope equipped with a 690 nm diode laser while the photosensitizer is still in the general circulation. Several well designed clinical studies in North America and Europe

showed that AMD patients treated with verteporfin-PDT were more likely to experience stabilized vision than those given a placebo (44-46). Verteporfin therapy should be considered as a first-line therapy in these difficult-to-manage conditions such as subfoveal choroidal neovascularisation secondary to AMD, pathological myopia or presumed ocular histoplasmosis syndrome. Therefore, the Verteporfin Roundtable Participants have published guidelines on the role of verteporfin therapy in the management of CNV due to AMD and other causes in 2002 and 2005, respectively. Photodynamic therapy with visudyne for choroidal neovascular disease (CNV) has proved effective at preventing moderate to severe visual loss in eyes with subfoveal predominantly classic CNV or occult-only CNV caused by age-related macular degeneration (AMD) and in eyes with subfoveal CNV caused by pathologic myopia. PDT is not meant to improve visual acuity. It should, therefore, be used in eyes with potentially useful macular vision. Several clinical trials are currently under way to evaluate the efficacy of AMD PDT for use with other photosensitizers. These include SnET2, motexafin lutetium, and Npe6 (44). SnET2 (Photrex, Miravant) has completed two phase III placebo-controlled, double-masked clinical trials and a New Drug Application (NDA) has been filed recently.

Several case reports have demonstrated that verteporfin-PDT could resolve the exudative retinal detachment associated with a diffuse choroidal haemangioma. For circumscribed choroidal haemangioma, a 10-case study showed evidence of regression with flattening of tumor, resolution of subretinal fluid, and reduction of choroidal vasculature on angiograms. The visual acuity either improved or remained stable in eight patients. Visual loss due to delayed choroidal atrophy was seen in two patients (47).

*Head and Neck Cancer*

Head and neck cancer is the term given to a variety of malignant tumors that develop in the oral cavity, the pharynx, the nasal cavity, and the larynx. The most extensively studied photosensitizers for SCCs of head and neck are Photofrin and Foscan (temoporfin, meta-tetrahydroxyphenylchlorin, mTHPC). Biel reported the largest series of Photofrin-PDT for head and neck cancers of 107 patients in 1998. Cure for early cancer of the vocal cords (T1 and *in situ* disease) was achieved with a single treatment. There was only one recurrence in 79 months in a follow-up of 25 patients. The cure rate for early oral cavity tumors was 80% after 70 months, but all patients responded initially. For patients with advanced disease the use of PDT as an adjunct with radiotherapy or surgery could also improve cure rates (48). Another Photosan-3 PDT study showed that for superficial tumors of the larynx and oropharynx the cure rate was 89% over a follow-up period of 13-71 months of 19 patients (49). Foscan-PDT was approved in Europe in 2001 for the palliative treatment of patients with advanced head and neck cancer who have exhausted other treatment options. PDT is particularly well suitable for head and neck cancer because it has little effect on underlying functional structures and has an excellent cosmetic outcome (50). A recent multicenter study of 128 patients with recurrent/refractory SCCs showed that by use of WHO criteria, 38% of evaluable patients achieved an overall tumor response, and 16% achieved a complete tumor response, 43% of assessable lesions achieved 100% tumor mass reduction, and 58% achieved 50% or greater tumor mass reduction. Fifty-three percent of evaluable patients experienced a significant clinical quality-of-life benefit. Subset analyses revealed two subgroups in which significantly better responses were seen in patients with tumors of 10 mm or less in depth and patients with fully illuminated lesions. In patients fulfilling both categories, overall tumor response was 54%, CR was 30% and 61%. This demonstrates that Foscan-PDT can achieve significant clinical benefits and improvement in the quality of life of patients (51). A long-term study (37 months) shows a cure rate of 86% with 4 recurrences in 25 patients (52).

*Brain Tumor*

Intracranial tumors are poor prognosis diseases and treatment options are few. Glioblastomas and astrocytomas also tend to form foci of tumor that spread beyond the main tumor site. Therefore, conserving healthy brain tissue while effectively killing cancerous cells remains a major challenge in the treatment of these diseases. Muller and Wilson introduced an intra-operative Photofrin-PDT procedure (cavitary illumination) in the 1990s, which utilizes an optical fiber in a light-diffusing medium, to irradiate the surgical bed immediately following resection to treat patients with malignant glial tumors, particularly glioblastoma, and anaplastic astrocytoma. The multicenter studies have shown prolongation of survival in patients with malignant gliomas. With surgery alone the median survival was only 20 weeks, PDT raised survival to 30, 44 and greater than 61 weeks for patients with recurrent glioblastoma, malignant astrocytoma, and astrocytoma-oligodendroglioma, respectively. In patients with newly diagnosed tumors, PDT after subtotal resection appears to be safe and can prolong survival (53). Optimizing photosensitizer uptake, elevating light dose, and fluerescence guided resection might further improve the efficacy of intra-operative PDT mediated with Photofrin or Foscan (54-59).

Stummer *et al*. have demonstrated in the late 1990s that ALA-induced porphyrin fluorescence may label malignant glioma tissue for better visualization and accurately enough to enhance the completeness of tumor removal (60). ALA mediated intra-operative photodynamic diagnostics (PDD) of tumor tissue and post-resection PDT may be a beneficial

combination (61). Recent preclinical study has demonstrated an interesting phenomenon which was named as "metronomic PDT or mPDT" and might be clinically relevant. This term is analogous to continuous metronomic low-dose chemotherapy, in which both the photosensitizer and light are delivered continuously at low rates for extended periods of time to increase selective tumor cell killing through apoptosis and meanwhile minimize surrounding normal tissue damage. Prototype light applicator uses LED coupled to an implanted optical fiber or a directly implanted LED (62). LED-based PDT is not new. Schmidt *et al*. have shown that LED array could achieve a similar therapeutic effect as laser in brain tumor PDT mediated with Photofrin or verteporfin (18, 63).

Photofrin-PDT for pituitary adenomas is currently under clinical investigation. A Phase I/II trial of 12 patients with recurrent pituitary adenomas has shown encouraging outcomes, such as long term improvement of visual acuity or field defects in most patients, complete recovery of visual fields in 3 patients, reduction in hormone levels in functional adenoma patients, and tumor volume reduction up to 46% within 2 years (64).

*Pulmonary and Pleural Mesothelial Cancer*

Kato *et al*. began using HpD-PDT for bronchogenic carcinoma treatment in Japan in the 1980s (65). The worldwide data now show that bronchoscopic PDT appears to be effective as a curative therapy for small (<1 cm), superficial and early stage non-small cell lung cancer (NSCLC) (*e.g*., SCCs) and as palliative therapy in obstructive cancers of the tracheobronchial tree (66, 67). Bronchoscopic PDT has now achieved the status of a standard protocol for centrally located early-stage lung cancer in Japan (68). PDT of endobronchial metastatic tumors effectively decreased the amount of endobronchial obstruction, and improved quality of life (69). Recently, a new protocol using percutaneous insertion and intra-tumoral illumination has been developed for the curative treatment of localized peripheral lung cancer (< 1cm) unfit for surgery or radiotherapy. Preliminary results have shown a partial response in the majority of patients (70). The same Japanese group also extensively studied another photosensitizer mono-L-aspartyl chlorin e6 (NPe6, also known as talaporfin sodium and LS11) for SCCs. Clinical trials of 41 patients have shown an 83% CR. NPe6 has less significant skin photosensitivity due to its rapid clearance (71). However, some clinicians argue that in the absence of a formal comparative study, it is still uncertain whether PDT is better than other endobronchial therapies (72).

Malignant pleural mesothelioma (MPM), generally linked to asbestos exposure, responds poorly to conventional therapies. There is a need to develop more aggressive local therapies. Photofrin-PDT has been tested as an adjuvant intra-operative modality in several countries. The data demonstrates the safety and feasibility of intrapleural PDT which offers good survival results for stage I or II pleural mesothelioma. However, for patients of stage III or IV, PDT does not significantly prolong survival or increase local control (73-76). Nonetheless, the advent of newer photosensitizers and PDT technology has led to a renewed interest in evaluating intrapleural PDT (77). Hyperoxygenation is an effective means to enhance PDT cytotoxicity (78, 79). Therefore, it is logical to carry out the intrapleural PDT under hyperbaric oxygenation (HBO) breathing to improve the therapeutic effect (80).

*Cardiovascular Disease*

Recent preclinical studies show Antrin (motexafin lutetium, MLu, lutetium(III) texaphyrin, Lu-Tex; Pharmacyclics, Inc.) could be taken up by atherosclerotic plaque and concentrated within macrophages and vascular smooth muscle cells (81). This leads to an effort to develop a motexafin lutetium-mediated endovascular photoangioplastic modality for the management of cardiovascular diseases such as intimal hyperplasia, and atherosclerosis or vulnerable plaque, and prevention of restenosis. Several Phase I trials suggest a future role for the treatment of flow-limiting coronary atherosclerosis or vulnerable plaque while sparing normal, surrounding vascular tissues (82, 83). A recent animal study suggests that PDT may be beneficial in reducing intimal hyperplasia (84). Miravant Cardiovascular Inc., a subsidiary of Miravant Medical Technologies, is also developing new photoensitizers for the treatment of vascular graft intimal hyperplasia, atheroclerotic vulnerable plaque and the prevention of restenosis.

*Gastroenterological Cancer*

In gastroenterology, endoscopically accessible premalignant or malignant lesions located within the esophagus, the stomach, the bile duct, or the colorectum with a high surgical risk have become suitable targets of endoscopic PDT (85-88). Photofrin-PDT has been approved for obstructing esophageal cancer, early-stage esophageal cancer, and Barrett's esophagus in several countries. PDT assisted with a longer diffuser tip and the light centering balloon (*e.g*., Xcell PDT Balloon; Wilson-Cook Medical Inc.) can treat large amounts of esophageal mucosa in a single application. It is suggested that optimizing light dose and re-treating small areas of residual or untreated Barrett's mucosa may reduce the post-PDT stricture formation and improve the overall efficacy (89, 90).

Recent pilot studies have demonstrated that endoscopic Photofrin-PDT is also effective in the palliative treatment of hilar cholangiocarcinoma (91). A Phase III trial compared stenting plus PDT (n=20) with stenting alone (n=19) and showed a prolongation of survival by almost a year in stenting plus PDT group (92). The most recent study of eight

patients, who underwent 1-5 treatments, showed that median survival from the date of the first PDT treatment was 276 days, whereas median survival times were 45 and 127 days for bismuth type III and IV tumors treated with stenting alone (93). The five-year follow-up data of 23 patients showed that median survival after treatment was 11.2 months for M0 patients and 9.3 months for all patients. The 1-year, 2-year, 3-year, and 4-year survival rates were estimated to be 47%, 21%, 11%, and 5%, respectively, for M0 patients and 39%, 17%, 9%, and 4%, respectively, for all patients (94). Preliminary results confirm that endoscopic illumination of the biliary tract is safe and effective for inoperable cholangiocarcinoma and can improve cholestasis, performance, and quality of life for an extended period. Since endoscopic PDT appears to be the first approach leading to an improvement in prognosis, it should be offered to patients with inoperable cholangiocarcinoma. Preliminary studies suggest that operative PDT might also improve survival for those patients undergoing surgical resection (95, 96).

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 liver and pancreas (97). A new approach has been developed based on intratumoral placement of a LED array that may expand the use of PDT to treat locally advanced refractory tumors. An earlier pilot study utilized LED to activate photosensitizer LS11 (NPe6, Light Sciences Corporation) for the treatment of radiation-resistant or chemotherapy-resistant or inoperable malignancies. An overall observed tumor response rate was 33% (19). This leads to a Phase II trial to treat colorectal liver metastases.

Pancreatic cancer is one of the leading causes of cancer deaths. A more aggressive treatment capable of local destruction of pancreatic cancer with low morbidity is needed. Several animal experiments undertaken in the 1990s, on cancers transplanted into the hamster pancreas, were shown to produce necrosis in the cancer and result in a significant increase in survival (98). These preclinical studies lead to the first pilot study of 16 patients by Bown *et al*. in UK. The effectiveness of Foscan-PDT on inoperable pancreatic cancer has been demonstrated under dose levels of 20-40 J per site and a total of 40-480 J per tumor. The percutaneous interstitial protocol, of multiple diffuser fiber illumination, could produce 1.4 to 5.1 $cm^3$ necrosis per fiber per site, which corresponds to 340%-40% tumor volume. Survival time ranges from 5 months (tumor diameter prior to PDT=5 cm) to > 31 months (tumor diameter prior to PDT=3.5 cm). In most cases, the necrotic area of the treated tumor healed safely without changing in size. There was no sign of a pseudocyst, abscess, or pancreatic duct leak. These promising results justify larger trials to further assess the feasibility and efficacy of PDT either as a single procedure or in combination with chemotherapy and/or radiotherapy (99).

*Urological Disease*

Photofrin obtained its first regulatory approval for recurrent papillary tumors in Canada in 1993. Intravenous Photofrin administration followed by transurethrally intravesical illumination became an option for patients with refractory tumors. The initial responses to a single treatment of the whole bladder tend to be good, but side effects such as bladder contraction and bladder irritation are noticeable and the incidence of relapse within a year is relatively high (70-80%) (100-102). Since the side effects are dose dependent, Nseyo suggests that by fractionating drug and light doses in a sequential PDT mode might subside cancerous cells and meanwhile reduce local toxicity (see report by Gail McBride) (103). Although Photofrin-PDT has been suggested as a second line or immediate therapy for Bacille Calmette-Guerin (BCG) or chemotherapy failures, it has not gained wide acceptance yet.

Bladder cancer tends to be a superficial condition, and for this reason it is proposed that a superficial treatment mediated with ALA or its ester derivatives may be a preferable means for local therapy. Nonetheless, an advantage of the intravesical instillation of photosensitizer is to eliminate cutaneous phototoxicity. 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 (104, 105). It has been shown that with repeated PDT treatments, it is possible to further inhibit the progression of the disease (106). White light has been proven to be an effective light source for ALA-PDT in destroying flat lesions without causing major side effects (107). However, some clinicians are concerned that ALA-PDT can cause pain and it would require some form of local anesthesia (108).

Prostate cancer is still a significant health problem mainly due to its high incidence, mortality, and cost associated with its diagnosis and treatment, and the lack of effective treatment for advanced disease. An attempt to develop an interstitial Photofrin-PDT procedure was made in the early 1990s (109). In following years, several preclinical studies in canine models demonstrated that, combined with interstitial light applicators, PDT-mediated with newer photosentitizers seems to have a great potential in the treatment of prostate cancer (110). Recent clinical trials of Foscan-PDT and ALA-PDA on patients who had failed radiotherapy showed a post-PDT decrease in prostate specific antigen (PSA) levels (111, 112). The preliminary results from two ongoing clinical trials of motexafin lutetium-PDT and Tookad-PDT designed to totally ablate the entire prostate gland are also encouraging (113, 114). The total ablation approach of interstitial PDT involves the implantation of multiple diffuser fibers into the prostate gland through a transperineal

brachytherapy template under trans-rectal ultrasound guide. It should be fully recognized that characterization of light penetration and distribution in prostate PDT 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 systems for monitoring drug concentrations and light fluences during interstitial PDT should be considered to ensure that sufficient drug and light fluence are delivered to the treatment area (115-118). It is also important that the possible side effects of the interstitial PDT on adjacent structures of the prostate gland be further investigated in order to preserve prostate nerve and minimize adverse effect on sexual and urinary functions in the process of total ablation (119).

In contrast to other photosensitizers currently being investigated clinically for prostate cancer, a new photosensitizing drug Pd-bacteriopheophorbide (Tookad, also known as WST09; Negma Lerads/Steba Biotech) is believed to be purely vascularly mediated. The clearance of Tookad from the circulation is very fast. For interstitial prostate PDT this has the significant practical advantage that the light may be delivered during, or shortly after, photosentitizer administration to complete PDT as a single operative session in a short period. Another advantage of Tookad-PDT is its capability of being activated at a relatively long wavelength (763 nm), with corresponding greater light attenuation depth (~ 4 mm) in prostatic tissue, and therefore inducing much larger prostate lesions than other photosensitizers (120-122). This supports the approach being used in current Phase I/II clinical trials of Tookad-PDT for recurrent prostate cancer (114).

Benign prostatic hyperplasia (BPH) is a common condition of aging males. Transurethral PDT was proposed for BPH in the 1990s (123), but it was never fully explored. There has been a renewed interest in transurethral PDT in recent years and there is an ongoing Phase I/II dose escalation study to assess the feasibility of transurethral PDT with lemuteporfin (formerly known as QLT0074; QLT Inc.) for the management of BPH.

*Gynecological Cancer*

Prior to and after Photofrin obtained regulatory approval in Japan in 1994, it has been used successfully to treat carcinoma *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%) (124). Although this modality is clinically useful for the treatment of early cervical cancer to preserve fertility, it has not gained wide acceptance in Western countries.

A modified protocol that combined topical administration of Photofrin and superficial illumination demonstrated that CR was light dose dependent for cervical intraepithelial neoplasia (CIN). An average of 73% CR (n=11) was obtained at light dose levels of 100-140 J/cm$^2$ (125). Several *in vivo* studies have demonstrated selective absorption of ALA by dysplastic cervical cells. This led to the presumption that ALA therefore represents a promising photosensitizing prodrug for the treatment of CIN with ALA-PDT. 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 minimal effect in the treatment of CIN 2 and CIN 3 (126-128).

***Summary***

Photodynamic therapy is a unique treatment modality in which a systemically or locally administered photosensitizer is activated locally by irradiating the lesion site with light of a suitable wavelength and power through a specially designed light applicator. PDT offers various treatment options in cancer management and has been used for localized superficial or endoluminal malignant and premalignant conditions. Its application has also been recently expanded to solid tumors. The antitumor efficacy of PDT might be enhanced through an effective immunoadjuvant to further expand its usefulness for a possible control of distant metastases (129). The non-invasive or minimally invasive nature of PDT also offers great promise in some non-malignant conditions in dermatology, ophthalmology, and cardiology. Although photodynamic diagnostics (PDD) is beyond the scope of this article, it needs to be pointed out that compared to X-ray, ultrasound, MRI, and other tomographic techniques, contrasting and visualizing lesions by fluorescent markers provide an innovative, non-invasive and safer imaging technology. Some of the fluorescent photosensitizers (*e.g.*, ALA) discussed in this article have shown a selective absorption by malignant cells, and their fluorescent signals can be a powerful tool for diagnostic purpose. There is no doubt that the duel function nature of these photosensitizers will play an important role in future clinical photodynamics.

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***References***

1. Lipson, R. L., Baldes, E. J. Hematoporphyrin Derivative: A New Aid for Endoscopic Detection of Malignant Disease. *J. Thorac. Cardiovasc. Surg. 42*, 623-629 (1961).
2. Dougherty, T. J., Henderson, B. W., Schwartz, S., Winkelman, J. W., Lipson, R. L. In *Historical Perspective in Photodynamic Therapy*, pp. 1-18, Eds., B. W. Henderson and T. J. Dougherty. Maurice Dekker, New York (1992).

3. Dougherty, T. J., Grindey, G. B., Fiel, R., Weishaupt, K. R., Boyle, D. G. Photoradiation Therapy II. Cure of Animal Tumors with Hematoporphyrin and Light. *J. Natl. Cancer Inst. 55*, 115-121 (1975).
4. Dougherty, T. J., Kaufman, J. E., Goldfarb, A., Weishaupt, K. R., Boyle, D., 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., Goldfarb, A. Photoradiation in the Treatment of Recurrent Breast Carcinoma. *J. Natl. Cancer Inst. 62*, 231-237 (1979).
6. Dougherty, T. J., Gomer, C. J., Henderson, B. W., Jori, G., Kessel, D., Korbelik, M., Moan, J., Peng, Q. Photodynamic Therapy. *J. Natl. Cancer Inst. 90*, 899-905 (1998).
7. Ackroyd, R., Kelty, C., Brown, N., Reed, M. The History of Photodetection and Photodynamic Therapy. *Photochem. Photobiol. 74*, 656-669 (2001).
8. Sibata, C. H., Colussi, V. C., Oleinick, N. L., Kinsella, T. J. Photodynamic Therapy in Oncology. *Expert Opin. Pharmacother. 2*, 917-927 (2001).
9. Gudgin Dickson, E. F., Goyan, R. L., Pottier, R. H. New Directions in Photodynamic Therapy. *Cell. Mol. Biol. 48*, 939-954 (2002).
10. Almeida, R. D., Manadas, B. J., Carvalho, A. P., Duarte C. B. Intracellular Signaling Mechanisms in Photodynamic Therapy. *Biochim. Biophys. Acta 1704*, 59-86 (2004).
11. Brown, S. B., Brown, E. A., Walker, I. The Present and Future Role of Photodynamic Therapy in Cancer Treatment. *Lancet Oncol. 5*, 497-508 (2004).
12. Solban, N., Ortel, B., Pogue, B., Hasan, T. Targeted Optical Imaging and Photodynamic Therapy. *Ernst Schering Res Found Workshop. 49*, 229-258 (2005).
13. Castano, A. P., Nemidova, T. N., Hamblin, M. R. Mechanisms in Photodynamic Therapy: Part I – Photosensitizers, Photochemistry and Cellular Location. *Photodiag. Photodyn. Therapy* (in press) (2005).
14. Castano, A. P., Nemidova, T. N., Hamblin, M. R. Mechanisms in Photodynamic Therapy: Part II – Cellular Signaling, Cell Metabolism and Modes of Cell Death. *Photodiag. Photodyn. Therapy* (in press) (2005).
15. Moser, J. G. Definitions and General Properties of 2nd & 3rd Generation Photosensitizers. In *Photodynamic Tumor Therapy - 2nd & 3rd Generation Photosensitizers*, pp. 3-8, Ed., J. G. Moser. Harwood Academic Publishers, London (1997).
16. Allison, R. R., Downie, G. H., Cuenca, R., Hu, X. H., Childs, C. J. H., Sibata, C. H. Photosensitizers in Clinical PDT. *Photodiag. Photodyn. Therapy 1*, 27-42 (2004).
17. Detty, M. R., Gibson, S. L., Wagner, S. J. Current Clinical and Preclinical Photosensitizers for Use in Photodynamic Therapy. *J. Med. Chem. 47*, 3897-3915 (2004).
18. Schmidt, M. H., Bajic, D. M., Reichert, K. W. II, Martin, T. S., Meyer, G. A., Whelan, H. T. Light-emitting Diodes as a Light Source for Intraoperative Photodynamic Therapy. *Neurosurgery 38*, 552-556 (1996).
19. Lustig, R. A., Vogl, T. J., Fromm, D., Cuenca, R., His, A. R., D'Cruz, A. K., Krajina, Z., Turic, M., Singhal, A., Chen, J. C. A Multicenter Phase I Safety Study of Intratumoral Photoactivation of Talaporfin Sodium in Patients with Refractory Solid Tumors. *Cancer 98*, 1767-1771 (2003).
20. Chen, J., Keltner, L., Christophersen, J., Zheng, F., Krouse, M., Singhal, A., Wang, S. S. New Technology for Deep Light Distribution in Tissue for Phototherapy. *Cancer J. 8*, 154-163 (2002).
21. Juzeniene, A., Juzenas, P., Ma, L. W., Iani, V., Moan, J. Effectiveness of Different Light Sources for 5-aminolevulinic Acid Photodynamic Therapy. *Lasers Med. Sci. 19*, 139-149 (2004).
22. Mang, T. S. Lasers and Light Sources for PDT: Past, Present and Future. *Photodiag. Photodyn. Therapy 1*, 43-48 (2004).
23. Lowdell, C. P., Ash, D. V., Driver, I., Brown, S. B. Interstitial Photodynamic Therapy. Clinical Experience with Diffusing Fibres in the Treatment of Cutaneous and Subcutaneous Tumours. *Br. J. Cancer. 67*, 1398-403 (1993).
24. Kennedy, J. C., Pottier, R. H. Endogenous Protoporphyrin IX, A Clinically Useful Photosensitizer for Photodynamic Therapy. *J. Photochem. Photobiol. B: Biol. 14*, 275-292 (1992).
25. Fink-Puches, R., Hofer, A., Smolle, J., Kerl, H., Wolf, P. Primary Clinical Response and Long-term Follow-up of Solar Keratoses Treated with Topically Applied 5-aminolevulinic Acid and Irradiation by Different Wave Bands of Light. *J. Photochem. Photobiol. B: Biol. 41*, 145-151 (1997).
26. Omrod, D., Jarvis B. Topical Aminolevulinic Acid HCl Photodynamic Therapy. *Am. J. Clin. Dermatol. 1*, 133-139 (2000).
27. Robinson, D. J., Collins, P., Stringer, M. R., Vernon, D. I., Stables, G. I., Brown, S. B., Sheehan-Dare, R. A. Improved Response of Plaque Psoriasis after Multiple Treatments with Topical 5-aminolaevulinic Acid Photodynamic Therapy. *Acta Dermato-Venereol. 79*, 451-455 (1999).
28. Stender, I. M., Na, R., Fogh, H., Gluud, C., Wulf, H. C. Photodynamic Therapy with 5-aminolaevulinic Acid or Placebo for Recalcitrant Foot and Hand Warts: Randomised Double-blind Trial. *Lancet 355*, 963-966 (2000).
29. Hongcharu, W., Taylor, C. R., Chang, Y., Aghassi, D., Suthamjariya, K., Anderson, R. R. Topical ALA-photodynamic Therapy for the Treatment of Acne Vulgaris. *J. Investig. Dermatol. 115*, 183-192 (2000).
30. Stender, I. M., Lock-Andersen, J., Wulf, H. C. Recalcitrant Hand and Foot Warts Successfully Treated with Photodynamic Therapy with Topical 5-aminolaevulinic Acid: A Pilot Study. *Clin. Exp. Dermatol. 24*, 154-159 (1999).
31. Cairnduff, F., Stringer, M. R., Hudson, E. J., Ash, D. V., Brown, S. B. Superficial Photodynamic Therapy with Topical 5-aminolaevulinic Acid for Superficial Primary and Secondary Skin Cancer. *Br. J. Cancer 69*, 605-608. (1994).
32. Stables, G. I., Stringer, M. R., Robinson, D. J., Ash, D. V. Large Patches of Bowen's Disease Treated by Topical Aminolaevulinic Acid Photodynamic Therapy. *Br. J. Dermatol. 136*, 957-960 (1997).
33. Morton, C. A., Whitehurst, C., McColl, J. H., Moore, J. V., MacKie, R. M. Photodynamic Therapy for Large or Multiple Patches of Bowen Disease and Basal Cell Carcinoma. *Arch. Dermatol. 137*, 319-324 (2001).
34. Leman, J. A., Dick, D. C., Morton, C. A. Topical 5-ALA Photodynamic Therapy for the Treatment of Cutaneous T-cell Lymphoma. *Clin. Exp. Dermatol. 27*, 516-518 (2002).
35. Horio, T., Horio, O., Miyauchi-Hashimoto, H., Ohnuki, M., Isei, T. Photodynamic Therapy of Sebaceous Hyperplasia with Topical 5-aminolaevulinic Acid and Slide Projector. *Br. J. Dermatol. 148*, 1274-1276 (2003).
36. Coors, E. A., von den Driesch, P. Topical Photodynamic Therapy for Patients with Therapy-resistant Lesions of Cutaneous T-cell Lymphoma. *J. Am. Acad. Dermatol. 50*, 363-367 (2004).
37. Gold, M. H., Bradshaw, V. L., Boring, M. M., Bridges, T. M., Biron, J. A., Lewis, T. L. Treatment of Sebaceous Gland Hyperplasia by Photodynamic Therapy with 5-aminolevulinic Acid and a Blue Light Source or Intense Pulsed Light Source *J. Drugs Dermatol. 3*, S6-S9 (2004).
38. Oseroff, A. R., Shieh, S., Frawley, N. P., Cheney, R., Blumenson, L. E., Pivnick, E. K., Bellnier, D. A. Treatment of Diffuse Basal Cell Carcinomas and Basaloid Follicular Hamartomas in Nevoid Basal Cell Carcinoma Syndrome by Wide-area 5-aminolevulinic Acid Photodynamic Therapy. *Arch. Dermatol. 141*, 60-67 (2005).
39. Calzavara-Pinton, P. G., Szeimies, R. M., Ortel, B., Zane, C. Photodynamic Therapy with Systemic Administration of Photosensitizers in Dermatology. *J. Photochem. Photobiol. B: Biol. 36*, 225-231 (1996).

40. Hunt, D. W. Rostaporfin (Miravant Medical Technologies). *IDrugs 5*, 180-186 (2002).
41. Schuh, M., Nseyo, U. O., Potter, W. R., Dao, T. L., Dougherty, T. J. Photodynamic Therapy for Palliation of Locally Recurrent Breast Carcinoma. *J. Clin. Oncol. 5*, 1766-1770 (1987).
42. Sperduto, P. W., DeLaney, T. F., Thomas, G., Smith, P., Dachowski, L. J., Russo, A., Bonner R, Glatstein E. Photodynamic Therapy for Chest Wall Recurrence in Breast Cancer. *Int. J. Radiat. Oncol. Biol. Phys. 21*, 441-446 (1991).
43. Wyss, P., Schwarz, V., Dobler-Girdziunaite, D., Hornung, R., Walt, H., Degen, A., Fehr, M. Photodynamic Therapy of Locoregional Breast Cancer Recurrences Using a Chlorin-type Photosensitizer. *Int. J. Cancer. 93*, 720-724 (2001).
44. Lim, J. I. Photodynamic Therapy for Choroidal Neovascular Disease: Photosensitizers and Clinical Trials. *Ophthalmol. Clin. North Am. 15*, 473-478 (2002).
45. Keam, S. J., Scott, L. J., Curran, M. P. Verteporfin: A Review of its Use in the Management of Subfoveal Choroidal Neovascularistion. *Drug 63*, 2521-2554 (2003).
46. Bessler, N. M. VAM Study Writing Committee. Verteporfin Therapy in Age-related Macular Degeneration (VAM): An Open-label Multicenter Photodynamic Therapy Study of 4,435 Patients. *Retina. 24*, 512-520 (2004).
47. Singh, A. D., Kaiser, P. K., Sears, J. E., Gupta, M., Rundle, P. A., Rennie, I. G. Photodynamic Therapy of Circumscribed Choroidal Haemangioma. *Br. J. Ophthalmol. 88*, 1414-1418 (2004).
48. Biel, M. A. Photodynamic Therapy and the Treatment of Head and Neck Neoplasia. *Laryngoscope 108*, 1259-1268 (1998).
49. Feyh, J. Photodynamic Therapy for Cancers of the Head and Neck. *J. Photochem. Photobiol. B: Biol. 36*, 175-177 (1996).
50. Lou, P. J., Jones, L., Hooper, C. Clinical Outcomes of Photodynamic Therapy for Head-and-neck Cancer. *Technol. Cancer Res. Treat. 2*, 311-317 (2003).
51. D'Cruz, A. K., Robinson, M. H., 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*, 232-40 (2004).
52. Copper, M. P., Tan, I. B., Oppelaar, H., Ruevekamp, M. C., Stewart, F. A. Meta-tetra(hydroxyphenyl)chlorin Photodynamic Therapy in Early-stage Squamous Cell Carcinoma of the Head and Neck. *Arch. Otolaryngol. Head Neck Surg. 129*, 709-711 (2003).
53. Muller, P. J., Wilson, B. C. Photodynamic Therapy for Recurrent Supratentorial Gliomas. *Semin. Surg. Oncol. 11*, 346-354 (1995).
54. Krishnamurthy, S., Powers, S. K., Witmer, P., Brown, T. Optimal Light Dose for Interstitial Photodynamic Therapy in Treatment for Malignant Brain Tumors. *Lasers Surg. Med. 27*, 224-234 (2000).
55. Goodell, T. T., Muller, P. J. Photodynamic Therapy: A Novel Treatment for Primary Brain Malignancy. *J. Neurosci. Nurs. 33*, 296-300 (2001).
56. Zimmermann, A., Ritsch-Marte, M., Kostron, H. mTHPC-mediated Photodynamic Diagnosis of Malignant Brain Tumors. *Photochem. Photobiol. 74*, 611-616 (2001).
57. Eljamel, M. S. New Light on the Brain: The Role of Photosensitizing Agents and Laser Light in the Management of Invasive Intracranial Tumors. *Technol. Cancer Res. Treat. 2*, 303-309 (2003).
58. Yang, V. X., Muller, P. J., Herman, P., Wilson, B. C. A Multispectral Fluorescence Imaging System: Design and Initial Clinical Tests in Intra-operative Photofrin-photodynamic Therapy of Brain Tumors. *Lasers Surg. Med. 32*, 224-232 (2003).
59. Stylli, S. S., Howes, M., MacGregor, L., Rajendra, P., Kaye, A. H. Photodynamic Therapy of Brain Tumours: Evaluation of Porphyrin Uptake Versus Clinical Outcome. *J. Clin. Neurosci. 11*, 584-596 (2004).
60. Stummer, W., Reulen, H. J., Novotny, A., Stepp, H., Tonn, J. C. Fluorescence-guided resections of malignant gliomas-an overview. Acta Neurochir. Suppl. 88, 9-12 (2003).
61. Friesen, S. A., Hjortland, G. O., Madsen, S. J., Hirschberg, H., Engebraten, O., Nesland, J. M., Peng, Q. 5-Aminolevulinic Acid-based Photodynamic Detection and Therapy of Brain Tumors. *Int. J. Oncol. 21*, 577-582 (2002).
62. Bisland, S. K., Lilge, L., Lin, A., Rusnov, R., Wilson, B. C. Metronomic Photodynamic Therapy as a New Paradigm for Photodynamic Therapy: Rationale and Preclinical Evaluation of Technical Feasibility for Treating Malignant Brain Tumors. *Photochem. Photobiol. 80*, 22-30 (2004).
63. Schmidt, M. H., Meyer, G. A., Reichert, K. W., Cheng, J., Krouwer, H. G., Ozker, K., Whelan, H. T. Evaluation of Photodynamic Therapy Near Functional Brain Tissue in Patients with Recurrent Brain Tumors. *J. Neurooncol. 67*, 201-207 (2004).
64. Marks, P. V., Belchetz, P. E., Saxena, A., Igbaseimokumo, U., Thomson, S., Nelson, M., Stringer, M. R., Holroyd, J. A., Brown, S. B. Effect of Photodynamic Therapy on Recurrent Pituitary Adenomas: Clinical Phase I/II Trial – An Early Report. *Br. J. Neurosurg. 14*, 317-325 (2000).
65. Kato, H., Konaka, C., Ono, J., Kawate, N., Nishimiya, K., Shinohara, H., Saito, M., Sakai, H., Noguchi, M., Kito, T. Preoperative Laser Photodynamic Therapy in Combination with Operation in Lung Cancer. *J. Thorac. Cardiovasc. Surg. 90*, 420-429 (1985).
66. McCaughan, J. S. Jr, Williams, T. E. Jr, Bethel, B. H. Photodynamic Therapy of Endobronchial Tumors. *Lasers Surg Med. 6*, 336-345 (1986).
67. Mathur, P. N., Edell, E., Sutedja, T., Vergnon, J. Treatment of Early Stage Non-small Cell Lung Cancer. *Chest 123*, 176s-180s (2003).
68. Kato, H., Harada, M., Ichinose, S., Usuda, J., Tsuchida, T., Okunaka, T. Photodynamic Therapy (PDT) of Lung Cancer: Experience of the Tokyo Medical University. *Photodiag. Photodyn. Therapy 1*, 49-55 (2004).
69. McCaughan, J. S. Jr. Survival After Photodynamic Therapy to Non-pulmonary Metastatic Endobronchial Tumors. *Lasers Surg. Med. 24*, 194-201 (1999).
70. Okunaka, T., Kato, H., Tsutsui, H., Ishizumi, T., Ichinose, S., Kuroiwa, Y. Photodynamic Therapy for Peripheral Lung Cancer. *Lung Cancer 43*, 77-82 (2004).
71. Kato, H., Furukawa, K., Sato, M., Okunaka, T., Kusunoki, Y., Kawahara, M., Fukuoka, M., Miyazawa, T., Yana, T., Matsui, K., Shiraishi, T., Horinouchi, H. Phase II Clinical Study of Photodynamic Therapy Using Mono-L-aspartyl Chlorin e6 and Diode Laser for Early Superficial Squamous Cell Carcinoma of the Lung. *Lung Cancer 42*, 103-111 (2003).
72. Moghissi, K. Role of Bronchoscopic Photodynamic Therapy in Lung Cancer Management. *Curr. Opin. Pulm. Med. 10*, 256-260 (2004).
73. Pass, H. I., Temeck, B. K., Kranda, K., Thomas, G., Russo, A., Smith, P., Friauf, W., Steinberg, S. M. Phase III Randomized Trial of Surgery With or Without Intraoperative Photodynamic Therapy and Postoperative Immunochemotherapy for Malignant Pleural Mesothelioma. *Ann. Surg. Oncol. 4*, 628-633 (1997).
74. Moskal, T. L., Dougherty, T. J., Urschel, J. D., Antkowiak, J. G., Regal, A. M., Driscoll, D. L., Takita, H. Operation and Photodynamic Therapy for Pleural Mesothelioma: 6-year Follow-up. *Ann. Thorac. Surg. 66*, 1128-1133 (1998).
75. Schouwink, H., Rutgers, E. T., van der Sijp, J., Oppelaar, H., van Zandwijk, N., van Veen, R., Burgers, S., Stewart, F. A., Zoetmulder, F., Baas, P. Intraoperative Photodynamic Therapy After Pleuropneumonectomy in Patients with Malignant Pleural Mesothelioma: Dose Finding and Toxicity Results. *Chest 120*, 1167-1174 (2001).
76. Bonnette, P., Heckly, G. B., Villette, S., Fragola, A. Intraoperative Photodynamic Therapy After Pleuropneumonectomy for Malignant Pleural Mesothelioma. *Chest 122*, 1866-1867 (2002).
77. Hahn, S. M., Smith, R. P., Friedberg, J. Photodynamic Therapy for Mesothelioma. *Curr. Treat. Options Oncol. 2*, 375-383 (2001).

78. Chen, Q., Huang, Z., Chen, H., Shapiro, H., Beckers, J., Hetzel, F. W. Improvement of Tumor Response by Manipulation of Tumor Oxygenation During Photodynamic Therapy. *Photochem. Photobiol. 76*, 197-203 (2002).
79. Huang, Z., Chen, Q., Shakil, A., Chen, H., Beckers, J., Shapiro, H., Hetzel, F. W. Hyperoxygenation Enhances the Tumor Cell Killing of Photofrin-mediated Photodynamic Therapy. *Photochem. Photobiol. 78*, 496-502 (2003).
80. Matzi, V., Maier, A., Sankin, O., Lindenmann, J., Woltche, M., Smolle, J., Smolle-Juttner, F. M. Photodynamic Therapy Enhanced by Hyperbaric Oxygenation in Palliation of Malignant Pleural Mesothelioma: Clinical Experience. *Photodiag. Photodyn. Therapy 1*, 57-64 (2004)
81. Woodburn, K., Fan, Q., Kessel, D., Wright, M., Mody, T. D., Hemmi, G., Magda, D., Sessler, J. L., Dow, W. C., Miller, R. A., Young, S. W. Phototherapy of Cancer and Atheromatousplaque with Texaphyrins. *J. Clin. Laser Med. Surg. 14*, 343-348 (1996).
82. Rockson, S. G., Kramer, P., Razavi, M., Szuba, A., Filardo, S., Fitzgerald, P., Cooke, J. P., Yousuf, S., DeVault, A. R., Renschler, M. F., 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).
83. 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., 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).
84. Cheung, J., Todd, M., Turnbull, R., Allison, B., Mornin, L., Carvalho, A. M., Spurr, G., Hsiang, Y. Longer Term Assessment of Photodynamic Therapy for Intimal Hyperplasia: A Pilot Study. *J. Photochem. Photobiol. B. Biol. 73*, 141-147 (2004).
85. Ell, C., Gossner, L., May, A., Schneider, H. T., Hahn, E. G., Stolte, M., Sroka, R. Photodynamic Ablation of Early Cancers of the Stomach by Means of mTHPC and Laser Irradiation: Preliminary Clinical Experience. *Gut 43*, 345-349 (1998).
86. Berr, F. Photodynamic Therapy for Cholangiocarcinoma. *Semin. Liver Dis. 24*, 177-187 (2004).
87. Webber, J., Fromm, D. Photodynamic Therapy for Carcinoma *In Situ* of the Anus. *Arch. Surg. 139*, 259-261 (2004).
88. Wiedmann, M. W., Caca, K. General Principles of Photodynamic Therapy (PDT) and Gastrointestinal Applications. *Curr. Pharm. Biotechnol. 5*, 397-408 (2004).
89. Wang, K. K., Kim, J. Y. Photodynamic Therapy in Barrett's Esophagus. *Gastrointest. Endosc. Clin. N. Am. 13*, 483-489 (2003).
90. Panjehpour, M., Overholt, B. F., Phan, M. N., 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).
91. Ortner, M. A. Photodynamic Therapy in Cholangiocarcinoma: An Overview Photodiag. *Photodyn. Therapy 1*, 85-92 (2004).
92. Ortner, M. A., Caca, K., Berr, F., Liebetruth, J., Mansmann, U., Huster, D., Voderholzer, W., Schachschal, G., Mossner, J., Lochs, H. Successful Photodynamic Therapy for Nonresectable Cholangiocarcinoma: A Randomized Prospective Study. *Gastroenterol. 125*, 1355-1363 (2003).
93. Harewood, G. C., Baron, T. H., Rumalla, A., Wang, K. K., Gores, G. J., Stadheim, L. M., de Groen, P. C. Pilot Study to Assess Patient Outcomes Following Endoscopic Application of Photodynamic Therapy for Advanced Cholangiocarcinoma. *J. Gastroenterol. Hepatol. 20*, 415-420 (2005).
94. Wiedmann, M., Berr, F., Schiefke, I., Witzigmann, H., Kohlhaw, K., Mossner, J., Caca, K. Photodynamic Therapy in Patients with Non-resectable Hilar Cholangiocarcinoma: 5-year Follow-up of a Prospective Phase II Study. *Gastrointest. Endosc. 60*, 68-75 (2004).
95. Wiedmann, M., Caca, K., Berr, F., Schiefke, I., Tannapfel, A., Wittekind, C., Mossner, J., Hauss, J., Witzigmann, H. Neoadjuvant Photodynamic Therapy as a New Approach to Treating Hilar Cholangiocarcinoma: A Phase II Pilot Study. *Cancer 97*, 2783-2790 (2003).
96. Nanashima, A., Yamaguchi, H., Shibasaki, S., Ide, N., Sawai, T., Tsuji, T., Hidaka, S., Sumida, Y., Nakagoe, T., Nagayasu, T. Adjuvant Photodynamic Therapy for Bile Duct Carcinoma After Surgery: A Preliminary Study. *J. Gastroenterol. 39*, 1095-1101 (2004).
97. Vogl, T. J., Eichler, K., Mack, M. G., Zangos, S., Herzog, C., Thalhammer, A., Engelmann, K. Interstitial Photodynamic Laser Therapy in Interventional Oncology. *Eur. Radiol. 14*, 1063-1073 (2004).
98. Ayaru, L., Bown, S. G., Pereira, S. P. Photodynamic Therapy for Pancreatic and Biliary Tract Carcinoma. Int. J. Gastrointest. Cancer 35, 1-14 (2005)
99. Bown, S. G., Rogowska, A. Z., Whitelaw, D. E., Lees, W. R., Lovat, L. B., Ripley, P., Jones, L., Wyld, P., Gillams, A., Hatfield, A. W. R. Photodynamic Therapy for Cancer of the Pancreas. *Gut 50*, 549-557 (2002).
100. Walther, M. M., Delaney, T. F., Smith, P. D., Friauf, W. S., Thomas, G. F., Shawker, T. H., Vargas, M. P., Choyke, P. L., Linehan, W. M., Abraham, E. H., Okunieff, P. G., Glatstein, E. Phase I Trial of Photodynamic Therapy in the Treatment of Recurrent Superficial Transitional Cell Carcinoma of the Bladder. *Urology 50*, 199-206 (1997).
101. Nseyo, U. O., Shumaker, B., Klein, E. A., Sutherland, K. Photodynamic Therapy Using Porfimer Sodium as an Alternative to Cystectomy in Patients with Refractory Transitional Cell Carcinoma *In Situ* of the Bladder. *J. Urol. 160*, 39-44 (1998).
102. Manyak, M. J., 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).
103. McBridge, G. Studies Expand Potential Uses of Photodynamic Therapy. *J. Natl. Cancer Inst. 94*, 1740-1742 (2002).
104. Kriegmair, M., Baumgartner, R., Lumper, W., Waidelich, R., Hofstetter, A. Early Clinical Experience with 5-aminolevulinic Acid for the Photodynamic Therapy of Superficial Bladder Cancer. *Br. J. Urol. 77*, 667-671 (1996).
105. Berger, A. P., Steiner, H., Stenzl, A., Akkad, T., Bartsch, G., 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).
106. Waidelich, R., Stepp, H., Baumgartner, R., Weninger, E., Hofstetter, A., Kriegmair, M. Clinical Experience with 5-aminolevulinic Acid and Photodynamic Therapy for Refractory Superficial Bladder Cancer. *J. Urol. 165*, 1904-1907 (2001).
107. Waidelich, R., Beyer, W., Knuchel, R., Stepp, H., Baumgartner, R., Schroder, J., Hofstetter, A., Kriegmair, M. Whole Bladder Photodynamic Therapy with 5-aminolevulinic Acid Using a White Light Source. *Urology 61*, 332-337 (2003).
108. Shackley, D. C., Briggs, C., Gilhooley, A., Whitehurst, C., O'Flynn, K. J., Betts, C. D., Moore, J. V., Clarke, N. W. Photodynamic Therapy for Superficial Bladder Cancer Under Local Anaesthetic. *B. J. Urol. Int. 89*, 665-670 (2002).
109. Whitehurst, C., Pantelides, M. L., Moore, J. V., Blacklock, N. J. Optimization of Multifiber Light Delivery for the Photodynamic Therapy of Localized Prostate Cancer. *Photochem. Photobiol. 58*, 589-593 (1993).

110. Muschter, R. Photodynamic Therapy: A New Approach to Prostate Cancer. *Curr. Urol. Rep. 4*, 221-228 (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., 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, S., Muschter, R., Knüchel, R., 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. Stripp, D. C. H., Mick, R., Zhu, T. C., Whittington, R., Smith, D., Dimofte, A., Finlay, J., Miles, J., Busch, T. M., Shin1, D., Kachur, A., Tochner, Z. A., Malkowicz, S. B., Glatstein, E., Hahn, S. M. Phase I Trial of Motexafin Lutetium-Mediated Interstitial Photodynamic Therapy in Patients with Locally Recurrent Prostate Cancer. *Proc. of SPIE 5315*, 88-99 (2004).
114. Gertner, M. R., Bogaards, A., Weersink, R. A., McCluskey, S. A., Haider, M. A., Yue, C. K. K., Savard, J., Simpson, S., Brun, P. H., Cohen, P., Scherz, A., Salomon, Y., Aprikian, A. G., Elhilali, M. M., Wilson, B. C., Trachtenberg, J. Initial Results of a Phase I/II Trial of WST09-mediated Photodynamic Therapy (WST09-PDT) for Recurrent Prostate Cancer Following Failed External Beam Radiation Therapy (EBRT). *Eur. Urol. Suppl. 3*, 212 (2004).
115. Jankun, J., Lilge, L., Douplik, A., Keck, R. W., Pestka, M., Szkudlarek, M., Stevens, P. J., Lee, R. J., Selman, S. H. Optical Characteristics of the Canine Prostate at 665 nm Sensitized with Tin Etiopurpurin Dichloride: Need for Real-time Monitoring of Photodynamic Therapy. *J. Urol. 172*, 739-743 (2004).
116. Zhu, T. C., Dimofte, A., Finlay, J. C., Stripp, D., Busch, T., Miles, J., Whittington, R., Malkowicz, S. B., Tochner, Z., Glatstein, E., Hahn, S. M. Optical Properties of Human Prostate at 732 nm Measured *In Vivo* During Motexafin Lutetium-mediated Photodynamic Therapy. *Photochem. Photobiol. 81*, 96-105 (2005).
117. Martin, N. E., Hahn, S. M. Interstitial Photodynamic Therapy for Prostate Cancer: A Developing Modality. *Photodiag. Photodyn. Therapy 1*, 123-136 (2004).
118. Weersink, R. A., Bogaards, A., Gertner, M., Davidson, S. R. H., Zhang, K., Netchev, G., Trachtenberg, T., Wilson, B. C. Techniques for Delivery and Monitoring of TOOKAD (WST09)-mediated Photodynamic Therapy of the Prostate: Clinical Experience and Practicalities. *Photochem. Photobiol. Sci.* (in press) (2005).
119. Dole, K. C., Chen, Q., Hetzel, F. W., Whalen, L. R., Blanc, D., 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).
120. Huang, Z., Chen, Q., Trncic, N., LaRue, S. M., Brun, P. H., Wilson, B. C., Shapiro, H., Hetzel, F. W. Effects of Pd-bacteriopheophorbide (TOOKAD)-mediated Photodynamic Therapy on Canine Prostate Pretreated with Ionizing Radiation. *Radiat. Res. 161*, 723-731 (2004).
121. Chen, Q., Huang, Z., Luck, D., Beckers, J., Brun, P. H., Wilson, B. C., Scherz, A., Salomon, Y., Hetzel, F. W. Preclinical Studies in Normal Canine Prostate of a Novel Palladium-bacteriopheophorbide (WST09) Photosensitizer for Photodynamic Therapy of Prostate Cancers. *Photochem. Photobiol. 76*, 438-445 (2002).
122. Huang, Z., Chen, Q., Luck, D., Beckers, J., Wilson, B. C., Trncic, N., LaRue, S. M., Blanc, D., Hetzel, F. W. Studies of a Vascular-acting Photosensitizer, Pd-bacteriopheophorbide (Tookad), in Normal Canine Prostate and Spontaneous Canine Prostate Cancer. *Lasers Surg. Med.* (in press) (2005).
123. Selman, S. H., Keck, R. W. The Effect of Transurethral Light on the Canine Prostate After Sensitization with the Photosensitizer Tin (II) Etiopurpurin Dichloride: A Pilot Study. *J. Urol. 152*, 2129-2132 (1994).
124. Muroya, T., Suehiro, Y., Umayahara, K., Akiya, T., Iwabuchi, H., Sakunaga, H., Sakamoto, M., Sugishita, T., Tenjin, Y. Photodynamic Therapy (PDT) for Early Cervical Cancer. *Gan To Kagaku Ryoho 23*, 47-56 (1996). (in Japanese)
125. Monk, B. J., Brewer, C., Van Nostrand, K., Berns, M. W., McCullough, J. L., Tadir, Y., Manetta, A. Photodynamic Therapy Using Topically Applied Dihematoporphyrin Ether in the Treatment of Cervical Intraepithelial Neoplasia. *Gynecol. Oncol. 64*, 70-75 (1997).
126. Hillemanns, P., Korell, M., Schmitt-Sody, M., Baumgartner, R., Beyer, W., Kimmig, R., Untch, M., Hepp, H. Photodynamic Therapy in Women with Cervical Intraepithelial Neoplasia Using Topically Applied 5-aminolevulinic Acid. *Int. J. Cancer 81*, 34-38 (1999).
127. Keefe, K. A., Tadir, Y., Tromberg, B., Berns, M., Osann, K., Hashad, R., Monk, B. J. Photodynamic Therapy of High-grade Cervical Intraepithelial Neoplasia with 5-aminolevulinic Acid. *Lasers Surg. Med. 31*, 289-293 (2002).
128. Barnett, A. A., Haller, J. C., Cairnduff, F., Lane, G., Brown, S. B., Roberts, D. J. 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).
129. Chen, W. R., Huang, Z., Korbelik, M., Nordquist R. E., Liu, H. Photoimmunotherapy for Cancer Treatment. *J. Environ. Pathol. Toxicol. Oncol.* (in press) (2005).

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