Clinical Policy Bulletin: Photodynamic Therapy

Number: 0375

Policy

I. Esophageal Cancer

Aetna considers photodynamic therapy with light-activated porfimer sodium (Photofrin) medically necessary for esophageal cancer in members with any of the following:

   A. Barrett's esophagus carcinoma in-situ and high-grade disease in members who are not candidates for esophagectomy; or
   B. Completely obstructing esophageal cancer; or
   C. Partially obstructing esophageal cancer, in members who cannot be satisfactorily treated with Nd:YAG laser therapy.

Aetna considers photodynamic therapy for esophageal cancer experimental and investigational when these criteria are not met.

II. Lung Cancer

Aetna considers photodynamic therapy with light-activated porfimer sodium medically necessary for members with any of the following:

   A. Completely obstructing endobronchial non-small cell lung cancer; or
   B. Microinvasive endobronchial non-small cell lung cancer at an early stage, for whom surgery and radiotherapy are not indicated; or
   C. Partially obstructing endobronchial non-small cell lung cancer.

Aetna considers photodynamic therapy for lung cancer experimental and investigational when these criteria are not met.

III. Non-Melanoma Skin Tumor

Aetna considers photodynamic therapy using topical photosensitizers (e.g., topical methyl aminolevulinate (Metvix PDT), topical 5-fluorouracil, aminolevulinic acid (Levulan Kerastik)) medically necessary for members
with any of the following non-melanoma skin tumors (including pre-malignant and primary non-metastatic skin lesions):

A. Basal cell carcinoma; or
B. Cutaneous lesions of Bowen's disease; or
C. Refractory actinic keratoses (see CPB 0567 - Actinic Keratoses Treatments).

Aetna considers photodynamic therapy using methyl aminolevulinate medically necessary for low-risk, squamous cell carcinoma in-situ where surgery or radiation is contraindicated or impractical.

Aetna considers photodynamic therapy experimental and investigational for other skin tumors because its effectiveness for skin tumors other than the ones listed above has not been established.

Aetna considers photodynamic therapy using intravenous photosensitizers (e.g., porfimer sodium) experimental and investigational for these indications.

IV. Cholangiocarcinoma

Aetna considers photodynamic therapy medically necessary as an adjunct to stenting for palliation of inoperable cholangiocarcinoma.

Aetna considers photodynamic therapy of cholangiocarcinoma experimental and investigational when these criteria are not met.

V. Prostate Cancer

Aetna considers interstitial motexafin lutetium-mediated photodynamic therapy for prostate cancer experimental and investigational because its effectiveness has not been established.

VI. Colon Cancer

Aetna considers photodynamic therapy for colon cancer experimental and investigational because its effectiveness for this indication has not been established.

VII. Gastric Cancer

Aetna considers photodynamic therapy experimental and investigational for gastric cancer because its effectiveness for this indication has not been established.

VIII. Squamous Cell Carcinoma in the Head and Neck

Aetna considers photodynamic therapy experimental and investigational for squamous cell carcinoma in the head and neck because its effectiveness for this indication has not been established.

IX. Breast Cancer

Aetna considers photodynamic therapy experimental and investigational for
breast cancer because the clinical evidence is not sufficient to permit conclusions on the health outcome effects of photodynamic therapy in the treatment of metastatic breast cancer lesions to the skin.

X. Pancreatic Cancer

Aetna considers photodynamic therapy experimental and investigational for pancreatic cancer because its effectiveness for this indication has not been established.

XI. Other Cancer Indications

Aetna considers photodynamic therapy experimental and investigational for cervical intraepithelial neoplasia/cervical cancer, pleural mesothelioma, and squamous dysplasia of the oral cavity because its effectiveness for these indications has not been established.

XII. Non-Cancer Indications

Aetna considers photodynamic therapy experimental and investigational for any of the following indications because its effectiveness for these indications has not been established:

- Actinic cheilitis
- Central serous chorioretinopathy
- Chronic ulcers (including diabetic ulcers)
- Condyloma (genital warts)
- Darier's disease (keratosis follicularis)
- Disseminated superficial actinic porokeratosis
- Granulomatous dermatitis
- Hidradenitis suppurativa
- Liposclerosis (lipodermatosclerosis)
- Keratitis
- Nekam's disease (also known as keratosis lichenoides chronica)
- Onychomycosis
- Periodontitis
- Plantar wart
- Psoriasis
- Radiation retinopathy
- Respiratory papillomatosis
- Rosacea
- Sebaceous hyperplasia
- Superficial mycosis.

For photodynamic therapy for ocular conditions, see CPB 0594 - Visudyne (Verteporfin) Photodynamic Therapy.

Also see CPB 0091 - Endometrial Ablation for photodynamic endometrial ablation, and CPB 0656 - Phototherapy for Acne.

Background
The United States Food and Drug Administration (FDA) has approved the use of Laserscope’s laser systems with QLT PhotoTherapeutics’ light-activated porfimer sodium (Photofrin) for injection in treating early-stage, microinvasive lung cancer. In clinical studies of photodynamic therapy (PDT) for lung cancer, no candidates for PDT had metastatic lesions, nodal involvement or cancer recurrence, and surgery or irradiation was contraindicated because they had an underlying respiratory disease, such as emphysema.

The FDA also recently approved the use of light-activated porfimer sodium for relief of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small cell lung cancer. Photodynamic therapy also shows promise as an alternative to esophageal resection for treatment for Barrett’s esophagus, a pre-malignant lesion.

Photodynamic therapy has also been evaluated as an adjunct to stenting and drainage as a palliative treatment for unresectable bile duct cancer. Small randomized controlled trials (RCTs) have demonstrated improvements in survival, and the results of a phase III study sponsored by the National Cancer Institute is pending publication. Zoepf et al (2005) conducted a RCT (phase IIb) of PDT in persons with advanced bile duct cancer. A total of 32 patients with non-resectable cholangiocarcinoma were randomized. Light activation was performed in the patients assigned to PDT 48 hours after intravenous application of 2 mg/kg body weight of Photosan-3, an oligomer of hematoporphyrin that has been approved for use in the European Union but is not approved by the FDA. In the control group, patients were treated with stenting and drainage without PDT. The investigators stated that the PDT group and the control group were comparable due to age, gender, performance status, bilirubin level, and bile duct cancer stage. The investigators reported that the median survival time after randomization was 7 months for the control group and 21 months for the PDT group (p = 0.0109). The investigators noted that, in 50% of the initially percutaneously treated patients, they were able to change from percutaneous to transpapillary drainage after PDT. The investigators noted that PDT was associated with a considerable rate of cholangitis: 4 patients showed infectious complications after PDT versus 1 patient in the control group.

Ortner et al (2003) reported on a prospective, open-label, randomized study with a group sequential design comparing PDT plus stenting (n = 20) to stenting alone (n = 19) in patients with non-resectable cholangiocarcinoma. For PDT, 2 mg/kg porfimer sodium (Photofrin) was injected intravenously 2 days before intraluminal photoactivation. Further treatments were performed in cases of residual tumor in the bile duct. The investigators reported that PDT resulted in prolongation of survival, with median survival of 493 days in persons assigned to PDT plus stenting, compared to a median survival of 98 days in persons assigned to stenting alone (p < 0.0001). The investigators noted that PDT also improved biliary drainage and quality of life. The investigators noted that this study was terminated prematurely because PDT proved to be so superior to simple stenting treatment that further randomization was deemed unethical.

Photodynamic therapy for tumors other than obstructing esophageal cancer, inoperable cholangiocarcinoma, and endobronchial non-small cell lung cancer is considered investigational, because it has not been proven to improve
the survival of patients with other tumors. Photodynamic therapy is being investigated as a treatment for cancers of the breast and brain.

Photodynamic therapy has been extensively studied for the treatment of various superficial non-melanoma skin cancers. For PDT for superficial skin cancers, a photosensitizing porphyrin (5-aminolevulinic acid, methyl aminolevulinate) is generally applied topically to the lesion. Although a porphyrin (porfimer sodium, Photofrin) can be administered systemically, this approach is avoided since systemic for treatment of skin cancers as such therapy can be associated with prolonged photosensitivity.

A recently published study found that PDT had good cosmetic results, but had a significantly higher recurrence rates than excision. Rhodes et al (2007) reported on the results of a prospective, multi-center, randomized study where 97 patients with 105 non-pigmented nodular basal cell carcinomas (BCCs) were treated with 2 to 4 courses of methyl aminolevulinate (MAL) PDT or with excision using 5-mm margins. The patients were followed for 5 years. The raw 5-year recurrence rate among successfully treated MAL-PDT patients was 14 %, significantly higher than the 4 % recurrence rate among excision patients. When initial treatment failures were included, the 5-year cure rates dropped to 66.0 % in the MAL-PDT group and to 91.5 % in the excision group. The overall cosmetic outcome at 5 years was rated as good or excellent in 87 % of the MAL-PDT patients, which was significantly better than the 54 % rated as good or excellent in the surgery patients.

In a prospective, multi-center, non-comparative study, Vinviullo et al (2005) examined the safety and effectiveness of PDT using topical MAL for basal cell carcinoma (BCC) defined as "difficult to treat", i.e., large lesions, in the H-zone (located in the mid-face), or in patients at high-risk of surgical complications. Patients were assessed 3, 12 and 24 months after the last PDT treatment. A total of 102 patients with "difficult-to-treat" BCC were treated with MAL PDT, using 160 mg g(-1) cream and 75 J cm(-2) red light (570 to 670 nm), after lesion preparation and 3 hours of cream exposure. A total of 95 patients with 148 lesions were included in the final analysis. The histologically confirmed lesion complete response rate at 3 months was 89 % (131 of 148). At 12 months, 10 lesions had re-appeared, and therefore the cumulative treatment failure rate was 18 % (27 of 148). At 24 months, an additional 9 lesions had re-appeared, resulting in a cumulative treatment failure rate of 24 % (36 of 148). The estimated sustained lesion complete response rate (assessed using a time-to-event approach) was 90 % at 3 months, 84 % at 12 months and 78 % at 24 months. Overall cosmetic outcome was judged as excellent or good in 79 % and 84 % of the patients at 12 and 24 months, respectively. Follow-up is continuing for up to 5 years. These investigators concluded that PDT by means of MAL is an attractive option for "difficult-to-treat" BCC.

Other photosensitizers are under investigation for skin cancers. In a clinical trial, Kaviani et al (2005) examined the use of PDT for the treatment of various pathological types of BCC. Six patients with 30 lesions underwent PDT. The photosensitizer used was Photoheme, a hematoporphyrin derivative IX. It was injected intravenously at the dose of 2 to 3.25 mg/kg. After 24 hours, the lesions were illuminated by laser light (lambda = 632 nm, light exposure dose = 100-200
J/cm²). Lesions were evaluated pre- and post-operatively and at follow-up sessions (of up to 6 months). After a single session of PDT, the average response rate in different histopathological types of BCC (e.g., ulcerative, superficial, nodular, and pigmented forms) were 100%, 62%, 90%, and 14%, respectively. In patients who responded completely, the cosmetic results were excellent and there were no recurrence at 6th month of follow-up. These researchers concluded that although PDT seems to be an effective treatment modality for superficial, ulcerative, and nodular BCC, it is not recommended for pigmented lesions.

In a phase I clinical trial, Chan et al (2005) examined the pharmacokinetic properties of Npe6 and clinical response to PDT with this photosensitizer. A single intravenous dose of Npe6 was administered to 14 cancer patients with superficial malignancies (BCC = 22 lesions, squamous cell cancer = 13 lesions, papillary carcinoma = 14 lesions). Patients received one of five ascending doses (0.5 mg/kg (n = 4), 1.0 mg/kg (n = 3), 1.65 mg/kg (n = 3), 2.5 mg/kg (n = 3), or 3.5 mg/kg (n = 1)) 4 to 8 hours prior to light activation. The total light dose (range 25 to 200 J/cm²) depended on the tumor shape and size. Light was delivered using an argon-pumped tunable dye laser. Serum NPe6 concentrations were measured over a 28-day period. The toxicity and cutaneous clinical efficacy of NPe6 were observed. Four weeks after PDT, 20 of 22 BCC tumors (91%) showed a complete response; 18 of 27 other malignant cutaneous tumors showed a complete (n = 15/27, 56%) or partial (n = 3/27, 11%) response. Fewer non-responders were seen at an Npe6 dose level of 1.65 mg/kg or higher. Only 2 of 14 patients experienced an adverse event that was definitely related to NPe6 administration. Photosensitivity resolved within 1 week of NPe6 dosing in 12 of 14 patients. Analysis of serum levels of 11 patients indicated that a 2-compartment model with a residual phase best fits the data. The mean alpha, beta, and terminal half-lives were 8.63 +/- 2.92, 105.90 +/- 37.59 and 168.11 +/- 53.40 hours (+/- 1 SD), respectively. The observed mean volume of distribution was 5.94 +/- 2.55 liters, and the mean clearance was 0.0394 +/- 0.0132 liters/hour. These values were independent of the dose administered. The authors concluded that the photosensitizer, NPe6, was well-tolerated with minimal phototoxic side effects, and demonstrated preliminary effectiveness against cutaneous malignancies.

In a review on photodynamic therapy for non-melanoma skin cancer, Szeimies et al (2005) stated that PDT is a treatment modality that has been shown to be effective mainly for the dermato-oncological conditions such as actinic keratoses, cutaneous lesions of Bowen's disease, in situ squamous cell carcinoma, and BCC. This is in agreement with the observations of Babilas et al (2005). Garcia-Zuazaga et al (2005) noted that PDT has been approved by the FDA to treat actinic keratoses. In Europe, PDT is currently being used in the treatment of actinic keratoses and BCC. Other off-label uses of PDT include cutaneous lesions of Bowen's disease, and cutaneous T-cell lymphoma. The Finnish Medical Society's guideline on skin cancer (2005) included PDT a treatment option for basilomas (e.g., BCC).

The National Institute for Health and Clinical Excellence (NICE, 2006) guideline on PDT for non-melanoma skin tumors (including pre-malignant and primary non-metastatic skin lesions) stated that "evidence of efficacy of this procedure for the treatment of basal cell carcinoma, Bowen's disease and actinic (solar) keratoses is adequate to support its use for these conditions .... Evidence is limited on the
efficacy of this procedure for the treatment of invasive squamous cell carcinoma”. The specialist Advisors of this report noted that PDT is appropriate for large superficial lesions of Bowen’s disease, actinic keratoses, and BCC, especially where there are multiple lesions and where repair would otherwise require extensive surgery. This report also stated that a Cochrane review is being developed on PDT for localized squamous cell carcinoma of the skin and its precursors.

The National Comprehensive Cancer Network has recently added MAL as an example of PDT that can be used in patients with low-risk, superficial basal cell skin cancer, where surgery or radiation is contraindicated or impractical.

Du et al (2006) stated that interstitial PDT is an emerging modality for the treatment of solid organ disease. These investigators have performed extensive research that showed the feasibility of interstitial PDT for prostate cancer. This study reported their pre-clinical and clinical experience in this therapeutic approach. These researchers have treated 16 dogs in pre-clinical studies, as well as 16 human subjects in a phase I study, using motexafin lutetium-mediated PDT for recurrent prostate adenocarcinoma. Dosimetry of light fluence, drug level and oxygen distribution for these patients were performed. They reported the safe and comprehensive treatment of the prostate using PDT. However, there was significant variability in the dose distribution and the subsequent tissue necrosis throughout the prostate. The authors concluded that PDT is an attractive option for the treatment of prostate adenocarcinoma. However, the observed variation in PDT dose distribution translates into uncertain therapeutic reproducibility. Their future focus will be on the development of an integrated system that is able to both detect and compensate for dose variations in real-time, in order to deliver a consistent overall PDT dose distribution.

In a review on the use of focal therapy for localized prostate cancer, Eggener and co-workers (2007) stated that several emerging technologies (e.g., high-intensity focused ultrasound, cryotherapy, radiofrequency ablation, and PDT) seem capable of focal destruction of prostate tissue with minimal morbidity. These researchers encouraged the investigation of focal therapy in select men with low-risk prostate cancer in prospective clinical trials that carefully document safety, functional outcomes and cancer control.

Moore et al (2009) noted that debate is ongoing about the treatment of organ-confined prostate cancer, particularly in men who have low-risk disease detected by PSA screening. A balance is needed between the harms and benefits of treatment. New techniques are being developed that aim to offer similar treatment effects to current radical therapies, while reducing the associated harmful effects of these treatments. These researchers explored the potential of PDT for the treatment of organ-confined prostate cancer. They stated that clinical studies are underway to investigate the use of PDT for primary and salvage treatment of organ-confined prostate cancer.

Recurrent respiratory papillomatosis (RRP), which is caused by human papillomavirus (HPV) types 6 and 11, is the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness. After changes in voice, stridor is the second most common symptom, first inspiratory and then biphasic. Less common presenting symptoms include
chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute respiratory distress, especially in infants with an upper respiratory tract infection. Differential diagnoses include asthma, croup, allergies, vocal nodules, or bronchitis. Reports estimate the incidence of RRP in the United States at 4.3 per 100,000 children and 1.8 per 100,000 adults. Infection in children has been associated with vertical transmission during vaginal delivery from an infected mother. Younger age at diagnosis is associated with more aggressive disease and the need for more frequent surgical procedures to decrease the airway burden. When surgical therapy is needed more frequently than 4 times in 12 months or there is evidence of RRP outside the larynx, adjuvant medical therapy should be considered. Adjuvant therapies that have been investigated include dietary supplements, control of extra-esophageal reflux disease, potent anti-viral and chemotherapeutic agents, and PDT; although several have shown promise, none to date has "cured" RRP, and some may have serious side effects (Derkay and Wiatrak, 2008).

In a parallel-arm, randomized study, Shikowitz and colleagues (2005) examined the effectiveness of PDT with meso-tetra (hydroxyphenyl) chlorin (m-THPC) photosensitizer for RRP. Disease extent was scored and papillomas were removed during direct endoscopy every 3 months after enrollment. Of 23 patients aged 4 to 60 years enrolled in the study, 15 patients, plus 2 in the late group without PDT owing to airway risk, completed the study. Six patients withdrew voluntarily after PDT. Subjects received intravenous administration of m-THPC 6 days before direct endoscopic PDT (80 to 100 J of light for adults and 60 to 80 J for children). Main outcome measures were difference in severity scores between the early and late groups and between pre- and post-PDT scores for all patients. Secondary measures were the associations between baseline characteristics and response and changes in immune response and the prevalence of latent viral DNA. There were significant differences between groups, with marked improvement in laryngeal disease across time after PDT (p = 0.006). Five of 15 patients were in remission 12 to 15 months after treatment, but there was recurrence of disease after 3 to 5 years. Tracheal disease was not responsive to PDT. No change occurred in the prevalence of latent human papillomavirus DNA. The immune response to virus improved with clinical response. The authors concluded that the use of m-THPC PDT reduces the severity of laryngeal papillomas, possibly through an improved immune response. However, failure to maintain remission with time suggested that this is not an optimal treatment.

Goon et al (2008) stated that HPV infection in benign laryngeal papillomas is well-established. The vast majority of RRP lesions are due to HPV types 6 and 11. Human papillomaviruses are small non-enveloped viruses (greater than 8 kb), that replicate within the nuclei of infected host cells. Infected host basal cell keratinocytes and papillomas arise from the disordered proliferation of these differentiating keratinocytes. Surgical debulking of papillomas is currently the treatment of choice; newer surgical approaches utilizing microdebriders are replacing laser ablation. Surgery aims to secure an adequate airway and improve and maintain an acceptable quality of voice. Adjuvant treatments currently used include cidofovir, indole-3-carbinol, ribavirin, mumps vaccine, and PDT. The recent licensing of prophylactic HPV vaccines is a most interesting development. The low incidence of RRP does pose significant problems in recruitment of
sufficient numbers to show statistical significance. The authors noted that large multi-center collaborative clinical trials are therefore needed.

Sebaceous hyperplasia (SH) is a common benign skin condition involving hypertrophy of sebaceous glands. Lesions occur particularly on the central face of adults. Patients usually are concerned about the lesions either because of fear of skin cancer or because of cosmesis. There is some evidence to suggest that chronic immunosuppression, such as from transplantation, can lead to the development of this condition. Treatment with electrodessication or laser ablation is successful; oral isotretinoin has been used in patients with multiple lesions. On the other hand, there is only limited evidence for the effectiveness of treatment with topical 5-aminolevulinic acid (Levulan Kerastick).

Richey (2007) stated that current therapies for SH have a high-risk for adverse effects and recurrence of treated lesions. The theoretic basis for the treatment of SH by PDT with 5-aminolevulinic acid (ALA) has been established. Studies show that 1 hour is sufficient ALA incubation time to achieve clearance, and ALA-induced protoporphyrin IX may be activated with a 585-nm pulsed dye laser device, blue light source, or an intense pulsed light device. Complete clearance may be achieved with 1 to 6 treatments; however, long-term recurrence rates are not established.

Wang and colleagues (2007) carried out a prospective, single-arm, phase II study of 5-ALA-PDT in the treatment of recalcitrant viral warts in an Asian population. Recalcitrant viral warts were surgically pared, and then treated with 20 % 5-ALA cream under occlusion for 4 hrs before irradiation with a red light source (Waldmann PDT1200; wavelength, 590 to 700 nm) at an irradiance of 50 mW/cm (2) and a total dose of 50 J/cm(2). Photodynamic therapy was repeated fortnightly for a maximum of 4 times. A total of 12 adult Asian patients were enrolled into the study (10 males, 2 females). The mean age of the patients was 32.8 years (range of 18 to 70). They had skin phototypes III-IV. Nine patients had plantar warts and 3 patients had hand warts (2 had warts on the fingers, 1 had a wart on the palm). Five patients (42 %) showed complete disappearance of their warts, 1 patient (8 %) showed partial clearance (greater than 50 % decrease in the wart area), 5 patients (42 %) had stable disease (less than 50 % decrease in the wart area), and 1 (8 %) showed progressive disease (increase in the wart area). Adverse effects included mild-to-moderate pain and erythema, which lasted no longer than 48 hrs and was well-tolerated by all patients. None of the patients withdrew from the study because of side-effects. The authors concluded that 5-ALA-PDT, given its non-invasiveness, minimal adverse effects, and good cosmetic results, is a promising alternative treatment for recalcitrant viral warts. They stated that further studies with a larger cohort of patients would be of value.

Hidradenitis suppurative (HS) is a chronic, apocrine, dermatological disorder that has a genetic predisposition. Rose and Stables (2008) reviewed the evidence on the use of PDT in the treatment of HS. Although small in number, there is considerable variation in the application of topical photosensitisers, light sources used and treatment regimes. In addition, there is often limited information about patient selection in terms of disease severity and measuring precise patient outcome. The authors stated that these issues need to be addressed in future studies in order to accurately determine the role of PDT in HS.
Hamilton et al (2009) performed a systematic review of randomized controlled trials of light and laser therapies for acne vulgaris. These investigators searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, PsycInfo, LILACS, ISI Science Citation Index and Dissertation Abstracts International for relevant published trials. They identified 25 trials (694 patients), 13 of light therapy and 12 of light therapy plus light-activated topical cream (PDT). Overall, the results from trials of light alone were disappointing, but the trials of blue light, blue-red light and infrared radiation were more successful, particularly those using multiple treatments. Red-blue light was more effective than topical 5% benzoyl peroxide cream in the short-term. Most trials of PDT showed some benefit, which was greater with multiple treatments, and better for non-inflammatory acne lesions. However, the improvements in inflammatory acne lesions were not better than with topical 1% adapalene gel, and the side-effects of therapy were unacceptable to many participants. The authors concluded that some forms of light therapy were of short-term benefit. Patients may find it easier to comply with these treatments, despite the initial discomfort, because of their short duration. However, very few trials comparing light therapy with conventional acne treatments were conducted in patients with severe acne or examined long-term benefits of treatment.

Reporting on the results of a case series (n = 3), Nayeemuddin and colleagues (2002) concluded that "[t]he results obtained in this small case series suggest that topical PDT is not a promising treatment for disseminated superficial actinic porokeratosis".

Exadaktylou et al (2003) evaluated the effectiveness of PDT in selected patients with Darier's disease (keratosis follicularis). A total of 6 patients with Darier's disease were assessed before and after treatment with PDT using 5-ALA and mean fluence rates of 110-150 mW cm-2. Of the 6 patients, 1 was unable to tolerate the treatment. Of the remaining 5, all experienced an initial inflammatory response that lasted 2 to 3 weeks. In 4 of the 5 patients, this was followed by sustained clearance or improvement over a follow-up period of 6 months to 3 years. Three of these 4 patients were on systemic retinoids and the 4th had discontinued acitretin prior to PDT. In the 5th patient partial improvement was followed by recurrence after etretinate therapy was discontinued. Biopsy specimens taken immediately after the procedure in 2 patients demonstrated a mild inflammatory cell infiltrate in the dermis. A biopsy obtained 18 months after PDT from a successfully treated area showed no signs of Darier's disease and a subtle increase of collagen in the upper dermis. The authors concluded that PDT can be viewed as a potential adjunctive modality for Darier's disease but should not be considered as a substitute for retinoids in patients who require systemic treatment.

Bryld and Jemec (2007) assessed the possible benefit of PDT in the treatment of rosacea. An exploratory review of case notes from rosacea patients treated with PDT was performed. Patients referred to the authors' department with rosacea were offered PDT if requesting an alternative to previously tried conventional therapy. Routine MAL-PDT with methylamino levulinate and red light was given 1 to 4 times; results were evaluated 1 to 2 months after PDT was initiated and subsequently followed-up. Good results were seen in 10 out of 17 patients, and
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fair results in another 4 patients. The majority of patients treated could stop or significantly reduce other rosacea therapy for a period lasting from about 3 months and up to 2 years. The study was limited by strong selection bias, and the clinical evaluation was obtained from case notes and photos. The authors concluded that an apparent effect of MAL-PDT on rosacea could be observed. This is in accordance with their previous experience, and observations made by other researchers. Thus, they stated that a future randomized controlled trial seems justifiable.

In a systematic review and meta-analysis, Azarpazhooh et al (2010) evaluated the effectiveness of PDT for periodontitis in adults as a primary mode of treatment or as an adjunct to non-surgical treatment of scaling and root planing (SRP) compared to a conventional non-surgical SRP treatment. MEDLINE, EMBASE, CINAHL, other relevant databases, and the International Pharmaceutical Abstracts were searched from their inception until May 2009 for randomized controlled trials of PDT compared to a placebo, no intervention, or non-surgical treatment in an adult population. Data on changes in clinical attachment level (CAL), probing depth, gingival recession, and full-mouth plaque or bleeding scores were extracted and meta-analyzed, and the pooled mean difference (MD) was reported. A total of 5 studies were included in this review. These studies had a small sample size for some of the performed analysis with a moderate to high risk of biases. There were clinical heterogeneities among included studies. Photodynamic therapy as an independent treatment or as an adjunct to SRP versus a control group of SRP did not demonstrate statistically or clinically significant advantages. Combined therapy of PDT + SRP indicated a probable efficacy in CAL gain (MD: 0.34; 95% confidence interval [CI]: 0.05 to 0.63) or probing depth reduction (MD: 0.25 mm; 95% CI: 0.04 to 0.45 mm). The authors concluded that PDT as an independent treatment or as an adjunct to SRP was not superior to control treatment of SRP. Thus, the routine use of PDT for clinical management of periodontitis can not be recommended. They stated that well-designed clinical trials are needed for proper evaluation of this therapy.

Nekam's disease, also known as keratosis lichenoides chronica (KLC), is a rare dermatosis characterized by violaceous papular and nodular lesions, often arranged in a linear or reticulate pattern on the dorsal hands and feet, extremities, and buttock. Lopez-Navarro et al (2008) stated that KLC is a rare, acquired disorder of keratinization of unknown etiology. The disease has a chronic and progressive course and is characterized by a poor response to almost all topical treatments and most systemic regimens. These investigators reported the first case of KLC in which there was a marked response in localized areas to PDT with methyl 5-ALA. The findings of this case study need to be validated by well-designed studies.

Radiation retinopathy (RR) is a chronic and progressive condition that results from exposure to any source of radiation. It might be secondary to radiation treatment of intra-ocular tumors such as choroidal melanomas, retinoblastomas, and choroidal metastasis, or from unavoidable exposure to excessive radiation from the treatment of extra-ocular tumors like cephalic, nasopharyngeal, orbital, and para-nasal malignancies. Giuliari et al (2011) reviewed the currently available therapeutic modalities for RR, including newer investigational interventions directed towards specific aspects of the pathophysiology of this refractory
complication. A review of the literature encompassing the pathogenesis of RR and the current therapeutic modalities available was performed. After the results of the Collaborative Ocular Melanoma Study, most of the choroidal melanomas were being treated with plaque brachytherapy increasing by that the incidence of this radiation complication. Radiation retinopathy has been reported to occur in as many as 60% of eyes treated with plaque radiation, with higher rates associated with larger tumors. Initially, the condition manifests as a radiation vasculopathy clinically seen as microaneurysms and telangiectases, with posterior development of retinal hard exudates and hemorrhages, macular edema, neovascularization and tractional retinal detachment. Photodynamic therapy, laser photocoagulation, oral pentoxyphylline and hyperbaric oxygen have been attempted as treatment modalities with inconclusive results. Intravitreal injections of anti-vascular endothelial growth factor (e.g., bevacizumab, ranibizumab and pegaptanib sodium) have been recently used, also with variable results. The authors concluded that RR is a common vision threatening complication following radiation therapy. The available therapeutic options are limited and show unsatisfactory results. They stated that further large investigative studies are needed for developing better therapeutic as well as preventive treatment strategies.

Szentmary et al (2012) noted that experimental studies have shown that PDT with higher concentrations of photosensitizers may induce necrosis and apoptosis of corneal cells and that survival of herpes simplex virus will be reduced on a LogMar scale by 4-5 lines, of Staphylococcus aureus, Pseudomonas aeruginosa or Candida albicans strains by 1-2 lines. Previous clinical studies have shown that PDT may heal bacterial or even acanthamoeba keratitis. Thus, some investigators claimed that PDT may be a potential alternative in therapy resistant infectious keratitis. However, the authors stated that the use of PDT in the treatment of infectious keratitis needs further investigation.

In a meta-analysis, Sgolastra et al (2013) examined the safety and the effectiveness of anti-microbial PDT used alone or adjunctive to scaling root planing in patients with chronic periodontitis. The meta-analysis was conducted according to the QUOROM statement and recommendations of the Cochrane Collaboration. An extensive literature search was performed on 7 databases, followed by a manual search. Weighted mean differences and 95% CI were calculated for clinical attachment level, probing depth and gingival recession. The I² test was used for inter-study heterogeneity; visual asymmetry inspection of the funnel plot, Egger's regression test and the trim-and-fill method were used to investigate publication bias. At 3 months, significant differences in clinical attachment level (p = 0.006) and probing depth reduction (p = 0.02) were observed for scaling root planing with anti-microbial PDT, while no significant differences were retrieved for anti-microbial PDT used alone; at 6 months no significant differences were observed for any investigated outcome. Neither heterogeneity nor publication bias was detected. The use of anti-microbial PDT adjunctive to conventional treatment provides short-term benefits, but microbiological outcomes are contradictory. There is no evidence of effectiveness for the use of anti-microbial PDT as alternative to scaling root planing. Long-term randomized controlled clinical trials reporting data on microbiological changes and costs are needed to support the long-term effectiveness of adjunctive anti-microbial PDT and the reliability of anti-microbial PDT as alternative treatment to scaling root planing.
Photodynamic Therapy

de Visscher et al (2013) evaluated available evidence on the use of mTHPC (Foscan®)-mediated PDT as curative and palliative treatment of head and neck squamous cell carcinoma (HNSCC). A systematic review was performed by searching 7 bibliographic databases on database specific mesh terms and free text words in the categories; "head and neck neoplasms", "Photodynamic Therapy" and "Foscan". Papers identified were assessed on several criteria by 2 independent reviewers. The search identified 566 unique papers; 12 studies were included for the review. Six studies reported PDT with curative intent and 6 studies reported PDT with palliative intent, of which 3 studies used interstitial PDT. The studies did not compare PDT to other treatments and none exceeded level 3 using the Oxford levels of evidence. Pooling of data (n = 301) was possible for 4 of the 6 studies with curative intent. T1 tumors showed higher complete response rates compared to T2 (86 % versus 63 %). PDT with palliative intent was predominantly used in patients unsuitable for further conventional treatment. After PDT, substantial tumor response and increase in quality of life was observed. Complications of PDT were mostly related to non-compliance to light restriction guidelines. The authors concluded that the studies on mTHPC-mediated PDT for HNSCC are insufficient for adequate assessment of the effectiveness for curative intent. They stated that to assess the effectiveness of PDT with curative intent, high quality comparative, randomized studies are needed. Palliative treatment with PDT seems to increase the quality of life in otherwise untreatable patients.

An UpToDate review on “Pathophysiology of chronic venous disease” (Alguire and Mathes, 2014) states that “Patients with significant venous insufficiency can develop a severe fibrosing panniculitis of the subcutaneous tissue; the clinical representation of the panniculitis is known as lipodermatosclerosis. Lipodermatosclerosis presents as an area of indurated inflammatory tissue that binds the skin down to the subcutaneous tissue. Lipodermatosclerosis is associated with abnormal, elongated, “glomerular-like” capillaries with increased vascular permeability. Dermal fibrosis may be the result of TGF-β1 fibrogenic cytokine release from activated leukocytes that have migrated out of the abnormally permeable vessels into the tissues. TGF-β1 cytokine increases the production of collagen and subcutaneous fibrosis. Capillaries are virtually absent in areas of fibrotic scars, leading to a condition known as atrophic blanche or livedoid vasculopathy. The lack of blood flow may explain the proclivity for these areas to develop ulcers. As with valvular incompetence, worsening lipodermatosclerosis may become part of a vicious cycle. As the fibrosis increases, it may become so extensive and constrictive as to girdle and strangle the lower leg, further impeding lymphatic and venous flow”.

An Institute for Clinical Systems Improvement (ICSI)’s clinical guideline on “Venous thromboembolism diagnosis and treatment” (Dupras et al, 2013) stated that “The post-thrombotic syndrome (PTS) is the most common complication of lower extremity DVT, occurring in 20 % to 50 % of patients. The syndrome is typically an under-recognized, under-diagnosed, and an under-treated condition. Clinically, the symptoms are characterized by chronic leg pain, swelling, fullness and heaviness that can have a significant impact on activities of daily living. Long- term sequelae include development of venous hypertensive ulcerations, which can be recalcitrant to standard treatment and often recurrent. Additional late physical signs include chronic lower extremity edema, hyperpigmentation,
lipodermatosclerosis and development of varicose veins. Without adequate recognition and treatment of PTS, patients may develop significant disabilities and a subsequent inability to perform daily activities of living, including gainful employment*.

Lipodermatosclerosis (liposclerosis) is usually treated with elastic compression therapy with either graded stockings or elastic bandages and fibrinolytic enhancement (e.g., the anabolic steroid stanozolol) (Kirsner et al, 1993; Miteva et al, 2010). Moreover, there is a lack of evidence regarding the effectiveness of PDT for the treatment of lipodermatosclerosis.

Brown (2012) stated that microbiologically based diseases continue to pose serious global health problems. Effective alternative treatments that are not susceptible to resistance are sorely needed, and the killing of photo-sensitized bacteria through PDT may ultimately emerge as such an option. In pre-clinical research and early in-vivo studies, PDT has demonstrated the ability to kill an assortment of microorganisms. The author stated that anti-microbial PDT has the potential to accelerate wound healing and prevent clinical infection, particularly in patients with chronic leg ulcers; larger trials are needed to confirm its early promise and suggest its ultimate role in caring for chronic wounds.

In a phase IIa randomized, placebo-controlled study, Morley et al (2013) examined if PDT in bacterially colonized chronic leg ulcers and chronic diabetic foot ulcers can reduce bacterial load, and potentially lead to accelerated wound healing. A total of 16 patients with chronic leg ulcers and 16 patients with diabetic foot ulcers (each 8 active treatment/8 placebo) were recruited into a blinded, randomized, placebo-controlled, single-treatment, phase IIa trial. All patients had ulcer duration greater than 3 months, bacterially colonized with greater than 10 colony-forming units cm. After quantitatively assessing pretreatment bacterial load via swabbing, PPA904 or placebo was applied topically to wounds for 15 mins, followed immediately by 50 J cm of red light and the wound again sampled for quantitative microbiology. The wound area was measured for up to 3 months following treatment. Treatment was well-tolerated with no reports of pain or other safety issues. In contrast to placebo, patients on active treatment showed a reduction in bacterial load immediately post-treatment (p < 0.001). After 3 months, 50 % (4 of 8) of patients with actively treated chronic leg ulcer showed complete healing, compared with 12 % (1 of 8) of patients on placebo. The authors concluded that this first controlled study of PDT in chronic wounds demonstrated significant reduction in bacterial load. They stated that an apparent trend towards wound healing was observed; further study of this aspect with larger patient numbers needed.

In a randomized, double-blind, placebo-controlled phase II study, Mannucci et al (2014) evaluated the anti-microbial effect and tolerability of a single dose of a photo-activated gel containing RLP068 in the treatment for infected foot ulcers in subjects with diabetes. This trial was performed with 3 concentrations of RLP068 (0.10, 0.30, and 0.50 %), measuring total and pathogen microbial load on Day 1 (before and 1 hr after topical gel application and photo-activation with 689 nm red light), on Days 3, 8, and 15, as add-on to systemic treatment with amoxicillin and clavulanic acid. Blood samples were also drawn 1, 2, and 48 hrs after administration for the assessment of systemic drug absorption. The trial was
performed on 62 patients aged greater than or equal to 18 years, with type 1 or type 2 diabetes and infected foot ulcer, with an area of 2 to 15 cm² and a maximum diameter less than or equal to 4.6 cm. A dose-dependent reduction in total microbial load was observed (-1.92 ± 1.21, -2.94 ± 1.60, and -3.00 ± 1.82 LogCFU/ml for 0.10, 0.30, and 0.50 % RLP068 versus -1.00 ± 1.02 LogCFU/ml with placebo) immediately after illumination, with a progressive fading of the effect during follow-up. No safety issues emerged from the analysis of adverse events. Systemic absorption of RLP068 was negligible. The authors concluded that photodynamic anti-microbial treatment with RLP068 of infected diabetic foot ulcers was well-tolerated and produced a significant reduction in germ load. Moreover, they stated that further clinical trials are needed to verify the effectiveness of this approach as add-on to systemic antibiotic treatment.

Gupta and Simpson (2012) onychomycosis is a fungal infection of the nail apparatus that affects 10 to 30 % of the global population. Current therapeutic options for onychomycosis have a low to moderate efficacy and result in a 20 to 25 % rate of relapse and reinfection. New therapeutic options are needed to broaden the spectrum of treatment options and improve the efficacy of treatment. These researchers discussed the emerging pharmacotherapeutics; including topical reformulations of terbinafine, newazole molecules for systemic and topical administration, topical benzoxaboroles and topical polymer barriers. They also discussed device-based options, which may be designed to activate a drug or to improve drug delivery, such as PDT and iontophoresis; laser device systems have also begun to receive regulatory approval for onychomycosis. The authors concluded that device-based therapeutic options for onychomycosis are expanding more rapidly than pharmacotherapy. Systemic azoles are the only class of pharmacotherapy that has shown a comparable efficacy to systemic terbinafine; however terbinafine remains the gold standard. The most notable new topical drugs are tavaborole, efinaconazole and luliconazole, which belong to the benzoxaborole and azole classes of drugs. Moreover, they stated that PDT, iontophoresis and laser therapy have shown positive initial results, but RCTs are needed to determine the long-term success of these devices.

Becker and Bershow (2013) noted that oral anti-fungal medications are currently the gold standard of care for onychomycosis, but treatment failure is common and oral therapy is contraindicated in many cases. There is a need for effective treatment without the systemic complications posted by oral therapy. Laser and PDT may have the potential to treat onychomycosis locally without adverse systemic effects; some small studies have even reported achieving clinical and mycologic cure. However, the authors stated that there is reason for restraint since these therapies are expensive and time-consuming and have not been proven effective with RCTs.

Huggett et al (2014) stated that patients with pancreatic cancer have a poor prognosis apart from the few suitable for surgery. Photodynamic therapy produces localized tissue necrosis but previous studies using the photo-sensitizer meso-tetrahydroxyphenylchlorin (mTHPC) caused prolonged skin photosensitivity. In a phase I/II clinical trial, these researchers assessed a shorter acting photo-sensitizer, verteporfin. A total of 15 inoperable patients with locally advanced cancers were sensitized with 0.4 mg/kg verteporfin. After 60 to 90 mins, laser light (690 nm) was delivered via single (13 patients) or multiple (2 patients)
fibers positioned percutaneously under computed tomography (CT) guidance, the
light dose escalating (initially 5 J, doubling after each 3 patients) until 12 mm of
necrosis was achieved consistently. In all, 12 mm lesions were seen consistently
at 40 J, but with considerable variation in necrosis volume (mean volume 3.5 cm³
at 40 J). Minor, self-limiting extra-pancreatic effects were seen in multi-fiber
patients. No adverse interactions were seen in patients given chemotherapy or
radiotherapy before or after PDT. After PDT, 1 patient underwent an R0 Whipple’s
pancreatoduodenectomy. The authors concluded that verteporfin PDT-induced
tumor necrosis in locally advanced pancreatic cancer is feasible and safe. These
findings need to be further studied in phase III clinical trials.

Moreover, the National Comprehensive Cancer Network's clinical practice
guideline on “Pancreatic adenocarcinoma” (Version 1.2014) does not mention the
use of PDT as a therapeutic option.

Almutawa et al (2015) stated that localized phototherapy including topical psoralen
plus ultraviolet A (PUVA) and targeted ultraviolet B (UVB), and PDT have been
increasingly used in the treatment of localized psoriasis. Yet, there are no
systematic reviews or meta-analyses that scientifically evaluated the pooled
effectiveness of these treatments in psoriasis. These investigators searched
Medline, Embase, and Cochrane databases during the period of January 1980 to
June 2012. Their systematic search resulted in 765 studies, 23 of them were
included in the review. The primary outcome was 75 % reduction in severity score
from baseline. A meta-analysis using random effect model found topical PUVA to
be more effective than non-laser targeted UVB [odds ratio: 3.48 (95 % CI: 0.56 to
21.84), p = 0.183]. The pooled effect estimate of the effectiveness (75 % reduction
in severity score) of topical PUVA, targeted UVB, and PDT were as follows: 77 %
topical PUVA, 61 % (targeted UVB), and 22 % (PDT). The authors concluded
that topical PUVA and targeted UVB phototherapy are very effective in the
treatment of localized psoriasis. Topical PUVA seems more effective than non-
laser targeted UVB phototherapy. On the other hand, PDT has low effectiveness
and high percentage of side effects in treating localized psoriasis.

Furthermore, an UpToDate review on “Treatment of psoriasis” (Feldman, 2014)
does not mention the use of PDT as a therapeutic option.

Calabro et al (2013) stated that the combination of the possibility of ablation of
lesion with an excellence aesthetic result has allowed the PDT an increasing role
in the treatment of skin diseases that range from skin cancer to cosmetic
treatment. Particular attention is paid in the last years to a developing area of
research, the anti-fungal PDT. The growing resistance against anti-fungal drugs
has renewed the search for alternative therapies and PDT seems to be a potential
candidate.

Fan and colleagues (1996) stated that pre-malignant changes in the mouth, which
are often widespread, are frequently excised or vaporized, whereas cancers are
treated by excision or radiotherapy, both of which have cumulative morbidity.
Photodynamic therapy is another option that produces local tissue necrosis with
light after prior administration of a photosensitizing agent. These researchers
described the use of PDT with the photosensitizing agent 5-ALA for pre-malignant
and malignant lesions of the mouth. A total of 18 patients with histologically
proven pre-malignant and malignant lesions of the mouth were sensitized with 60
mg/kg ALA by mouth and treated with laser light at 628 nanometers (100 or 200 Joules/cm²). The results were assessed macroscopically and microscopically. Biopsies were taken immediately prior to PDT for fluorescence studies, a few days after PDT to assess the depth of necrosis, when healing was complete, and up to 88 weeks later. The depth of necrosis varied from 0.1 to 1.3 mm, but complete epithelial necrosis was present in all cases. All 12 patients with dysplasia showed improvement (repeat biopsy was normal or less dysplastic) and the treated areas healed without scarring. Some benefit was observed in 5 of 6 patients with squamous cell carcinoma, but only 2 became tumor free (1 with persistent mild dysplasia). No patient had cutaneous photosensitivity for longer than 2 days. The authors concluded that PDT produced consistent epithelial necrosis with excellent healing and is a simple and effective way to manage these patients. Results in invasive cancers are less satisfactory, mainly because the PDT effect is too superficial with current treatment regimens using ALA as the photosensitizing agent.

Rigual et al (2013) evaluated safety of 3-(1'-hexyloxyethyl)pyropheophorbide-a (HPPH) PDT (HPPH-PDT) for dysplasia and early HNSCC. Secondary objectives were the assessment of treatment response and reporters for an effective PDT reaction. Patients with histologically proven oral dysplasia, carcinoma in-situ, or early-stage HNSCC were enrolled in 2 sequentially conducted dose escalation studies with an expanded cohort at the highest dose level. These studies used an HPPH dose of 4 mg/m² and light doses from 50 to 140 J/cm². Pathologic tumor responses were assessed at 3 months. Clinical follow-up ranged from 5 to 40 months. Photodynamic therapy induced cross-linking of STAT3 were assessed as potential indicators of PDT effective reaction. A total of 40 patients received HPPH-PDT. Common adverse events were pain and treatment site edema. Biopsy proven complete response rates were 46 % for dysplasia and carcinoma in-situ and 82 % for SCC lesions at 140 J/cm². The responses in the carcinoma in-situ/dysplasia cohort are not durable. The PDT-induced STAT3 cross-links was significantly higher (p = 0.0033) in SCC than in carcinoma in-situ/dysplasia for all light doses. The authors concluded that HPPH-PDT is safe for the treatment of carcinoma in-situ/dysplasia and early-stage cancer of the oral cavity. Early-stage oral HNSCC seems to respond better to HPPH-PDT in comparison with premalignant lesions.

The findings from these small studies need to be validated by well-designed studies.

In a Cochrane review, Lieder et al (2014) evaluated the effects of PDT in the management of RRP in children and adults. These investigators searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; Cambridge Scientific Abstracts; ICTR and additional sources for published and unpublished trials. The date of the search was January 27, 2014. Randomized controlled trials utilizing PDT as sole or adjuvant therapy in participants of any age with proven RRP versus control intervention were selected for analysis. Primary outcome measures were symptom improvement (respiratory distress/dyspnea and voice quality), quality of life improvement and recurrence-free interval. Secondary outcomes included reduction in the frequency of surgical intervention, reduction in disease volume and adverse effects of treatment.
These researchers used the standard methodological procedures expected by The Cochrane Collaboration. Meta-analysis was not possible and results were presented descriptively. These investigators included 1 trial with a total of 23 participants. This study was at high risk of bias. None of the primary outcomes and only 1 of the secondary outcomes (reduction in volume of disease, assessed endoscopically) was measured in the study. There was no significant difference between the groups (very low-quality evidence). Adverse effects reported included airway swelling requiring intubation in a child with severe RRP a few hours after PDT. The authors concluded that there was insufficient evidence from high-quality RCTs to determine whether PDT altered the course of disease or provided an added benefit to surgery in patients with RRP. Moreover, they stated that multi-center RCTs with appropriate sample sizes and long-term follow-up are needed to examine if PDT is of benefit. Outcomes such as improvement in symptoms (respiratory function and voice quality) and quality of life should be measured in future trials.

Yazdani Abyaneh et al (2015) noted that actinic cheilitis (AC) is a pre-malignant lesion of the lips that can progress to squamous cell carcinoma and metastasize. Actinic cheilitis is difficult to treat because surgical treatments have significant adverse effects whereas less invasive procedures have uncertain efficacy. Photodynamic therapy may offer a noninvasive yet effective treatment option for AC. These investigators reviewed the safety and effectiveness of PDT for AC. The terms "photodynamic," "actinic," "solar," "cheilitis," and "cheilosis" were used in combinations to search the PubMed database. Studies we considered for inclusion based on eligibility criteria, and specific data were extracted from all studies. The authors identified 15 eligible case series encompassing a total of 242 treated subjects. Among studies that evaluated subjects for complete clinical response, 139 of 223 subjects (62 %) showed complete response at final follow-ups ranging from 3 to 30 months. Among studies that evaluated subjects for histological outcome, 57 of 121 subjects (47 %) demonstrated histological cure at final follow-ups ranging from 1.5 to 18 months. Cosmetic outcomes were good to excellent in the majority of subjects, and adverse events were well-tolerated. The authors concluded that PDT is safe and has the potential to clinically and histologically treat AC, with a need for future RCTs.

In a retrospective, case-series study, Lim and colleagues (2014) evaluated the visual and anatomic outcomes of central serous chorioretinopathy (CSC) after verteporfin PDT. Members of the Macula Society were surveyed to retrospectively collect data on PDT treatment for CSC. Patient demographic information, PDT treatment parameters, fluorescein angiographic information, optical coherence tomography (OCT) metrics, pre- and post-treatment visual acuity (VA), and adverse outcomes were collected online using standardized forms. Main outcome measures were VAs over time and presence or absence of sub-retinal fluid (SRF). Data were submitted on 265 eyes of 237 patients with CSC with a mean age of 52 (standard deviation [± 11]) years; 61 were women (26 %). Mean baseline logarithm of the minimum angle of resolution (logMAR) VA was 0.39 ± 0.36 (20/50). Baseline VAs were greater than or equal to 20/32 in 115 eyes (43 %), 20/40 to 20/80 in 97 eyes (37 %), and less than or equal to 20/100 in 47 eyes (18 %). Normal fluence was used for PDT treatment in 130 treatments (49 %), half-fluence was used in 128 treatments (48 %), and very low fluence or missing information was used in 7 treatments (3 %). The number of PDT treatments was 1
Post-PDT follow-up ranged from 1 month to more than 1 year. Post-PDT VA was correlated with baseline VA ($r = 0.70, p < 0.001$). Visual acuity improved greater than or equal to 3 lines in less than 1%, 29%, and 48% of eyes with baseline VA greater than or equal to 20/32, 20/40 to 20/80, and less than or equal to 20/100, respectively. Sub-retinal fluid resolved in 81% by the last post-PDT visit. There was no difference in the response to PDT when analyzed by age, race, fluence setting, fluorescein angiography (FA) leakage type, corticosteroid exposure, or fluid location (sub-retinal or pigment epithelial detachment; all $p > 0.01$). Complications were rare -- retinal pigment epithelial atrophy was seen in 4% of patients, and acute severe visual decrease was seen in 1.5% of patients. The authors concluded that PDT was associated with improved VA and resolution of SRF; adverse side effects were rare. The main drawback of this study was its retrospective nature; there was no control group. There may also be selection bias. These investigators stated that data from large, appropriately controlled and bias-free studies are needed to fully define the best treatment regimen, treatment response rates, visual efficacy, and side effects of this promising therapy.

Erikitola et al (2014) assessed the current literature on the safety and effectiveness of PDT as a treatment option for CSC. A total of 7 databases (PubMed, CENTRAL, MEDLINE, Web of Science, Embase, Scopus, and The Cochrane Database of Systematic Reviews) were searched without restrictions on time or location. These researchers followed PRISMA guidelines and evaluated quality according to STROBE criteria. In total, 117 citations were identified and 31 studies describing 787 eyes were included for review. Data on indications for PDT in CSC, dosing regimens of verteporfin PDT (which includes treatment dose of verteporfin, treatment time, fluence, and spot size), number of treatment sessions, response to treatment, mean length of follow-up, and complications were extracted and analyzed. Since the introduction of PDT for the treatment of CSC in 2003, there have been 3 RCTs, 1 for acute and 2 chronic CSCR and 28 further studies that met the STROBE criteria that compared the use of PDT with other treatment options. All studies showed short-term effectiveness of PDT in CSC. The studies were of small sample size and lacked sufficient follow-up to draw conclusions on long-term safety and effectiveness. The authors concluded that there is sufficient scientific evidence to suggest that PDT may be a useful treatment option for chronic CSC in the short-term. They stated that the review identified a need for robust RCTs with longer follow-up to ascertain the role of PDT as a useful treatment option for CSC.

Ma and colleagues (2014) evaluated the effect of PDT on CSC compared with laser therapy and intra-vitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs, and determined the maximum treatment effect with minimal dose and fluence of PDT. These researchers performed a systematic electronic search in February 2013 in PubMed, Embase, ISI Web of Knowledge and the Cochrane library. The main outcome factors were compared in best-corrected visual acuity (BCVA), central macular thickness (CMT) and resolution of SRF. Meta-analysis was performed when it is appropriate. The comparisons were designed into 4 groups: (i) PDT versus laser photocoagulation; (ii) PDT versus intra-vitreal injection of anti-VEGF drugs; (iii) half-dose verteporfin PDT versus placebo; and (iv) half-fluence PDT versus full-fluence PDT. These investigators retrieved 9 reports of studies including a total of 319 patients. In group (i), the
summary result indicated that PDT was superior in resolution of SRF (p = 0.005) than laser photocoagulation. In group (ii), PDT could resolve SRF (p = 0.007) and decrease CMT (p = 0.002) more rapidly than intra-vitreal injection of anti-VEGF drugs. In group (iii), half-dose PDT was effective in improving BCVA (p < 0.00001), decreasing CMT (p = 0.001) and resolving SRF (p < 0.001). In group (iv), half-fluence PDT was effective and could significantly decrease the hypoxic damage which was caused by PDT (p < 0.001). The authors concluded that PDT is a promising therapy for CSC patients and the parameters of PDT can be adjusted to obtain the maximum treatment effect with minimal adverse effects.

Tao et al (2014) noted that the current treatment of cervical intraepithelial neoplasia (CIN) is primarily based on surgical excision using laser, a loop electrosurgical procedure, or a cold knife technique. Unfortunately, these treatments often lead to obstetrical problems during the subsequent pregnancy, particularly in young women. Photodynamic therapy offers a minimally invasive alternative. These researchers assessed the safety and effectiveness of PDT in the treatment of CIN. Following Cochrane guidelines, a comprehensive systematic review of all clinical studies and reports examining the use of PDT for CIN was conducted. Study quality was assessed using the Oxford Levels of Evidence Scale. The 14 studies included 2 RCTs, 1 case-control study, and 11 case series. Among the 506 patients studied, 472 were included to study the effectiveness of PDT on CIN and 10 were lost to follow-up. An assessment of clinical effectiveness included the response of the lesion to treatment (may include lesion recurrence) reported by all 14 studies. The complete response rate (CRR) of PDT on CIN ranged from 0 % to 100 %. HPV eradication rate (HER) was reported in 7 studies, with rates ranging from 53.4 % to 80.0 %. The authors concluded that PDT is a safe and tolerable treatment for CIN. They stated that evidence regarding the effectiveness of PDT for CIN is conflicting, which may, in part, be explained by the limited number of controlled comparative clinical trials.

Hillemanns et al (2014) examined the safety and effectiveness of hexaminolevulinate (HAL) PDT, a novel therapy for women with CIN1/2; and defined the appropriate population and end-points for a phase III program. This was a double-blind, randomized, placebo-controlled, dose-finding study that included a total of 262 women with biopsy-confirmed CIN1/2 based on local pathology. Patients received 1 or 2 topical treatments of HAL hydrochloride 0.2 %, 1 %, 5 %, and placebo ointment and were evaluated for response after 3 to 6 months based on biopsy, Papanicolaou test, and oncogenic HPV test. All efficacy analyses were performed on blinded central histology review to avoid inter-reader variability. Adverse events, blood biochemistry, and vital signs were assessed after 3 months. There were no statistically significant differences between placebo and either the CIN1 or combined CIN1/2 populations. A clear dose effect with a statistically significant response in the HAL 5 % group of 95 % (18/19 patients) compared to 57 % (12/21 patients) in the placebo group (p < 0.001) was observed at 3 months in women with CIN2, including an encouraging 83 % (5/6 patients) clearance of HPV 16/18 compared to 33 % (2/6 patients) in the placebo group at 6 months. The treatment was easy to use and well accepted by patients and gynecologists. Only local self-limiting adverse reactions including discharge, discomfort, and spotting were reported. The authors concluded that HAL PDT is a novel therapy that showed promise in the treatment of CIN2 including clearance of oncogenic HPV, but not of CIN1. They stated that positive risk/benefit balance
makes HAL PDT a tissue-preserving alternative in women of childbearing age who wish to preserve the cervix; however confirmatory studies are planned.

An UpToDate review on “Cervical intraepithelial neoplasia: Treatment and follow-up” (Wright, 2015) states that “Other treatments -- Several alternative methods for treatment of CIN have been developed, all of which are currently investigational. Such techniques include photodynamic therapy, cyclooxygenase-2 inhibitors, vaccines, environmental alterations, use of topical agents (e.g., cidofovir, difluoromethylornithine, all-trans retinoic acid), and oral agents”.

Furthermore, the National Comprehensive Cancer Network (NCCN)’s clinical practice guideline on “Cervical cancer” (Version 2.2015) does not mention PDT as a therapeutic option.

Friedberg et al (2011) noted that PDT is a light-based cancer treatment that acts to a depth of several millimeters into tissue. This study reviewed the results of patients who underwent a macroscopic complete resection, by 2 different surgical techniques, and intra-operative PDT as a treatment for malignant pleural mesothelioma. From 2004 to 2008, 28 patients with malignant pleural mesothelioma underwent macroscopic complete resection, 14 by modified extrapleural pneumonectomy (MEPP) and 14 by radical pleurectomy (RP) and intra-operative PDT. The surgical technique evolved over this period such that 13 of the last 16 patients underwent lung-sparing procedures, even in the setting of large-bulk tumors. Demographics in the MEPP and RP cohorts were similar in age, sex, stage, nodal status, histology, and adjuvant treatments. Stage III/IV disease was present in 12 of 14 patients (86 %), with 50 % or more with +N2 disease. The median overall survival (OS) for the MEPP group was 8.4 months, but has not yet been reached for the RP group at a median follow-up of 2.1 years. The authors concluded that in addition to the inherent advantages of sparing the lung, RP plus PDT yielded a superior OS than MEPP plus PDT in this series. The OS for the RP plus PDT group was, for unclear reasons, superior to results reported in many surgical series, especially for a cohort with such advanced disease. Given these results, the authors believed RP plus PDT is a reasonable option for appropriate patients pursuing a surgical treatment for malignant pleural mesothelioma and that this procedure can serve as the backbone of surgically based multi-modal treatments. The major drawbacks of this study were its small sample size, its retrospective, non-randomized nature. Furthermore, adjuvant treatments were not standardized. All patients received PDT, so it was not possible to define or isolate the role of PDT in these results. The authors noted that “Given that our study was limited enough that it should be considered suggestive, rather than conclusive …. Further exploring the immunologic effect of PDT in this setting, and exploring ways to capitalize on it, are subjects of ongoing investigations in our institution”.

Friedberg et al (2012) reviewed their experience using RP and intra-operative PDT for mesothelioma. A total of 38 patients (aged 42 to 81 years) underwent RP-PDT; 35 of 38 (92 %) patients also received systemic therapy. Standard statistical techniques were used for analysis. Thirty seven of 38 (97 %) patients had stage III/IV cancer (according to the American Joint Committee on Cancer [AJCC manual 7th Edition, 2010]) and 7/38 (18 %) patients had non-epithelial subtypes. Macroscopic complete resection was achieved in 37/38 (97 %) patients; there was
1 post-operative mortality (stroke). At a median follow-up of 34.4 months, the median survival was 31.7 months for all 38 patients, 41.2 months for the 31/38 (82%) patients with epithelial subtypes, and 6.8 months for the 7/38 (18%) patients with non-epithelial subtypes. Median progression-free survival (PFS) was 9.6, 15.1, and 4.8 months, respectively. The median survival and PFS for the 20/31 (64%) patients with N2 epithelial disease were 31.7 and 15.1 months, respectively. The authors concluded that it was possible to achieve a macroscopic complete resection using lung-sparing surgery in 97% of these patients with stage III/IV disease. The survival observed with this approach was unusually long for the patients with the epithelial subtype but, interestingly, the PFS was not. The reason for this prolonged survival despite recurrence is not clear, but is potentially related to preservation of the lung or some PDT-induced effect, or both. These researchers stated that the results of this lung-sparing approach are safe, encouraging, and warrant further investigation.

An UpToDate review on “Systemic treatment for unresectable malignant pleural mesothelioma” (Tsao and Vogelzang, 2015) does not mention photodynamic therapy as a therapeutic option. An UpToDate review on “Management of localized malignant pleural mesothelioma” (Pass et al, 2015) states that “Randomized trials — There are no adequately powered randomized trials that have defined the benefit of combining surgery using an MCR [macroscopic complete resection] with chemotherapy and RT in patients with localized MPM .... As a result of this trial, and the interest in lung preservation in mesothelioma, a randomized trial comparing radical pleurectomy with photodynamic therapy and postoperative chemotherapy to radical pleurectomy with postoperative chemotherapy will be initiated at University of Pennsylvania (NCT02153229). In Europe, plans for a comparison of preoperative versus postoperative chemotherapy with lung sparing surgery for mesothelioma are being formulated”.

Furthermore, the NCCN’s clinical practice guideline on “Malignant pleural mesothelioma” (Version 1.2015) states that “Intraoperative adjuvant therapy, such as heated chemotherapy or photodynamic therapy, is still under investigation but may be considered as part of a reasonable multidisciplinary approach to this locally aggressive disease”.

CPT Codes / HCPCS Codes / ICD-9 Codes

Photodynamic therapy with light-activated porfimer sodium (Photofrin):

CPT codes covered if selection criteria are met:

+ 96570 Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and esophagus)

+ 96571 Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); each additional 15 minutes (list separately in addition to code
for endoscopy or bronchoscopy procedures of lung and esophagus)

**Other CPT codes related to the CPB:**

31641 Bronchoscopy (rigid or flexible); with destruction of tumor or relief of stenosis by any method other than excision (e.g., laser therapy, cryotherapy)

43229 Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)

43270 Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)

43278 Endoscopic retrograde cholangiopancreatography (ERCP); with ablation of tumor(s), polyp(s), or other lesion(s), including pre- and post-dilation and guide wire passage, when performed

**HCPCS codes covered if selection criteria are met:**

J9600 Porfimer sodium, 75 mg

**ICD-9 codes covered if selection criteria are met:**

150.0 - 150.9 Esophageal cancer [obstructing]

162.0 - 162.9 Lung cancer [microinvasive endobrachial non-small cell] [obstructing]

230.1 Esophageal cancer in situ [Barrett's]

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

173.0 - 173.99 Other malignant neoplasm of skin

185 Malignant neoplasm of prostate

198.82 Secondary malignant neoplasm of genital organs [prostate]

232.0 - 232.9 Carcinoma in situ of skin [cutaneous lesions of Bowen's disease]

233.4 Carcinoma in situ of prostate

702.0 Actinic keratosis [refractory]

**Other ICD-9 codes related to the CPB:**

530.85 Barrett's esophagus
Photodynamic Therapy

Photodynamic therapy using photosensitizers:

CPT codes covered if selection criteria are met:

96567  Photodynamic therapy by external application of light to destroy pre-malignant and/or malignant lesions of the skin and adjacent mucosa (e.g., lip) by activation of photosensitive drug(s) each phototherapy exposure session

HCPCS codes covered if selection criteria are met:

J7308  Aminolevulinic acid HCL for topical administration, 20%, single unit dosage form (354 mg)

J7309  Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 gram

ICD-9 codes covered if selection criteria are met:

173.01, Basal cell carcinoma
173.11,
173.21,
173.31,
173.41,
173.51,
173.61,
173.71,
173.81,
173.91

232.0 - 232.9  Carcinoma in situ of skin [cutaneous lesions of Bowen's disease]

702.0  Actinic keratosis [refractory]

ICD-9 codes not covered for indications listed in the CPB:

140.0 - 149.9  Malignant neoplasm of lip, oral cavity and pharynx [squamous cell carcinoma]

151.0 - 151.9  Malignant neoplasm of stomach

153.0 - 153.9  Malignant neoplasm of colon

157.0 - 157.9  Malignant neoplasm of pancreas

160.0 - 161.9  Malignant neoplasm of nasal cavities, middle ear, accessory sinuses and larynx [squamous cell carcinoma]

172.0 - 172.9  Malignant melanoma of skin

174.0 - 175.9  Malignant neoplasm of breast
Photodynamic Therapy

195.0  Malignant neoplasm of head, face, and neck [squamous cell carcinoma]

Other ICD-9 codes related to the CPB:

198.2  Other ICD-9 codes related to the CPB:

Photodynamic therapy as an adjunct to stenting for palliation of inoperable cholangiocarcinoma:

Other CPT codes related to the CPB:

43272  Endoscopic retrograde cholangiopancreatography (ERCP); with ablation of tumor(s), polyt(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique

ICD-9 codes covered if selection criteria are met:

155.0 - 155.1  Malignant neoplasm of liver and intrahepatic bile ducts [cholangiocarcinoma]

Photodynamic therapy for non-cancer indications:

CPT codes not covered for indications listed in the CPB:

96567  Photodynamic therapy by external application of light to destroy pre-malignant and/or malignant lesions of the skin and adjacent mucosa (e.g., lip) by activation of photosensitive drug(s) each phototherapy exposure session

96570  Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and esophagus)

+ 96571  Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); each additional 15 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and esophagus)

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

078.11  Condyloma acuminatum [condyloma NOS] [genital warts NOS]

078.12  Plantar wart

110.0, 110.3, 110.4  Dermatophytosis of scalp and beard, groin and perianal area and foot [superficial mycosis]

110.1  Dermatophytosis of nail
111.0  Pityriasis versicolor [superficial mycosis]
212.3  Benign neoplasm of bronchus and lung
216.3  Benign neoplasm of skin of other and unspecified parts of face
362.10 - 362.12  Other background retinopathy and retinal vascular changes
                [radiation retinopathy]
370.00 - 370.9  Keratitis
522.4  Acute apical periodontitis of pulpal origin
522.6  Chronic apical periodontitis
523.30 - 523.33  Aggressive and acute periodontitis
523.40 - 523.42  Chronic periodontitis
523.45  Periodontosis
523.8  Other specified periodontal disease
523.9  Unspecified gingival and periodontal disease
692.75  Disseminated superficial actinic porokeratosis
695.3  Rosacea
695.89  Other specified erythematous conditions [Nekam's disease]
696.1  Other psoriasis
705.83  Hidradenitis
706.1  Other acne
706.8 - 706.9  Other and unspecified disease of sebaceous glands
707.00 - 707.9  Chronic ulcer of skin
729.39  Panniculitis of other sites [liposclerosis (lipodermatosclerosis)]
757.39  Other specified anomalies of skin [Darier's disease (keratosis follicularis)]
990  Effects of radiation, unspecified [radiation retinopathy]

The above policy is based on the following references:


3. F-D-C Reports, Inc. Estimated FDA user fee review goals for pending NDAs/PLAs: Photofrin. F-D-C Reports Pharmaceutical Approvals Monthly. 1998 Dec 1; 3(8).


82. Alguire PC, Mathes BM. Pathophysiology of chronic venous disease. UpToDate Inc., Waltham, MA. Last reviewed February 2014.


94. Wright JD. Cervical intraepithelial neoplasia: Treatment and follow-up. UpToDate Inc. Waltham, MA. Last reviewed January 2015.


