General Principles of Photodynamic Therapy (PDT) and Gastrointestinal Applications

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Abstract: The purpose of this review article is to describe the history of photodynamic therapy (PDT), its current medical applications, the mechanism of action, contraindications of the method, and different types of photosensitizers used. The second part of the article deals with applications for gastrointestinal diseases. The treatment of obstructing oesophageal cancer, early-stage oesophageal cancer, Barrett`s esophagus, hilar cholangiocarcinoma, stomach-, colon- and pancreatic cancer are discussed. The final part focuses on future directions of PDT like certain innovative ideas, which are currently under investigation.

INTRODUCTION

History of Photodynamic Therapy (PDT) and Applications

In 1900 Oscar Raab, a German medical student, discovered that the combination of the chemical acridine and light at certain wavelengths was lethal to *Paramecium caudatum*, a certain infusoria species [1]. Three years later, H. von Tappeiner and A. Jesionek treated skin tumours with eosin and white light [2]. In 1904 they described their observation as "photodynamic action". Seven years later, W. Hausmann discovered the outstanding photodynamic effect of hematoporphyrin, an iron-deficient derivative of hem. He induced cell death with hematoporphyrin and light in red blood cells and paramecium and, in addition, reported skin reactions in mice after treatment with this combination [3]. F. Meyer-Betz, another German scientist, was the first to inject 200 mg of hematoporphyrin into his own vein in 1912. He experienced pain and swelling of the skin after light exposure [4]. In 1942, Auler and Banzer discovered tumour selectivity of porphyrins by porphyrin fluorescence in tumour tissue of rats after systemic application. Then, in 1955 Samuel Schwartz developed hematoporphyrin derivative (HPD) by acetylation and reduction of hematoporphyrin, which was found to be twice as phototoxic as hematoporphyrin [5]. R. Lipson and E. J. Baldes at the Mayo Clinic were the first to use this new compound for photodetection of tumours in 1960 [6]. It took another twelve years until I. Diamond was able to show the phototoxicity of HPD against gliomas *in vivo* and *in vitro* [7]. In 1961, T. Dougherty treated the first patients with skin tumours [8] and J.F. Kelly treated the first patients with bladder cancer successfully [9]. Other groups continued and extended their investigations [10-21]. Following this success, Y. Hayata demonstrated the effectiveness of PDT in obstructing lung tumours [22], which was confirmed by other groups who treated also early-stage lung cancer [23-33]. In 1984, J.S. McCaughan extended the procedure to patients with oesophageal cancer [34]. Patients with gynaecological tumours [35-38], including breast cancer [39-42], intraocular tumours [43-45], brain tumours [46-53], head and neck tumours [54-56], oral cavity tumours [57-59], intraperitoneal tumours [60, 61], mesothelioma [62-64], prostate cancer [65], cholangiocarcinoma [66-70], gastric carcinoma [71-74], colorectal cancer [75-80], and pancreatic cancer [81] were subsequently treated with PDT. Finally, the use of PDT has been extended to non-oncologic indications, such as Barrett's esophagus [82-84], psoriasis [85, 86], laryngeal papillomatosis [87, 88], actinic keratosis [89-94], and age-related macular degeneration [95-102]. In 1993, the purified HPD Photofrin^{R} (porfimer sodium) was first officially approved in Canada for the treatment of bladder cancer, followed by the U.S. Food and Drug Administration (FDA) and numerous other health agencies throughout the world. Then, FDA extended the license to obstructive oesophageal cancer and Barrett's esophagus, in addition to early stage and advanced lung cancer. In August 2002, Photosan^{R}, another HPD derivative has gained approval in Europe. In the meantime, Levulan^{R} (5-aminolevulanic acid; ALA) has been approved for the treatment of actinic keratosis and Vertiporfin (benzoporphyrin derivative; BPD) for age-related macular degeneration in the USA. Certain other so-called "second generation photosensitizers" as discussed below are now under way for approval in the USA and Europe.

PRINCIPLES OF PHOTODYNAMIC THERAPY

Mechanism of Action

PDT is based on the administration of a photosensitizer, which localises selectively within the target, mostly tumour tissue. The mechanisms by which this localisation occurs are complex and not fully understood. High vascular permeability of the agents, as well as their affinity for proliferating endothelium and the lack of lymphatic drainage in tumours may contribute to an accumulation in tumours [103]. Moreover, tumours might have increased lipid content, elevated numbers of low-density lipoprotein receptors, abnormal vasculature, and decreased pH. In a second step, non-thermal laser light of a specific wavelength is applied, adapted to the

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absorption spectrum of the sensitizer to be excited. Following the absorption of light the compound is transformed into a relatively long-lived electronically excited state via a short-lived excited singlet state [104]. This so called triplet state can undergo two kinds of reaction. In a Type I reaction, it can react directly with a substrate, such as the cell membrane or a molecule, and transfer a hydrogen atom or electron to form radicals. The radicals interact with oxygen to produce oxygenated products. Alternatively, in a Type II reaction, which is more common, the triplet can transfer its energy directly to oxygen to generate singlet oxygen (Fig. (**1**)). Therefore, the effects of both PDT reaction types are oxygen dependent. Tumour destruction, mediated by oxygenated products and singlet oxygen, can be explained by several mechanisms causing necrosis and apoptosis. First, PDT kills tumour cells directly [105], secondly it damages the tumour-associated vasculature, leading to tumour infarction [106], and finally can activate an immune response against tumour cells [104]. In detail, singlet oxygen degenerates lipids in cell membranes (cytoplasma and mitochondria), increases prostaglandin E2 level, causes haematin clumps, stases in blood vessels, stop of neo-angiogenesis, and directly releases cytochrome C from mitochondria. The extend of photodamage and cytotoxicity is multifactorial and depends on the type of photosensitizer used, its localisation and administered dose, the light source used, generating the light exposure dose and light fluence rate, the oxygen availability in the target, and finally the time interval between the administration of the photosensitizer and the light treatment. Because PDT is a cold photochemical process, there is no tissue heating, and connective tissues such as collagen and elastin are largely unaffected.

Contraindications

PDT should not be performed in patients with acute porphyria, poor kidney or liver function (creatinine > 3 mg/dL, international normalised ratio of prothrombin time [INR] > 2.2), encasement or thrombosis of the main blood vessels, leucopoenia (leucocytes < 2000/cmm), thrombocy-topenia (< 50, 000/cmm), and terminal tumour stage.

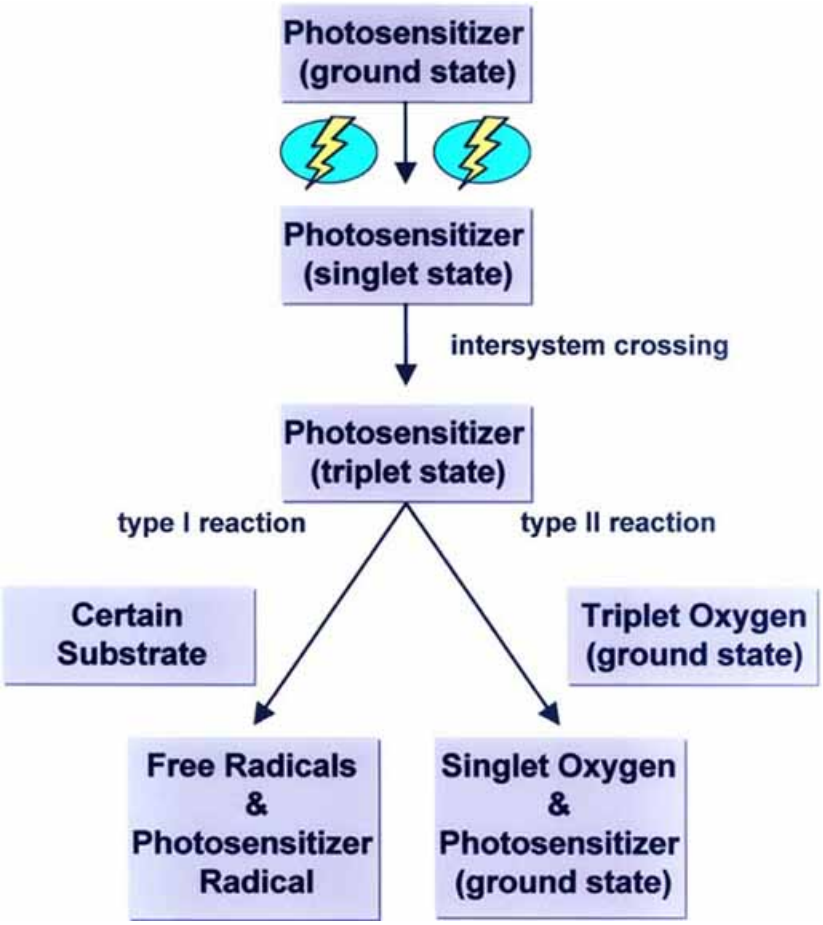

Fig. (1). The main photochemical reactions after porphyrin photoactivation. In both reactions the ground state photosensitizer is excited by the absorption of light to a higher short-lived excited singlet state, followed by the intersystem crossing to a long-lived triplet state. One reaction involves then the generation of free radicals (type I photochemical reaction) and in the other singlet oxygen is generated (type II photochemical reaction).

Photosensitizers

The ideal photosensitizer a) should be chemically pure and of known specific composition, b) should have a high quantum yield for singlet oxygen production, c) should have a strong absorption with high extinction coefficient ε at longer wavelength (red) region preferably between 700-800nm, and d) should have an excellent photochemical reactivity. It also e) should possess minimal dark toxicity and f) only be toxic in the presence of light, g) should have preferable retention by target tissue (tumour cells), h) should be rapidly excreted from the body, and finally i) should be synthesisable from easy available precursors and should be stable and easy to dissolve in the body's tissue fluids and be capable of formulation. Starting from the development of the first generation porphyrin based photosensitizers, HPD and the purified hematoporphyrin derivatives Photofrin^{R}, Photosan^{R}, and Photoheme^{R} (Table **1**), a second generation of photosentizers has been developed and is now under trial. The first group consists of the porphyrin, chlorin and bacteriochlorin derivatives. Boronated protoporphyrin [107], isohematoporphyrin, tetrasulfonated meso-tetraphenyl porphyrin (H_2TPPS_4) [108], 5, 10, 15, 20-tetrakis (4-sulphonato-phenyl)-21, 23-dichalcogenaporphyrin [109], *o*-, *m*- and *p*-isomers of tetra(hydroxyphenyl)-porphyrin [110], picket fence porphyrins [111], monoaspartyl chlorin e_6 (MACE, Npe_6) [112], diaspartyl chlorin e_6 (DACE) [113], chlorin p_6 lysyl derivative [114], hexylether derivative of pyropheophorbide (HPPH) [115], benzoporphyrin derivatives (BPD) [116], ring A-reduced monoacid benzoporphyrin derivative (BPDMA, Vertiporfin, Visudyne^{R}) [117], Sn etiopurpurin ($SnEt_2$, Rostaporphin, Purlytin^{R}) [118], *meso*-tetra (hydroxyphenyl) chlorins [H_2(THPC)] (Temoporfin, Foscan^{R}) [119], bacteriochlorin [120], and 5-aminolevulinic acid (ALA, Levulan^{R}) [121] are their representatives (Table **1**). ALA is already marketed and accepted by FDA for the treatment of actinic keratosis. Phase III trials for Vertiporfin in the treatment of cutaneous non-melanoma skin cancer and age related macula degeneration, and for Temoporfin for head and neck cancer and upper aero-digestive tract cancers are presently performed. The second group consists of photosensitizers based on isomeric porphyrins, like porphycene [122], corrphycene [123], isoporphycene [124], hemiporphycene [125], N-confused porphyrin [126], doubly N-confused porphyrin [127], and porphycene ATMPn (9-acetoxy-2, 7, 12, 17-tetrakis-(β-methoxy-ethyl)-porphycene) [128]. The third group are phthalocyanine and naphthalocyanine based photosensitizers, like zinc phthalocyanine CGP 55847 [129], sulphonated aluminium phthalocyanine (Photosense) [130] and naphthalocyanines [131] (Table **1**). The fourth group consists of cationic photosensitizers, like Pt (II) complex of bis (N, N-dimethylaminomethyl) deuteroporphyrin IX dimethyl ester [132], copper iminium salt of octaethylbenzochlorin [133], and unsymmetrically substituted benzonaphthopyrazines [134] (Table **1**). Other potential candidates are expanded porphyrin based photosensitizers. Their representatives are sapphyrin [135], vinylogous porphyrins, texaphyrins [136] (e.g. gadolinium (III) texaphyrin (XCYTRIN^{R}) or Lutetium (III) texaphyrin (LUTRIN^{R})), and core-modified expanded porphyrins [137] (e.g. ammonium salt of 5, 10, 15, 20-tetrakis (*meso*-p-sulfonato phenyl)-25, 27, 29-trithia sapphyrin) (Table **1**).

APPLICATIONS IN GASTROINTESTINAL DISEASES

Obstructing Oesophageal Cancer

Patients with advanced oesophageal cancers often present with dysphagia, ranging from the inability to swallow food to difficulty managing their own secretions. Tumours that are unresectable, unresponsive to chemotherapy or radiation, or have recurred almost all require palliative therapy to help manage symptoms. Several studies have been performed demonstrating that PDT is effective in the palliation of dysphagia. In a prospective phase II study by Luketich *et al*. [138] Photofrin-mediated PDT had been used in 77 patients with inoperable obstructive disease (64 adenocarcinoma, 13 squamous cell carcinoma). Photofrin (1.5 to 2.0 mg/kg) was administered, followed 48 hours later by treatment with 630 nm laser light. 90.8% of patients showed a significant improvement in the mean dysphagia score at 4 weeks post-PDT. PDT adequately controlled bleeding in six patients, the mean dysphagia-free interval was 80 days and the median survival 5.9 months (Table **2**). Another study included 40 patients with oesophageal tumours (19 adenocarcinomas, 19 squamous carcinomas, and two melanomas) in whom conventional treatments were unsuccessful [139]. At one month after PDT, the average minimal diameter opening of 28 accessible tumours increased from 6 to 9 mm and 35 patients improved in food intake from a liquid to a soft diet. Average survival time was 7.7 months for adenocarcinoma and 5.8 months for squamous carcinoma (Table **2**).

An alternative method for palliation of obstructing oesophageal tumours is Nd:YAK laser therapy. However, a major limitation is the need for frequent treatments. Two randomised trials have compared Photofrin-mediated PDT with Nd:YAK laser therapy. In the first trial [140] 32 patients with dysphagia caused by biopsy-proven oesophageal malignancy were treated with PDT and 20 patients with Nd:YAK laser treatment. Among randomised patients, both PDT and Nd:YAK therapy relieved dysphagia, but PDT resulted in improved Karnovsky performance status at 1 month and longer duration of response (Table **2**). In the second prospective multicentre trial [141], 110 patients with advanced oesophageal cancer were randomised to PDT and 108 to Nd:YAK. Improvement in dysphagia was equivalent between two treatment groups. Objective tumour response was also equivalent at week 1, but at month 1 was 32% after PDT and 20% after Nd:YAK ($p<0.05$). Nine complete tumour responses occurred after PDT and two after Nd:YAK. Trends for improved responses for PDT were seen in tumours located in the upper and lower third of the esophagus, in long tumours, and in patients who had prior therapy. Perforations from laser treatments or associated dilations occurred after PDT in 1%, Nd:YAK 7% ($p<0.05$). Termination of laser sessions due to adverse events occurred in 3% with PDT and in 19% with Nd:YAK ($p<0.05$) (Table **2**).

A newer prospective single-centre study compared 84 consecutive patients with advanced (group A) oesophageal cancer who were treated with Photofrin-PDT with a historical control group comprising over 1100 patients who were treated with different modalities like dilatation plus external beam radiotherapy, gastrostomy plus external beam radiotherapy, intubation/stent, bypass operation and laser plus brachytherapy [142]. Additional 18 PDT-patients with

Table 1. Types of Photosensitizers

Sensitizer	Trade name	Potential Indications	Activation wavelength (nm)
A. First Generation Photosensitizers			
Purified HPD	Photofrin^{R}, Photosan^{R}, and Photoheme^{R}	Head-, neck-, tracheobronchial, gynaecological, oesophageal, bladder, brain, gastric, bile duct cancer, skin basalioma, Barrett`s oesophagus, Psoriasis, papilloma virus	630
B. Second Generation Photosensitizers			
B.1. Porphyrin, Chlorin and Bacteriochlorin Derivatives			
Boronated protoporphyrin	BOPP	Brain tumours	630
Monoaspartyl chlorin e_6, (Npe_6)	MACE	Skin cancer	654
Ring A-reduced monoacid benzoporphyrin derivative (BPDMA, Vertiporfin)	Visudyne	Non-melanoma skin cancer, AMD, rheumatoid arthritis, bone marrow purging, Barett`s oesophagus, psoriasis	689
Sn etiopurpurin ($SnEt_2$, Rostaporfin)	Purlytin	Metastatic breast cancer, Kaposi`s sarcoma, prostatic cancer, brain, lung, skin, head and neck cancer, AMD	663
Meso-tetra (hydroxyphenyl) chlorins [H_2(THPC)] (Temoporfin)	Foscan	Head and neck, upper aerodigestive tract cancers, gastric and prostate cancer	652
5-aminolevulinic acid (ALA)	Levulan	AK, BCC and SCC, head and neck and gynaecological tumours, Barrett`s esophagus, gastrointestinal tumours Photodetection of bladder cancer, oesophageal cancer, gastrointestinal cancer	635 410
5-ALA-methylesther	Metvix	BCC, AK	635
5-ALA-benzylesther	Benzvix	Gastrointestinal cancer	635
Hexylether derivative of pyropheophorbide (HPPH)	Photochlor	BCC	665
B.2. Phthalocyanine and Naphthalocyanine Based Photosensitizers			
Zinc phthalocyanine	CGP 55847	SCC	670
Sulphonated aluminium phthalocyanine	Photosense	Skin, breast, lung, bladder, pancreatic, brain, gastrointestinal cancers	670
B.3. Expanded Porphyrin Based Photosensitizers			
Gadolinium (III) texaphyrin	XCYTRIN	Brain metastases	700-780
Lutetium (III) texaphyrin	LUTRIN, ANTRIN, OPTRIN	Breast, cervical, prostate and rain tumours, angioplasty, AMD	732

AK, actinic keratosis; AMD, age related macula degeneration; BCC, basal cell carcinoma; SCC, squamous cell carcinomas

early stage cancer (group E) were compared with curative surgery. There was no mortality with PDT. All patients expressed satisfaction to the treatment. Post PDT complications consisted of photosensitivity skin reaction in 5 patients (5%) and oesophageal stricture in 8 (8%) patients. PDT was at least as good as other treatments in group A, with a slight advantage in patients with cervical oesophageal cancer. In early cases (group E), PDT appeared capable of replicating surgical results in selected cases (Table **2**). If PDT is combined with brachyradiotherapy (BRT) the benefit can be even higher for patients as shown in a study by Maier *et al*. [139], which compared BRT alone (n=75) with a combination of PDT followed by BRT (n=44). In some patients of both groups external beam radiation was delivered after the initial treatment. PDT produced a significant difference in relieving tumour stenosis and improving dysphagia score. A drawback was the occurrence of four oesophagorespiratory tract fistulas, one perforation and one haemmorhage with combination therapy in patients with T4 tumours (Table **2**).

Finally, another clinical situation in which PDT has been shown to be effective is in patients with oesophageal cancer who have tumour ingrowth after placement of expandable stents [143].

In summary, PDT is a safe and efficient method for the treatment of obstructing oesophageal cancer by relieving dysphagia in selected patients, however still has not become a first line procedure for the majority of patients. Additional randomised studies are required to compare PDT with stent insertion, radiotherapy, and radiochemotherapy, the current standard methods, which are most commonly used for palliation. Patients with tumours that have eroded into the tracheobronchial tree or a major vessel, patients with oesophageal varices, and patients who have received prior external beam and high dose brachytherapy probably should be excluded from PDT because of the risk for major complications [144].

Early-stage Oesophageal Cancer and Barrett's Oesophagus

PDT has been investigated as a treatment for superficial cancers of the esophagus. A retrospective study by Sibille *et al*. [145] analysed the effect of Photofrin-PDT in 123 patients with tumours 0.5-4 cm in diameter (104 squamous cell carcinoma, 19 adenocarcinoma; 116 T1 and 7 T2 stage) who were ineligible for surgery based on patient's history or refusal of surgery. In 56 patients PDT was applied alone, in the other 67 patients PDT was part of a multimodal therapeutic protocol including radiation and/or chemotherapy. A complete tumour response at 6 months was obtained in 99 of 114 patients (87%), in 87.5% in patients with squamous cell carcinoma, and in 89% in patients with adenocarcinoma. Re-treatment after recurrence was successful in 83% and 62.5%, respectively. The 5-year survival rate was 25% for all patients, 21% in squamous cell and 46% in adenocarcinoma. It was higher in patients receiving PDT alone than those with multimodality treatment (28% vs. 20%). Cutaneous photosensitization occurred in 16 patients but was not severe. Oesophageal stenosis requiring at least one session of dilation was a common consequence of PDT-induced sequential necrosis, occurring in 43 patients (Table **2**). Another pilot study reported the use of PDT in 21 cases of superficial oesophageal cancer [146]. Radiation therapy was used as a salvage treatment for those patients who did not respond to PDT. Interestingly, a complete response was achieved in 11 of 21 patients (Table **2**). Savary *et al*. [147] treated 31 patients with early squamous cell carcinomas (Tis or T1a) and cured 84% of the patients after a mean follow-up period of 2 years. Nine patients were treated with hematoporphyrin derivative, eight with Photofrin II and 14 with m-THPC, with the last one being the most efficient photosensitizer. Unfortunately, two oesophageal strictures and two tracheo-esophgaeal fistulas occurred post-treatment. The authors suggested that these complications could be avoided by using a low-penetrating wavelength of laser light and by using a 180 degrees or 240 degrees windowed cylindrical light distributor (Table **2**). Finally, another group from Italy investigated PDT-therapy in a group of 62 patients [148]. 18 patients (29.5%) had in situ carcinoma (Tis), 30 (48.5%) had T1-stage cancer, 7 (11%) had T2-stage cancer, and 7 (11%) had recurrent disease in the anastomotic area after previous surgery without evidence of invasion outside the lumen. Patients with residual disease after two rounds of PDT received definitive radiotherapy. The complete response rate (CR) was 37% (23 of 62) in patients who received PDT alone and 82% (51 of 62) in those who also received radiotherapy. The CR rate after PDT alone was statistically higher ($p = 0.04$) for patients who had Tis/T1 lesions (21 of 48; 44%) than for those with T2-stage disease (2 of 7; 28%) or recurrent tumours (0 of 7; 0%). Fifty-two percent of patients who had CR following PDT alone did not suffer local tumour recurrence. The median local progression-free survival times after PDT and additional radiotherapy (in cases with incomplete response) was 49 months for Tis- and T1-stage lesions, 30 months for those with T2-stage disease, and 14 months for patients with locally recurrent disease. Patients who completely responded to PDT had a median overall survival of 50 months, which was significantly longer ($p < 0.003$) than that of patients not responding to PDT. Toxicity was minimal with three cases of oesophageal stenosis (7%) and one case of tracheo-oesophageal fistula (2.5%) after combined PDT and radiotherapy.

Barrett's esophagus is the development of intestinal-type metaplasia in the esophagus and is associated with gastro-intestinal reflux disease. Dysplasia may arise in the setting of Barrett's esophagus and can lead to the development of carcinoma. Surgical resection is the current standard treatment approach for patients with high-grade dysplasia. Given the potential for morbidity associated with esophagectomy, the development of less invasive treatment such as PDT is warranted. Several studies have been published that investigated the efficacy of PDT in the treatment of Barrett's dysplasia and early Barrett's carcinoma. Tan *et al*. [149] treated 12 patients with oesophageal adenocarcinoma arising from Barrett's metaplasia with ALA (60 and 75 mg/kg body weight). PDT was performed using laser light (630 nm) delivered via a cylindrical diffuser 4-6 h after the first dose of ALA. The patients received one to four sessions of PDT. One patient with carcinoma-*in-situ* had the tumour eradicated after one treatment with no recurrence at 28 months. Another patient with a small T1 tumour required four ALA/PDT treatments, and died of other disease after 36 months. There was no evidence of recurrence. The tumour bulk in the other carcinomas was not significantly reduced (Table **2**). Overholt *et al*. [83] treated 100 patients including 13 with superficial cancers with Photofrin-PDT. Nd:YAG laser was required to ablate small residual areas of Barrett's mucosa during-long-term follow-up. Patients were maintained on omeprazole and were followed for 4 to 84 months (mean 19 months). Conversion of approximately 75% to 80% of treated Barrett's mucosa to normal squamous epithelium was found in all patients; complete elimination of Barrett's mucosa was noted in 43 patients. Dysplasia was eliminated in 78 patients. Dysplasia developed during follow-up in 11 of 48 patients in untreated Barrett's mucosa requiring additional therapy. Ten of the 13 malignancies were ablated. Oesophageal strictures occurred in 34%. Use of longer centring balloons reduced the incidence of strictures (Table **2**). The first randomised controlled trial of PDT for Barrett's oesophagus randomised 36 patients with dysplastic Barrett's oesophagus receiving acid suppression medication with omeprazole to receive oral 5-aminolaevulinic acid (ALA) 30 mg/kg or placebo,

Table 2. Selected Clinical Trials- Gastrointestinal PDT Applications

Study Type	Patients	Patient Response		Improvements	Conclusions	Ref.
		Response	Survival			
A. Obstructing Oesophageal Cancer						
prospective, phase II	PDT (n=77)		median 5.9 months	dysphagia improved significantly in 90.8% of patients	PDT is safe and effective for the palliation of obstructing and bleeding oesophageal cancer	[138]
prospective, phase II	PDT (n=40)		average 7.7 months for adenocarcinoma and 5.8 months for squamous carcinoma	improvement in food intake in 35 patients at one month	PDT is safe and improves quality of life by excellent palliation of dysphagia	[194]
randomised, phase III, PDT *vs*. Nd:YAG	PDT (n=32) *vs*. Nd:YAG (n=20)	2 CR with PDT 1 CR with Nd:YAK	median 145 days (PDT) and 128 days (Nd:YAK)	Karnovsky performance status improved significantly with PDT	PDT relieves oesophageal obstruction with longer duration of response	[140]
prospective, multicenter, randomized, PDT *vs*. Nd:YAG	PDT (n=110) *vs*. Nd:YAG (n=108)	9 CR with PDT 2 CR with Nd:YAK	median 123 days (PDT) and 140 days (Nd:YAK)	equivalent dysphagia improvement, fewer adverse events with PDT	PDT has overall efficacy of Nd:YAK for palliation of dysphagia in oesophageal cancer, and equal or better objective response rate	[141]
prospective, phase II, group A = advanced cancer, group E = early cancer	PDT (n=102) *vs*. historical multimodality group (n>1100)	PR in all, 6 CR (group A) and 18 CR (group E)	median 9.5 months (group A) and 60.5 months (group E)	significant symptom and dysphagia grade improvement in group A	No mortalitiy with PDT, 5% photosensitivity, 8% strictures; PDT is at least as good as other treatments	[142]
prospective, nonrandomised, phase II	PDT plus RBT (n=44) *vs*. RBT (n=75)		mean overall survival 7.7 months	PDT plus RBT improved tumour stenosis and dysphagia score	PDT is an effective palliative tool but proper patient selection is needed	[139]
B. Early-stage Oesophageal Cancer and Barrett`s Oesophagus						
retrospective, phase II	PDT (n=56) PDT plus CT/RT (n=67)	CR 99/114 (87%) CR 87.5% in squamous cell and 83% of retreated patients CR 89% in adenocarcinoma and 62.5% of retreated patient	5 year survival 25% for all patients, 21% in squamous cell, and 46% in adenocarcinoma, 28% for PDT alone, 20% for mulitmodality treatment		PDT is an effective treatment in patients with small oesophageal tumours who pose high surgical risk	[145]
prospective, phase II	PDT (n=21), RT for salvage	CR 11/21 (52%)			high rate of complete response was achieved with PDT	[146]
prospective, phase II	PDT (n=31)	84% cure after 2 years			PDT eradicates early squamous cell carcinomas efficiently	[147]
prospective, phase II	PDT (n=23) and PDT plus RT (n=39)	CR 37% for PDT alone and 82% for PDT plus RT	median local progression free survival 49 months after PDT plus RT (Tis- and T1-stage)		PDT is an effective regimen for early oesophageal cancer; additional RT in cases of incomplete response to PDT is effective and potentially curative	[148]

(Table 2) contd….

Study Type	Patients	Patient Response		Improvements	Conclusions	Ref.
		Response	Survival			
B. Early-stage Oesophageal Cancer and Barrett`s Oesophagus						
prospective, phase II	PDT (n=12)	CR 2/12 (17%)			ALA/PDT has a potential for the eradication of small tumours but careful patient selection is needed	[149]
prospective, phase II	PDT (n=100), Nd:YAK laser for residual areas of Barrett`s mucosa	43/83 (52%) complete elimination of Barrett`s mucosa, CR 10/13 (77%) for superficial cancers		conversion of 75-80% of treated Barrett`s mucosa to normal squamous epithelium	PDT ± Nd:YAK laser thermal ablation is an effective endoscopic therapy, but 34% oesophageal strictures occurred	[83]
prospective, randomized, double blind, phase II	PDT (n=18) *vs*. placebo (n=18)	16/18 (89%) *vs*. 2/18 (11%) response ($p<0.001$)		no dysplasia in the columnar epithelium within PDT treatment area	ALA induced PDT provides safe and effective ablation of low grade dysplastic epithelium	[150]
prospective, phase II	PDT (n=27)	CR 9/9 (100%) high grade dysplasias, CR 10/19 (53%) early carcinoma		no method related morbiclity and mortality	5-ALA-PDT can completely ablate severe dysplasia and superficial mucosa carcinoma	[151]
prospective, phase II	PDT (n=14)	CR 7/7 (100%) low grade dysplasia, 21% complete ablation of Barrett`s metaplasia after 1st treatment		low post-endoscopic pain and photosensitivity reactions	topical ALA administration is safe and well tolerated, but Barrett´s oesophagus is not consistently eradicated	[152]
C. Hilar Cholangiocarcinoma						
prospective, phase II	PDT (n=9) after unsuccessful bile duct endoprosthesis		median 439 days	cholestasis and quality of life improved significantly	PDT is effective in restoring bilary drainage and improving quality of life, survival seems to be prolonged	[66]
prospective, phase II	PDT (n=23) plus bile duct endoprostheses		6 month survival 91%	improvement in cholestasis, performance, quality of life	PDT can prevent tumour occlusion of hilar bile ducts with apparent benefit in survival time	[67]
randomized, phase III, PDT plus bile duct endoprostheses *vs*. bile duct endoprostheses only	PDT plus endoprostheses (n=20) *vs*. endoprostheses (n=19)		median 493 days *vs*. median 98 days ($P < 0.0001$)	improvement in cholestasis was significantly higher with PDT in combination with endoprostheses	survival was significantly longer with PDT in combination with endoprostheses	[163]
prospective, phase II	PDT (n=24) followed by metal stent insertion *vs*. historic control group with biliary drainage (n=20)		median 9.9 months for PDT group and 5.6 months for control group	significant decrease in bilirubin, stability of quality of life	PDT with consecutive metal stent insertion is feasible with a small benefit in survival	[70]
prospective, phase II	PDT (n=7) prior to surgery		1 year recurrence free survival 83%		neoadjuvant PDT for hilar CC is a low risk procedure with efficient selective tumour destruction	[69]

CC, cholangiocarcinoma; CR, complete response; CT, chemotherapy; PR, partial response; RBT, radiobrachytherapy; RT, radiotherapy

followed four hours later by laser endoscopy [150]. Of 18 patients in the ALA group, a response was seen in 16. In the placebo group, a decrease in the area of 10% was observed in two patients with no change in 16. No dysplasia was seen in the columnar epithelium within the treatment area of any patient in the PDT group. However, in the placebo group, persistent low-grade dysplasia was found in 12 patients ($p<0.001$). There were no short or long term major side effects. The effects of the treatment were maintained for up to 24 months (Table **2**). Finally, two smaller studies by Gossner *et al*. [151] and Ortner *et al*. [152] report on their experiences with PDT in 27 patients (nine with histologically proven high grade dysplasia and 19 with early carcinoma of the esophagus) and 14 patients (seven with low-grade dysplasia), respectively. In the first study, approximately 4-6 hours after oral ingestion of 5-ALA in a dosage of 60 mg/kg of body weight, laser light irradiation was conducted with a dye laser system with a wavelength of 635 nanometers at a light dose of 150 J/cm. High grade dysplasia was eradicated in all patients. In addition, 19 mucosal tumours in 18 patients were treated successfully in 10 of 19 cases with an average of 1.7 treatment sessions and a mean follow-up of 16.9 months (range, 3-37 months). Method-related morbidity and mortality were not observed. In the second study, patients underwent endoscopic treatment with topical delta-ALA and photoactivation (wavelength, 632 nm) was performed at 1.5 - 2 hours after drug administration using an argon dye laser. Re-treatment with high-dose topical delta-ALA was offered to the 11 patients with remaining metaplasia and was carried out in five of them. Low-grade dysplasia was eradicated in all patients. One patient with no dysplasia before PDT developed a high-grade dysplasia after PDT. Complete ablation of Barrett's metaplasia was observed in 21 % of the patients after the first treatment session and in 20 % after the second treatment session. Post-endoscopic pain and photosensitivity reactions were less frequent with low-dose delta-ALA PDT than with high-dose PDT.

In summary, photodynamic therapy alone or with Nd:YAG laser thermal ablation combined with long-term acid inhibition is cost-effective [153] and provides an effective endoscopic therapy to eliminate Barrett's mucosal dysplasia and superficial oesophageal cancer and reduce the extent of and, in some cases, eliminate Barrett's mucosa. However, the high occurrence rate of up to 30% of post-treatment oesophageal strictures, which cannot be lowered by oral steroids [154], is a problem that very often requires endoscopic dilation and/or bouginage. Besides this, genetic abnormalities may persist after PDT despite phenotypical improvement of dysplasia [155], a phenomenon that has also been described for argon plasma coagulation method [156]. Finally, with the occurrence of endoscopic mucosectomy within the last years, a new technique that is associated with a 5-year survival rate similar to that of surgery (over 80%), PDT is currently more and more abandoned. Mucosectomy improves accessibility to representative histological tissue sections including assessment of the submucosal layer, has a low rate of side effects, and frequently can be accomplished in a single treatment session [157-160]. However, a niche for PDT as first line therapy may be the treatment of multifocal high-grade dysplasia Barrett's oesophagus and early oesophageal cancer in patients with absolute contraindications for surgery and/or radio-/radiochemotherapy.

Hilar Cholangiocarcinoma

Interest in using PDT for palliative treatment of advanced non-resectable bile duct carcinoma has been given rise to by a case report, documenting the success of PDT performed via percutaneous cholangioscopy in a single patient with incompletely resected bile duct carcinoma [161]. This type of treatment caused a prolonged survival time of more than four years in a tumour entity with a median survival of only 4 to 6 months. The first prospective non-randomised single-arm study included nine patients with advanced Bismuth type III and IV hilar cholangiocarcinoma (CC), who showed no sufficient drainage after endoscopic stent insertion [66]. Two days after intravenous application of Photofrin^{R} at 2 mg/kg body weight, intraluminal photoactivation was performed cholangioscopically. After PDT, biliruin serum levels declined significantly with no increase during the two monthly follow-ups. Quality of life indices improved dramatically and remained stable. Thirty-day mortality was 0%, and median survival 439 days (Table **2**). Our own study including 23 patients (Bismuth type III, n=2; type IV; n=21) who were treated with a combination of bile duct stenting and Photofrin-PDT, showed a 91% 6 months survival rate after diagnosis with a median local tumour response of 74, 54, 29, and 67% after the first, second, third, and fourth PDT session [67]. Cholestasis, performance, and quality of life of the patients improved clearly. Cholangitis rate with PDT was not higher than in historical control patients with Bismuth type III tumours and bile duct drainage, only. After a five-year follow-up, median survival time after diagnosis was 18 months for patients without peritoneal carcinosis (n=19) and 12 months for all patients (n=23). Survival was 63, 26, 16, and 5% after one, two, three, and four years, respectively [162] (Table **2**). In a retrospective analysis from 1994 to 2003 including a total of 124 non-resectable patients with hilar CC of our hospital, 56 patients who were treated with endoprosthesis alone and 68 patients who were treated with a combination of PDT and endoprosthesis, PDT was significantly superior in terms of median survival ($p<0.05$) (data not published). A prospective, randomised multicentre study, including our hospital, confirmed this result. Patients with histologically proven cholangiocarcinoma fulfilling inclusion criteria were randomised to group A (stenting and subsequent PDT) and group B (stenting alone). For PDT, Photofrin 2 mg/kg body wt was injected intravenously 2 days before intraluminal photoactivation (wavelength, 630 nm; light dose, 180 J/cm^2). Further treatments were performed in cases of residual tumour in the bile duct. The primary outcome parameter was survival time. Secondary outcome parameters were cholestasis and quality of life. PDT resulted in prolongation of survival (group A: n = 20, median 493 days; group B: n = 19, median 98 days; $P < 0.0001$). It also improved biliary drainage and quality of life. The study was terminated prematurely because PDT proved to be so superior to simple stenting treatment that further randomisation was deemed unethical. It was remarkable that an additional group of 31 patients who were excluded from randomisation especially because of a statistically significant lower Karnovsky performance status, but received PDT

treatment voluntarily, performed as well as the randomised PDT group (Table **2**) [163]. Another phase II study investigated PDT and consecutive metal stent insertion for palliation of hilar CC [70]. It was feasible but there was only a modest benefit in overall survival in comparison to a historical control group (Table **2**).

A new approach might be the use of PDT for the treatment of hilar cholangiocarcinoma in a neoadjuvant setting, because of the high tumour recurrence rate of up to 76% after curative (R0) resection. Having accomplished a successful treatment in a single case [68], we investigated the use of PDT prior to tumour resection in 6 patients and in one patient prior to liver transplantation in a small pilot study [69]. In all patients, R0 resection was achieved. Four patients developed minor surgical complications, even though the bilioenteric anastomoses were sewn to PDT-treated bile ducts. No viable tumour cells were found in the inner 4mm layer of the surgical specimens. The PDT-pretreated epithelium of the tumour-free proximal resection margins exhibited only minimal inflammatory infiltration. The 1-year recurrence free survival rate was 83% (Table **2**).

Finally, a small study investigated the use of 5-aminolevulinic acid for the palliative treatment of hilar CC. Light activation was performed 5 to 7 hours after oral administration of 5-ALA. All patients had an endoprosthesis placed in the bile duct after PDT. However, 4 weeks after PDT, 5-ALA had failed to significantly reduce malignant bile duct obstruction and thus cannot be recommended for the palliative treatment of bile duct cancer [164].

In summary, palliative PDT for non-resectable hilar CC is effective in restoring biliary drainage and improving quality of life, survival seems to be prolonged, thus PDT has become a standard treatment. In contrast, neoadjuvant PDT for hilar CC is a new approach that needs further evaluation.

Stomach-, Colon- and Pancreatic Cancer

A few studies have been published describing the use of PDT in the treatment of stomach-, colon- and pancreatic cancer. Patrice *et al*. [73] report the treatment of 54 patients with inoperable gastrointestinal neoplasms, amongst them were 14 patients with adenocarcinoma of the stomach or lower third of the esophagus. Complete local tumour destruction and negative histology were observed in 24 of 54 cases. Eleven patients with biopsy-proven early gastric cancer were treated with Photofrin^{R} by a Japanese group [72] and 22 patients with mTHPC by a German group [71]. Both groups concluded that PDT represents a safe and efficient method, but the current indication is mainly the treatment of high-risk patients. PDT has also been investigated for therapy of massive advanced rectal cancer [78], for patients with colorectal cancer unsuitable for operation [75], in combination with endoscopic polypectomy [77], and for patients with recurrent or residual colorectal cancer in the pelvis [76]. Both, clinical and radiological responses could be demonstrated. PDT was even effective for therapy of colosigmoid villous adenomas that had previously been incompletely treated with Nd-YAK laser therapy [79]. Finally, Bown *et al*. [81] report a phase I study of photodynamic therapy for cancer of the pancreas. Sixteen patients with inoperable adenocarcinomas localised in the region of the head of the pancreas were studied. Patients were photosensitized with 0.15 mg/kg mTHPC intravenously and three days later exposed to laser light. All patients had substantial tumour necrosis on scans after the treatment. There was no treatment related mortality and median survival time was 9.5 months. Seven of 16 patients (44%) were alive one year after PDT.

In summary, a few studies describe the efficacy of PDT in the treatment of stomach-, colon- and pancreatic cancer which has to be confirmed in larger trials and compared with other procedures like mucosectomy for the therapy of early gastric cancer [165] and colorectal stent insertion for preoperative decompression and for palliation of cancerous large-bowel obstruction [166].

DIRECTIONS FOR THE FUTURE

In addition to the development of new photosensitizers and new light applicators, certain innovative ideas are currently under investigation. For instance, fractionated drug-dose PDT regimens were reported to result in a superior therapeutic effect, compared to single-dose regimens, and were able to induce long-term tumour growth control [167]. Moreover, the use of specific targeting carriers, such as conjugated antibodies directed to tumour-associated antigens or vascular antigens are supposed to direct the photosensitizer to a certain cell type or compartment [168-175]. Others suggest the use of different advanced delivery systems, such as liposomes [176, 177], ligand-based targeting with insulin [178, 179], epidermal growth factor [180] or adenoviral proteins [181], protease-mediated drug delivery [182], photosensitizing adenoviruses [183], water-soluble polymer carriers [184-190], and pH-responsive polymeric micelles [191, 192]. A completely different approach is the protection of normal tissue with drugs like WR-2721 and WR-77913 [193] from possible PDT side effects if the photosensitizer is used in a high dose.

REFERENCES

[1] Raab, O. (1900) *Zeitung Biol.*, **39**, 524-526.
[2] von Tappeiner, H. and Jesionek, A. (1903) *Muench. Med. Wochenschrift*, **47**, 2042-2044.
[3] Hausmann, W. (1911) *Biochem. Zeitung*, **30**, 276-316.
[4] Meyer-Betz, F. (1913) *Dtsch. Arch. Klin.*, **112**, 476-503.
[5] Schwartz, S.K., Abolon, K. and Vermund, H. (1955) *Univ. Minn. Med. Bull*., **27**, 7-8.
[6] Lipson, R.L. and Baldes, E.J. (1960) *Arch. Dermatol*., **82**, 508-516.
[7] Diamond, I., Granelli, S.G., McDonagh, A.F., Nielsen, S., Wilson, C.B. and Jaenicke, R. (1972) *Lancet*, **2**, 1175-7.
[8] Dougherty, T.J., Grindey, G.B., Fiel, R., Weishaupt, K.R. and Boyle, D.G. (1975) *J. Natl. Cancer Inst*., **55**, 115-21.
[9] Kelly, J.F., Snell, M.E. and Berenbaum, M.C. (1975) *Br. J. Cancer*, **31**, 237-44.
[10] Zeitouni, N.C., Oseroff, A.R. and Shieh, S. (2003) *Mol. Immunol.*, **39**, 1133-6.
[11] Allison, R.R., Mang, T.S. and Wilson, B.D. (1998) *Semin. Cutan. Med. Surg.*, **17**, 153-63.
[12] Taber, S.W., Fingar, V.H., Coots, C.T. and Wieman, T.J. (1998) *Clin. Cancer Res.*, **4**, 2741-6.
[13] Nseyo, U.O., Shumaker, B., Klein, E.A. and Sutherland, K. (1998) *J. Urol.*, **160**, 39-44.
[14] Uchibayashi, T., Koshida, K., Kunimi, K. and Hisazumi, H. (1995) *Br. J. Cancer*, **71**, 625-8.
[15] Kriegmair, M., Baumgartner, R., Lumper, W., Waidelich, R. and Hofstetter, A. (1996) *Br. J. Urol.*, **77**, 667-71.

[16] Wilson, B.D., Mang, T.S., Stoll, H., Jones, C., Cooper, M. and Dougherty, T.J. (1992) *Arch. Dermatol.,* **128**, 1597-601.

[17] Fijan, S., Honigsmann, H. and Ortel, B. (1995) *Br. J. Dermatol.*, **133**, 282-8.

[18] Cairnduff, F., Stringer, M.R., Hudson, E.J., Ash, D.V. and Brown, S.B. (1994) *Br. J. Cancer,* **69**, 605-8.

[19] Kubler, A.C., Haase, T., Staff, C., Kahle, B., Rheinwald, M. and Muhling, J. (1999) *Lasers Surg. Med.,* **25**, 60-8.

[20] Nseyo, U.O., DeHaven, J., Dougherty, T.J., Potter, W.R., Merrill, D.L., Lundahl, S.L. and Lamm, D.L. (1998) *J. Clin. Laser. Med. Surg.,* **16**, 61-8.

[21] Benson, R.C., Jr. (1986) *Mayo Clin. Proc.,* **61**, 859-64.

[22] Hayata, Y., Kato, H., Konaka, C., Ono, J. and Takizawa, N. (1982) *Chest,* **81**, 269-77.

[23] Furuse, K., Fukuoka, M., Kato, H., Horai, T., Kubota, K., Kodama, N., Kusunoki, Y., Takifuji, N., Okunaka, T., Konaka, C., Wada, H. and Hayata, Y. (1993) *J. Clin. Oncol.,* **11**, 1852-7.

[24] Moghissi, K. and Dixon, K. (2003) *Eur. Respir.,* J **22**, 535-41.

[25] Moghissi, K., Dixon, K., Stringer, M., Freeman, T., Thorpe, A. and Brown, S. (1999) *Eur. J. Cardiothorac. Surg.,* **15**, 1-6.

[26] Cortese, D.A., Edell, E.S. and Kinsey, J.H. (1997) *Mayo. Clin. Proc.,* **72**, 595-602.

[27] Diaz-Jimenez, J.P., Martinez-Ballarin, J.E., Llunell, A., Farrero, E., Rodriguez, A. and Castro, M.J. (1999) *Eur. Respir. J.,* **14**, 800-5.

[28] Kato, H., Okunaka, T. and Shimatani, H. (1996) *J. Clin. Laser Med. Surg.,* **14**, 235-8.

[29] Edell, E.S. and Cortese, D.A. (1987) *Mayo Clin. Proc.,* **62**, 8-14.

[30] Kato, H. (1998) *J. Photochem. Photobiol.,* B **42**, 96-9.

[31] McCaughan, J.S., Jr. and Williams, T.E. (1997) *J. Thorac. Cardiovasc. Surg.,* **114**, 940-6; discussion 946-7.

[32] Lam, S., Kostashuk, E.C., Coy, E.P., Laukkanen, E., LeRiche, J.C., Mueller, H.A. and Szasz, I.J. (1987) *Photochem. Photobiol.,* **46**, 893-7.

[33] Imamura, S., Kusunoki, Y., Takifuji, N., Kudo, S., Matsui, K., Masuda, N., Takada, M., Negoro, S., Ryu, S. and Fukuoka, M. (1994) *Cancer*, **73**, 1608-14.

[34] McCaughan, J.S., Jr., Hicks, W., Laufman, L., May, E. and Roach, R. (1984) *Cancer*, **54**, 2905-10.

[35] Ward, B.G., Forbes, I.J., Cowled, P.A., McEvoy, M.M. and Cox, L.W. (1982) *Am. J. Obstet. Gynecol.,* **142**, 356-7.

[36] Hornung, R. (2001) *Curr. Drug Targets Immune. Endocr. Metabol. Disord.,* **1**, 165-77.

[37] Fehr, M.K., Hornung, R., Schwarz, V.A., Simeon, R., Haller, U. and Wyss, P. (2001) *Gynecol. Oncol.,* **80**, 62-6.

[38] Corti, L., Mazzarotto, R., Belfontali, S., De Luca, C., Baiocchi, C., Boso, C. and Calzavara, F. (1996) *J. Photochem. Photobiol.,* B **36**, 193-7.

[39] Dougherty, T.J., Lawrence, G., Kaufman, J.H., Boyle, D., Weishaupt, K.R. and Goldfarb, A. (1979) *J. Natl. Cancer Inst.,* **62**, 231-7.

[40] Mang, T.S., Allison, R., Hewson, G., Snider, W. and Moskowitz, R. (1998) *Cancer J. Sci. Am.,* **4**, 378-84.

[41] Dimofte, A., Zhu, T.C., Hahn, S.M. and Lustig, R.A. (2002) *Lasers Surg. Med.,* **31**, 305-12.

[42] Sperduto, P.W., DeLaney, T.F., Thomas, G., Smith, P., Dachowski, L.J., Russo, A., Bonner, R. and Glatstein, E. (1991) *Int. J. Radiat. Oncol. Biol. Phys.,* **21**, 441-6.

[43] Gomer, C.J., Doiron, D.R., Jester, J.V., Szirth, B.C. and Murphree, A.L. (1983) *Cancer Res.,* **43**, 721-7.

[44] Favilla, I., Favilla, M.L., Gosbell, A.D., Barry, W.R., Ellims, P., Hill, J.S. and Byrne, J.R. (1995) *Melanoma. Res.,* **5**, 355-64.

[45] Landau, I.M., Steen, B. and Seregard, S. (2002) *Acta. Ophthalmol. Scand.,* **80**, 531-6.

[46] Friesen, S.A., Hjortland, G.O., Madsen, S.J., Hirschberg, H., Engebraten, O., Nesland, J.M. and Peng, Q. (2002) *Int. J. Oncol.,* **21**, 577-82.

[47] Sandeman, D.R. (1986) *Lasers Med. Sci.,* **1**, 163-167.

[48] Hill, J.S., Kaye, A.H., Sawyer, W.H., Morstyn, G., Megison, P.D. and Stylli, S.S. (1990) *Neurosurgery,* **26**, 248-54.

[49] Popovic, E.A., Kaye, A.H. and Hill, J.S. (1996) *J. Clin. Laser. Med. Surg.,* **14**, 251-61.

[50] Rosenthal, M.A., Kavar, B., Hill, J.S., Morgan, D.J., Nation, R.L., Stylli, S.S., Basser, R.L., Uren, S., Geldard, H., Green, M.D., Kahl, S.B. and Kaye, A.H. (2001) *J. Clin. Oncol.,* **19**, 519-24.

[51] Muller, P.J. and Wilson, B.C. (1996) *J. Clin. Laser. Med. Surg.,* **14**, 263-70.

[52] Muller, P.J. and Wilson, B.C. (1995) *Semin. Surg. Oncol.,* **11**, 346-54.

[53] Goodell, T.T. and Muller, P.J. (2001) *J. Neurosci. Nurs.,* **33**, 296-300.

[54] Schweitzer, V.G. (1990) Otolaryngol. *Head Neck Surg.,* **102**, 225-32.

[55] Biel, M.A. (1998) *Laryngoscope,* **108**, 1259-68.

[56] Biel, M.A. (2002) *Curr. Oncol. Rep.,* **4**, 87-96.

[57] Grant, W.E., Hopper, C., Speight, P.M., Macrobert, A.J. and Bown, S.G. (1993) *J. Laryngol. Otol.,* **107**, 1140-5.

[58] Fan, K.F., Hopper, C., Speight, P.M., Buonaccorsi, G., MacRobert, A.J. and Bown, S.G. (1996) *Cancer,* **78**, 1374-83.

[59] Fan, K.F., Hopper, C., Speight, P.M., Buonaccorsi, G.A. and Bown, S.G. (1997) *Int. J. Cancer,* **73**, 25-32.

[60] DeLaney, T.F., Sindelar, W.F., Tochner, Z., Smith, P.D., Friauf, W.S., Thomas, G., Dachowski, L., Cole, J.W., Steinberg, S.M. and Glatstein, E. (1993) *Int. J. Radiat. Oncol. Biol. Phys.,* **25**, 445-57.

[61] Tochner, Z.A. (1994) *Cancer Treat. Res.,* **70**, 83-91.

[62] Pass, H.I., DeLaney, T.F., Tochner, Z., Smith, P.E., Temeck, B.K., Pogrebniak, H.W., Kranda, K.C., Russo, A., Friauf, W.S., Cole, J.W., Mitchell, J.B. and Thomas, G. (1994) *Ann. Surg. Oncol.,* **1**, 28-37.

[63] Takita, H. and Dougherty, T.J. (1995) *Semin. Surg. Oncol.,* **11**, 368-71.

[64] Moskal, T.L., Dougherty, T.J., Urschel, J.D., Antkowiak, J.G., Regal, A.M., Driscoll, D.L. and Takita, H. (1998) *Ann. Thorac. Surg.,* **66**, 1128-33.

[65] Muschter, R. (2003) *Curr. Urol. Rep.,* **4**, 221-8.

[66] Ortner, M.A., Liebetruth, J., Schreiber, S., Hanft, M., Wruck, U., Fusco, V., Muller, J.M., Hortnagl, H. and Lochs, H. (1998) *Gastroenterology,* **114**, 536-42.

[67] Berr, F., Wiedmann, M., Tannapfel, A., Halm, U., Kohlhaw, K.R., Schmidt, F., Wittekind, C., Hauss, J. and Mossner, J. (2000) *Hepatology,* **31**, 291-8.

[68] Berr, F., Tannapfel, A., Lamesch, P., Pahernik, S., Wiedmann, M., Halm, U., Goetz, A.E., Mossner, J. and Hauss, J. (2000) *J. Hepatol,* **32**, 352-7.

[69] Wiedmann, M., Caca, K., Berr, F., Schiefke, I., Tannapfel, A., Wittekind, C., Mossner, J., Hauss, J. and Witzigmann, H. (2003) *Cancer*, **97**, 2783-90.

[70] Dumoulin, F.L., Gerhardt, T., Fuchs, S., Scheurlen, C., Neubrand, M., Layer, G. and Sauerbruch, T. (2003) *Gastrointest Endosc,* **57**, 860-7.

[71] Ell, C., Gossner, L., May, A., Schneider, H.T., Hahn, E.G., Stolte, M. and Sroka, R. (1998) *Gut.,* **43**, 345-9.

[72] Nakamura, T., Fukui, H., Ishii, Y., Fujita, M., Hori, K., Ejiri, K., Ejiri, M. and Fujimori, T. (2000) *Endoscopy,* **32**, 609-13.

[73] Patrice, T., Foultier, M.T., Yactayo, S., Adam, F., Galmiche, J.P., Douet, M.C. and Le Bodic, L. (1990) *Dig. Dis. Sci.,* **35**, 545-52.

[74] Hayata, Y., Kato, H., Okitsu, H., Kawaguchi, M. and Konaka, C. (1985) *Semin. Surg. Oncol.,* **1**, 1-11.

[75] Barr, H., Krasner, N., Boulos, P.B., Chatlani, P. and Bown, S.G. (1990) *Br. J. Surg.,* **77**, 93-6.

[76] Herrera-Ornelas, L., Petrelli, N.J., Mittelman, A., Dougherty, T.J. and Boyle, D.G. (1986) *Cancer,* **57**, 677-84.

[77] Nakamura, T., Fukui, H., Ishii, Y., Ejiri, K. and Ejiri, M. (2003) *Gastrointest Endosc*, **57**, 266-9.

[78] Kashtan, H., Papa, M.Z., Wilson, B.C., Deutch, A.A. and Stern, H.S. (1991) *Dis. Colon. Rectum.*, **34**, 600-4; discussion 604-5.

[79] Loh, C.S., Bliss, P., Bown, S.G. and Krasner, N. (1994) *Endoscopy,* **26**, 243-6.

[80] Spinelli, P., Dal Fante, M. and Mancini, A. (1992) *Semin. Surg. Oncol.,* **8**, 204-13.

[81] Bown, S.G., Rogowska, A.Z., Whitelaw, D.E., Lees, W.R., Lovat, L.B., Ripley, P., Jones, L., Wyld, P., Gillams, A. and Hatfield, A.W. (2002) *Gut.,* **50**, 549-57.

[82] Overholt, B.F. and Panjehpour, M. (1996) *Am. J. Gastroenterol.*, **91**, 1719-23.

[83] Overholt, B.F., Panjehpour, M. and Haydek, J.M. (1999) *Gastrointest Endosc,* **49**, 1-7.

[84] Barr, H., Shepherd, N.A., Dix, A., Roberts, D.J., Tan, W.C. and Krasner, N. (1996) *Lancet*, **348**, 584-5.

[85] Bissonnette, R., Zeng, H., McLean, D.I., Korbelik, M. and Lui, H. (2001) *Photochem. Photobiol.,* **74**, 339-45.

[86] Boehncke, W.H., Elshorst-Schmidt, T. and Kaufmann, R. (2000) *Arch. Dermatol.,* **136**, 271-2.
[87] Shikowitz, M.J., Abramson, A.L., Freeman, K., Steinberg, B.M. and Nouri, M. (1998) *Laryngoscope,* **108**, 962-7.
[88] Feyh, J. and Kastenbauer, E. (1992) *Laryngorhinootologie,* **71**, 190-2.
[89] Marcus, L. (2003) *Dermatol. Surg.,* **29**, 1061-4; discussion 1064-5.
[90] Goldman, M. and Atkin, D. (2003) *J. Cosmet. Laser. Ther.,* **5**, 107-10.
[91] Pariser, D.M., Lowe, N.J., Stewart, D.M., Jarratt, M.T., Lucky, A.W., Pariser, R.J. and Yamauchi, P.S. (2003) *J. Am. Acad. Dermatol.,* **48**, 227-32.
[92] Epstein, E. (2003) *J. Am. Acad. Dermatol.,* **48**, 304; author reply 304-6.
[93] Lang, K., Schulte, K.W., Ruzicka, T. and Fritsch, C. (2001) *Skin Therapy Lett.,* **6**, 1-2, 5.
[94] Jeffes, E.W., McCullough, J.L., Weinstein, G.D., Kaplan, R., Glazer, S.D. and Taylor, J.R. (2001) *J. Am. Acad. Dermatol.,* **45**, 96-104.
[95] Hooper, C.Y. and Guymer, R.H. (2003) *Clin. Experiment. Ophthalmol.,* **31**, 376-91.
[96] Foot, B., Foy, R., Chakravarthy, U. and Wormald, R. (2003) *Eye,* **17**, 583-6.
[97] Wormald, R., Evans, J., Smeeth, L. and Henshaw, K. (2003) *Cochrane Database Syst. Rev.,* CD002030.
[98] Meads, C., Salas, C., Roberts, T., Moore, D., Fry-Smith, A. and Hyde, C. (2003) *Health Technol Assess,* **7**, 1-108.
[99] Grossniklaus, H.E., Brooks, H.L., Jr., Sippy, B.D. and Liu, P. (2002) *Retina,* **22**, 818-24.
[100] Jaakkola, A. (2002) *Duodecim,* **118**, 813-9.
[101] Rechtman, E., Ciulla, T.A., Criswell, M.H., Pollack, A. and Harris, A. (2002) *Expert. Opin. Pharmacother.,* **3**, 931-8.
[102] Franks, W. (2002) *Age. Ageing.,* **31**, 5-6.
[103] Dougherty, T.J., Gomer, C.J., Henderson, B.W., Jori, G., Kessel, D., Korbelik, M., Moan, J. and Peng, Q. (1998) *J. Natl. Cancer. Inst.,* **90**, 889-905.
[104] Henderson, B.W. and Dougherty, T.J. (1992) *Photochem. Photobiol.,* **55**, 145-57.
[105] Moan, J. and Berg, K. (1991) *Photochem. Photobiol.,* **53**, 549-53.
[106] Henderson, B.W. and Fingar, V.H. (1989) *Photochem. Photobiol.,* **49**, 299-304.
[107] Hill, J.S., Kahl, S.B., Kaye, A.H., Stylli, S.S., Koo, M.S., Gonzales, M.F., Vardaxis, N.J. and Johnson, C.I. (1992) *Proc. Natl. Acad. Sci. USA.,* **89**, 1785-9.
[108] Kessel, D., Thompson, P., Saatio, K. and Nantwi, K.D. (1987) *Photochem. Photobiol.,* **45**, 787-90.
[109] Stilts, C.E., Nelen, M.I., Hilmey, D.G., Davies, S.R., Gollnick, S.O., Oseroff, A.R., Gibson, S.L., Hilf, R. and Detty, M.R. (2000) *J. Med. Chem.,* **43**, 2403-10.
[110] Berenbaum, M.C., Akande, S.L., Bonnett, R., Kaur, H., Ioannou, S., White, R.D. and Winfield, U.J. (1986) *Br. J. Cancer,* **54**, 717-25.
[111] Hagan, W.J., Jr., Barber, D.C., Whitten, D.G., Kelly, M., Albrecht, F., Gibson, S.L. and Hilf, R. (1988) *Cancer Res.,* **48**, 1148-52.
[112] Nelson, J.S., Roberts, W.G. and Berns, M.W. (1987) *Cancer Res.,* **47**, 4681-5.
[113] Roberts, W.G., Shiau, F.Y., Nelson, J.S., Smith, K.M. and Berns, M.W. (1988) *J. Natl. Cancer. Inst.,* **80**, 330-6.
[114] Leach, M.W., Higgins, R.J., Autry, S.A., Boggan, J.E., Lee, S.J. and Smith, K.M. (1993) *Photochem. Photobiol.,* **58**, 653-60.
[115] Pandey, R.K., Sumlin, A.B., Constantine, S., Aoudla, M., Potter, W.R., Bellnier, D.A., Henderson, B.W., Rodgers, M.A., Smith, K.M. and Dougherty, T.J. (1996) *Photochem. Photobiol.,* **64**, 194-204.
[116] Pandey, R.K., Potter, W.R., Meunier, I., Sumlin, A.B. and Smith, K.M. (1995) *Photochem. Photobiol.,* **62**, 764-8.
[117] Richter, A.M., Kelly, B., Chow, J., Liu, D.J., Towers, G.H., Dolphin, D. and Levy, J.G. (1987) *J. Natl. Cancer Inst.,* **79**, 1327-32.
[118] Morgan, A.R., Rampersaud, A., Keck, R.W. and Selman, S.H. (1987) *Photochem. Photobiol.,* **46**, 441-4.
[119] Ma, L., Moan, J. and Berg, K. (1994) *Int. J. Cancer,* **57**, 883-8.
[120] Beems, E.M., Dubbelman, T.M., Lugtenburg, J., Van Best, J.A., Smeets, M.F. and Boegheim, J.P. (1987) *Photochem. Photobiol.,* **46**, 639-43.
[121] Kennedy, J.C., Pottier, R.H. and Pross, D.C. (1990) *J. Photochem. Photobiol.,* B **6**, 143-8.
[122] Steiner, E. and Fowler, P.W. (2003) *Org. Biomol. Chem.,* **1**, 1785-9.
[123] Ohgo, Y., Neya, S., Ikeue, T., Takahashi, M., Takeda, M., Funasaki, N. and Nakamura, M. (2002) *Inorg. Chem.,* **41**, 4627-9.
[124] Vogel, E., Scholz, P., Demuth, R., Erben, C., Broring, M., Schmickler, H., Lex, J., Hohlneicher, G., Bremm, D. and Wu, Y.D. (1999) *Angew. Chem. Int. Ed. Engl.,* **38**, 2919-2923.
[125] Fowler, C.J., Sessler, J.L., Lynch, V.M., Waluk, J., Gebauer, A., Lex, J., Heger, A., Zuniga, Y.R.F. and Vogel, E. (2002) *Chemistry*, **8**, 3485-96.
[126] Pushpan, S.K., Srinivasan, A., Anand, V.G., Venkatraman, S., Chandrashekar, T.K., Joshi, B.S., Roy, R. and Furuta, H. (2001) *J. Am. Chem. Soc.,* **123**, 5138-9.
[127] Furuta, H., Maeda, H. and Osuka, A. (2001) *J. Org. Chem.,* **66**, 8563-72.
[128] Szeimies, R.M., Karrer, S., Abels, C., Steinbach, P., Fickweiler, S., Messmann, H., Baumler, W. and Landthaler, M. (1996) *J. Photochem. Photobiol.,* B **34**, 67-72.
[129] Rodal, G.H., Rodal, S.K., Moan, J. and Berg, K. (1998) *J. Photochem. Photobiol.,* B **45**, 150-9.
[130] Soncin, M., Busetti, A., Biolo, R., Jori, G., Kwag, G., Li, Y.S., Kenney, M.E. and Rodgers, M.A. (1998) *J. Photochem. Photobiol.,* B **42**, 202-10.
[131] Brasseur, N., Nguyen, T.L., Langlois, R., Ouellet, R., Marengo, S., Houde, D. and van Lier, J.E. (1994) *J. Med. Chem.,* **37**, 415-20.
[132] Adler, A.D., Ostfeld, D.L. and Abbott, E.H. (1977) *Bioinorg. Chem.,* **7**, 187-8.
[133] Hampton, J.A., Skalkos, D., Taylor, P.M. and Selman, S.H. (1993) *Photochem. Photobiol.,* **58**, 100-5.
[134] Michelsen, U., Kliesch, H., Schnurpfeil, G., Sobbi, A.K. and Wohrle, D. (1996) *Photochem. Photobiol.,* **64**, 694-701.
[135] Sessler, J.L. and Davis, J.M. (2001) *Acc. Chem. Res.,* **34**, 989-97.
[136] Sessler, J.L. and Miller, R.A. (2000) *Biochem. Pharmacol.,* **59**, 733-9.
[137] Chandrashekar, T.K. and Venkatraman, S. (2003) *Acc. Chem. Res.,* **36**, 676-91.
[138] Luketich, J.D., Christie, N.A., Buenaventura, P.O., Weigel, T.L., Keenan, R.J. and Nguyen, N.T. (2000) *Surg. Endosc.,* **14**, 653-7.
[139] Maier, A., Tomaselli, F., Gebhard, F., Rehak, P., Smolle, J. and Smolle-Juttner, F.M. (2000) *Ann. Thorac. Surg.,* **69**, 1006-9.
[140] Heier, S.K., Rothman, K.A., Heier, L.M. and Rosenthal, W.S. (1995) *Gastroenterology,* **109**, 63-72.
[141] Lightdale, C.J., Heier, S.K., Marcon, N.E., McCaughan, J.S., Jr., Gerdes, H., Overholt, B.F., Sivak, M.V., Jr., Stiegmann, G.V. and Nava, H.R. (1995) *Gastrointest Endosc.,* **42**, 507-12.
[142] Moghissi, K. and Dixon, K. (2003) *Technol. Cancer Res. Treat.,* **2**, 319-26.
[143] Scheider, D.M., Siemens, M., Cirocco, M., Haber, G.B., Kandel, G., Kortan, P. and Marcon, N.E. (1997) *Endoscopy,* **29**, 271-4.
[144] Sanfilippo, N.J., Hsi, A., DeNittis, A.S., Ginsberg, G.G., Kochman, M.L., Friedberg, J.S. and Hahn, S.M. (2001) *Lasers Surg. Med.,* **28**, 278-81.
[145] Sibille, A., Lambert, R., Souquet, J.C., Sabben, G. and Descos, F. (1995) *Gastroenterology,* **108**, 337-44.
[146] Calzavara, F., Tomio, L., Corti, L., Zorat, P.L., Barone, I., Peracchia, A., Norberto, L., D'Arcais, R.F. and Berti, F. (1990) *J. Photochem Photobiol,* B **6**, 167-74.
[147] Savary, J.F., Grosjean, P., Monnier, P., Fontolliet, C., Wagnieres, G., Braichotte, D. and van den Bergh, H. (1998) *Endoscopy,* **30**, 258-65.
[148] Corti, L., Skarlatos, J., Boso, C., Cardin, F., Kosma, L., Koukourakis, M.I., Giatromanolaki, A., Norberto, L., Shaffer, M. and Beroukas, K. (2000) *Int. J. Radiat. Oncol. Biol. Phys.,* **47**, 419-24.
[149] Tan, W.C., Fulljames, C., Stone, N., Dix, A.J., Shepherd, N., Roberts, D.J., Brown, S.B., Krasner, N. and Barr, H. (1999) *J. Photochem Photobiol,* B **53**, 75-80.
[150] Ackroyd, R., Brown, N.J., Davis, M.F., Stephenson, T.J., Marcus, S.L., Stoddard, C.J., Johnson, A.G. and Reed, M.W. (2000) *Gut.,* **47**, 612-7.
[151] Gossner, L., May, A., Sroka, R., Stolte, M., Hahn, E.G. and Ell, C. (1999) *Cancer,* **86**, 1921-8.
[152] Ortner, M.A., Zumbusch, K., Liebetruth, J., Ebert, B., Fleige, B., Dietel, M. and Lochs, H. (2002) *Endoscopy.,* **34**, 611-6.

[153] Hur, C., Nishioka, N.S. and Gazelle, G.S. (2003) *Dig. Dis. Sci.,* **48**, 1273-83.
[154] Panjehpour, M., Overholt, B.F., Haydek, J.M. and Lee, S.G. (2000) *Am. J. Gastroenterol.,* **95**, 2177-84.
[155] Krishnadath, K.K., Wang, K.K., Taniguchi, K., Sebo, T.J., Buttar, N.S., Anderson, M.A., Lutzke, L.S. and Liu, W. (2000) *Gastroenterology*, **119**, 624-30.
[156] Shand, A., Dallal, H., Palmer, K., Ghosh, S. and MacIntyre, M. (2001) *Gut.,* **48**, 580-1.
[157] Lambert, R. (2000) *Recent Results Cancer Res.,* **155**, 183-92.
[158] Barr, H. (2003) *Gut.,* **52**, 14-5.
[159] Fitzgerald, R.C. (2003) *Gut.,* **52**, 16-7.
[160] Pech, O., May, A., Rabenstein, T., Gossner, L. and Ell, C. (2003) *Langenbecks. Arch. Surg.*, **388**, 421-4.
[161] McCaughan, J.S., Jr., Mertens, B.F., Cho, C., Barabash, R.D. and Payton, H.W. (1991) *Arch. Surg.,* **126**, 111-3.
[162] Wiedmann, M., Caca, C., Witzigmann, H., Hauss, J., Mössner, J. and Berr, F. (2002) *Z. Gastroenterol.,* **40**, 727A.
[163] Ortner, M.E.J., Caca, K., Berr, F., Liebetruth, J., Mansmann, U., Huster, D., Voderholzer, W., Schachschal, G., Mössner, J. and Lochs, H. (2003) *Gastroenterology.,* **125**, 1355-1363.
[164] Zoepf, T., Jakobs, R., Rosenbaum, A., Apel, D., Arnold, J.C. and Riemann, J.F. (2001) *Gastrointest Endosc.,* **54**, 763-6.
[165] Ono, H., Kondo, H., Gotoda, T., Shirao, K., Yamaguchi, H., Saito, D., Hosokawa, K., Shimoda, T. and Yoshida, S. (2001) *Gut.,* **48**, 225-9.
[166] Baron, T.H. (2001) *N. Engl. J. Med.,* **344**, 1681-7.
[167] Dolmans, D.E., Kadambi, A., Hill, J.S., Flores, K.R., Gerber, J.N., Walker, J.P., Rinkes, I.H., Jain, R.K. and Fukumura, D. (2002) *Cancer Res.*, **62**, 4289-94.
[168] Ruoslathi, E. (2002) *Nature Rev. Cancer*, **2**, 83-90.
[169] Vrouenraets, M.B., Visser, G.W., Stewart, F.A., Stigter, M., Oppelaar, H., Postmus, P.E., Snow, G.B. and van Dongen, G.A. (1999) *Cancer Res.,* **59**, 1505-13.
[170] Oseroff, A.R., Ohuoha, D., Hasan, T., Bommer, J.C. and Yarmush, M.L. (1986) *Proc. Natl. Acad. Sci. USA,* **83**, 8744-8.
[171] Goff, B.A., Blake, J., Bamberg, M.P. and Hasan, T. (1996) *Br. J. Cancer,* **74**, 1194-8.
[172] Jiang, F.N., Liu, D.J., Neyndorff, H., Chester, M., Jiang, S.Y. and Levy, J.G. (1991) *J. Natl. Cancer Inst.,* **83**, 1218-25.
[173] Mew, D., Wat, C.K., Towers, G.H. and Levy, J.G. (1983) *J. Immunol.,* **130**, 1473-7.
[174] Molpus, K.L., Hamblin, M.R., Rizvi, I. and Hasan, T. (2000) *Gynecol. Oncol.,* **76**, 397-404.
[175] Del Governatore, M., Hamblin, M.R., Shea, C.R., Rizvi, I., Molpus, K.G., Tanabe, K.K. and Hasan, T. (2000) *Cancer Res.,* **60**, 4200-5.
[176] Soncin, M., Polo, L., Reddi, E., Jori, G., Kenney, M.E., Cheng, G. and Rodgers, M.A. (1995) *Cancer Lett.,* **89**, 101-6.
[177] Reddi, E., Zhou, C., Biolo, R., Menegaldo, E. and Jori, G. (1990) *Br. J. Cancer,* **61**, 407-11.
[178] Akhlynina, T.V., Rosenkranz, A.A., Jans, D.A. and Sobolev, A.S. (1995) *Cancer Res.,* **55**, 1014-9.
[179] Sobolev, A.S., Akhlynina, T.V., Yachmenev, S.V., Rosenkranz, A.A. and Severin, E.S. (1992) *Biochem Int.,* **26**, 445-50.
[180] Gijsens, A., Missiaen, L., Merlevede, W. and de Witte, P. (2000) *Cancer Res.,* **60**, 2197-202.
[181] Allen, C.M., Sharman, W.M., La Madeleine, C., Weber, J.M., Langlois, R., Ouellet, R. and van Lier, J.E. (1999) *Photochem. Photobiol.*, **70**, 512-23.
[182] Kennedy, J.C., Ringuet, M. and Pottier, R.H. (1997).
[183] Gagnebin, J., Brunori, M., Otter, M., Juillerat-Jeanneret, L., Monnier, P. and Iggo, R. (1999) *Gene. Ther.*, **6**, 1742-50.
[184] Shiah, J.J., Sun, Y., Peterson, C.M. and Kopecek, J. (1999) *J. Control Release*, **61**, 145-57.
[185] Westerman, P., Glanzmann, T., Andrejevic, S., Braichotte, D.R., Forrer, M., Wagnieres, G.A., Monnier, P., van den Bergh, H., Mach, J.P. and Folli, S. (1998) *Int. J. Cancer,* **76**, 842-50.
[186] Ris, H.B., Im Hof, V., Stewart, C.M., Mettler, D. and Altermatt, H.J. (1998) *Lasers Surg. Med.,* **23**, 25-32.
[187] Reuther, T., Kubler, A.C., Zillmann, U., Flechtenmacher, C. and Sinn, H. (2001) *Lasers Surg. Med.,* **29**, 314-22.
[188] Rovers, J.P., Saarnak, A.E., de Jode, M., Sterenborg, H.J., Terpstra, O.T. and Grahn, M.F. (2000) *Photochem. Photobiol.,* **71**, 211-7.
[189] Brasseur, N., Ouellet, R., La Madeleine, C. and van Lier, J.E. (1999) *Br. J. Cancer,* **80**, 1533-41.
[190] Hamblin, M.R., Miller, J.L., Rizvi, I., Ortel, B., Maytin, E.V. and Hasan, T. (2001) *Cancer Res.,* **61**, 7155-62.
[191] Taillefer, J., Jones, M.C., Brasseur, N., van Lier, J.E. and Leroux, J.C. (2000) *J. Pharm. Sci.,* **89**, 52-62.
[192] Taillefer, J., Brasseur, N., van Lier, J.E., Lenaerts, V., Le Garrec, D. and Leroux, J.C. (2001) *J. Pharm. Pharmacol.,* **53**, 155-66.
[193] Dillon, J., Kennedy, J.C., Pottier, R.H. and Roberts, J.E. (1988) *Photochem. Photobiol.,* **48**, 235-8.
[194] McCaughan, J.S., Jr., Nims, T.A., Guy, J.T., Hicks, W.J., Williams, T.E., Jr. and Laufman, L.R. (1989) *Arch. Surg.,* **124**, 74-80.