

# Intravenous and interstitial photodynamic laser therapy: New options in oncology

By Dr. M. WEBER

## Summary

**Objective:** Introduction of a new treatment option in oncology: Photodynamic tumor therapy.

## Method:

Combined application of natural and chemically derived highly specific photosensitizers and new catheter- based laser technology for light activation of these photosensitizers to induce selective destruction of tumor tissue. Additional low-dose chemotherapy with light activation of chemotherapeutic drugs.

The combination with hyperbaric oxygenation is an option to optimize therapeutic results because oxygen radicals are responsible for tumor necrosis and apoptosis. Combination with immunotherapy like macrophage activating factor GcMAF can be of benefit as well.

**Results:** Different case reports indicate the great potential of the treatment regime.

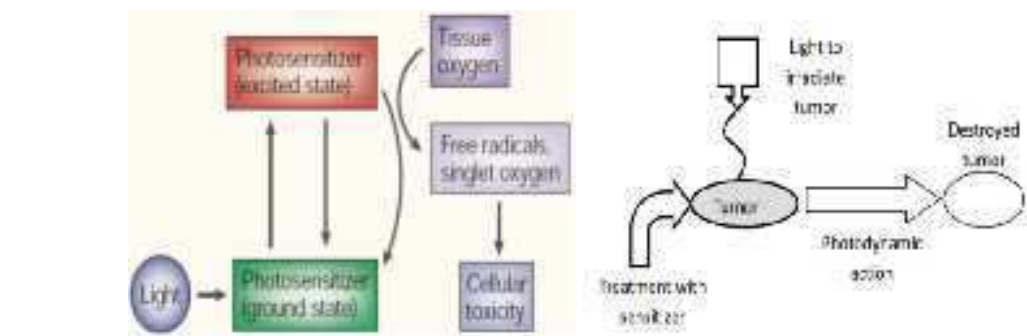
**Conclusion:** Photodynamic tumor therapy and additional low-dose chemotherapy with light activation of chemotherapeutic drugs seems to be a promising new treatment regime in future oncology.

**Keywords:** PDT (photodynamic therapy), intravenous laser therapy, interstitial laser therapy, low-dose chemotherapy, hyperbaric oxygen, macrophage activating factor GcMAF, light activation.

## 1) Introduction

Photodynamic therapy is one of the most interesting and promising approaches for treatment of various cancers. It has a long history and is already approved for some superficial cancers on the skin or on superficial layers in the esophagus or bronchial system.(1,2,3,4,5) Treatments are easy to perform and – in contrast to chemotherapy – go normally along without severe side effects. The principle is the stimulation of a light sensitive drug (photosensitizer) that is either applied on the skin as a cream or injected into the blood circulation. Through endocytosis the photosensitizer will be transported into the tumor cells anywhere in the body with high specificity. The process takes several hours (depending on the photosensitizer) and tumor cells will be light sensitive

at the end. Tumor tissue is subsequently irradiated with light of specific wavelength that matches the absorption spectra of the various photosensitizers to activate the latter. This light activation process induces various chemical processes such as the development of radical oxygen species that ultimately lead to the destruction of tumor tissue. Other than chemo therapy, photodynamic therapy thereby even stimulates the immune system in different ways (8,9).



Figures 1-2: The principle of photodynamic therapy

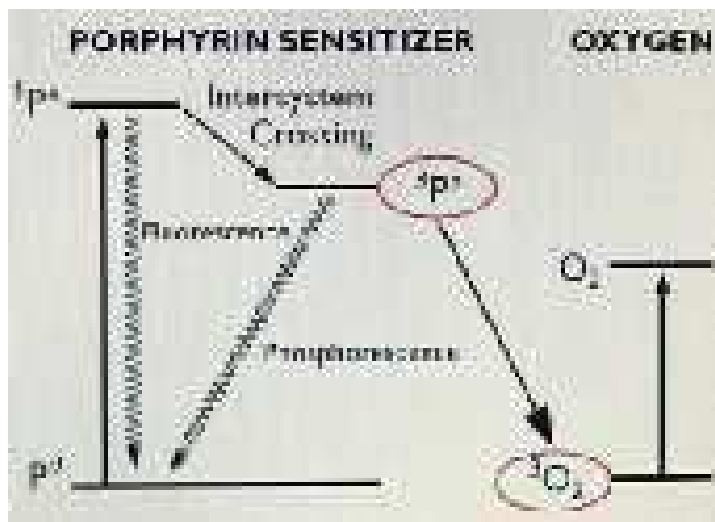


Figure 3: The principle of photodynamic therapy

Until recently, PDT has been limited to treatment of superficial cancers as there was no technology available that would facilitate light application in deeper areas of the body. The relevance of that stems from the limited penetration depth of light in general and laser light of most wavelengths in particular: most of the light energy is absorbed by the skin and an effective light activation of photosensitizers that have accumulated at inner

tumors was thus impossible in most of the cases. Due to this limitation, progress of PDT has been slow until today and consequently, the great challenge for application of this method for inner cancers is the delivery of light to into the body (10,11).

Nowadays, new technological developments facilitate “systemic photodynamic therapies” and interstitial laser therapies and are thus able to overcome the “skin barrier”. They constitute the basis for extensive growth in this field.

## **2) History of Photodynamic Tumor Therapy**

The method of interstitial laser therapy in interventional oncology was first introduced in 2004 by Vogl et al. from the Faculty of Interventional Oncology of the University Frankfurt, Germany (10). In their study the authors tried to overcome the problem of limited penetration depth by using fiber-optic laser catheters which were inserted directly into the tumor tissue or in metastases. With this method, they were able to document an effective and controlled necrosis and apoptosis and could show convincingly that liver metastases can be treated by PDT. They further mentioned that one of the key advantages of this treatment modality is that there are almost no side effects or pain so that the procedure is suitable for outpatients without necessary hospitalization. This fact increases compliance in patients as well.

In several other studies in the last years a successful fiber-optic PDT in combination with low-level-laser could be demonstrated, even in pancreatic cancer (12).

The idea of treating cancer patients with intravenous laser irradiation in combination with porphyrin-derived photosensitizers (“systemic PDT”) was first introduced by Kaplan et al. in 2008 (13). They ran a study with 76 patients with metastasizing malignant melanomas which were treated with intravenous Chlorin E6 and followed by intravenous laser irradiation. 34 patients felt an improvement of their life quality, reduction of pain, less weakness and increased appetite. The lymph nodes of 16 patients disappeared completely and the dissemination of metastases of 25 other patients could be stopped for 6-12 months. Besides a general boost of the immune system the authors further assumed that circulating tumor cells and tumor stem cells in the blood were destroyed by the therapy. This lead to an additional immunization through damaged tumor products. Lastly, the elimination of microorganisms in the blood stream by PDT can cure and prevent patients from concomitant infections.

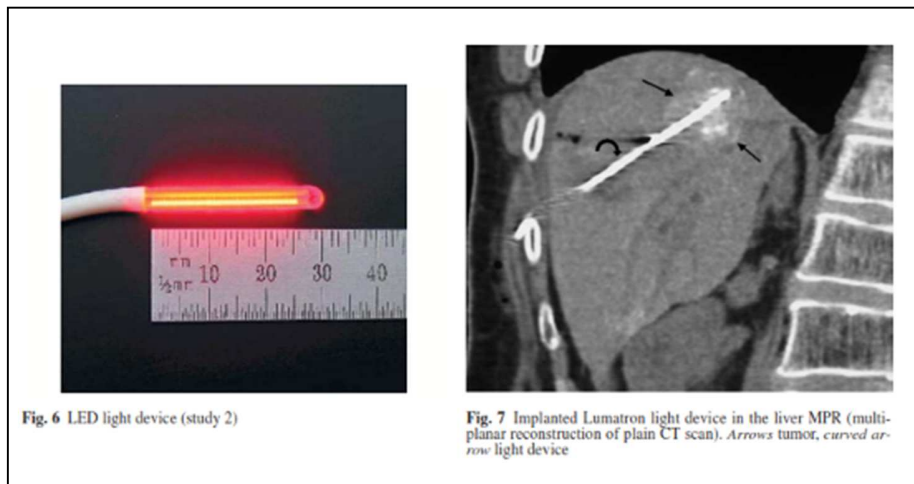


Figure 4-5: Interstitial PDT of liver metastasis (Vogl. Et al.)

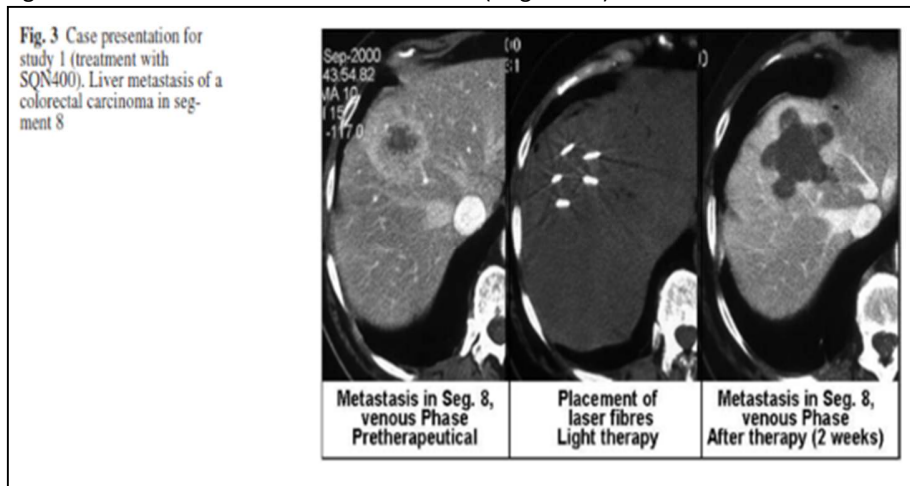


Figure 6: Interstitial PDT of liver metastasis (Vogl. Et al.)

Further publications include an article by Jaeger et al. and Bown et al.:

Jaeger et al. published a study on successful application of interstitial photodynamic laser therapy to treat head- and neck- tumors in 2005 (Jaeger 2005). (14)

Brown et al. reported in the Journal "Gut" that pancreatic cancers can successfully be treated with interstitial photodynamic laser therapy already in 2002 (Bown 2002). (15)

These studies provided first results that suggested that a combination of "systemic PDT" via intravenously applied photosensitizers and subsequent intravenous irradiation as one component and interstitial PDT with fiber optic laser catheters and direct laser activation as the other component might be established as a new treatment regime for various types of cancer.

### 3) Photosensitizers

#### 3.1) Overview

Photosensitizers are mostly porphyrin molecules and derivatives either from the human haem (without the central iron atom) or plant-derived chlorophyll (without the central magnesium atom) (6,7) Accordingly, they are called hematoporphyrins or chlorines.

Various photosensitizers are commercially available and therapeutically used since more than 10 years, but most of them do not fulfill important quality criteria such as sufficient specificity. Photofrin is approved for PDT in many countries and can be regarded as the “mother substance” of PDT, but Photofrin leads to increased light sensitivity of healthy tissue as it does not bind exclusively to tumor cells (lack of specificity). Its use has the potential to cause damage of the surrounding healthy tissue as well. In addition, Photofrin has to be infused 48 hours in advance and patients will have to avoid sunlight for several weeks after their treatment. Another general disadvantage of many photosensitizers is the high price.

**Table 1** Currently available photosensitizers.

Platform	Drug	Substance	Manufacturer	Web site
Porphyrin	Photofrin®	HpD	Axcan Pharma, Inc.	<a href="http://www.axcan.com">www.axcan.com</a>
Porphyrin	Levulan®	ALA	DUSA Pharmaceuticals, Inc.	<a href="http://www.dusapharma.com">www.dusapharma.com</a>
Porphyrin	Metvix®	M-ALA	PhotoCure ASA	<a href="http://www.photocure.com">www.photocure.com</a>
Porphyrin	Visudyne®	Vertiporfin	Novartis Pharmaceuticals	<a href="http://www.visudyne.com">www.visudyne.com</a>
Texaphyrin	Antrin®	Lutexaphyrin	Pharmacylics	<a href="http://www.pharmacylics.com">www.pharmacylics.com</a>
Chlorin	Foscan®	Temoporfin	Biolitec Pharma Ltd.	<a href="http://www.bioletcpharma.com">www.bioletcpharma.com</a>
Chlorin	LS11	Talaporfin	Light Science	<a href="http://www.lightsciences.com">www.lightsciences.com</a>
Chlorin	Photochlor	HPPH	RPCI	<a href="http://www.roswellpark.org">www.roswellpark.org</a>
Dye	Photosens®	Phthalocyanine	General Physics Institute	<a href="http://www.gpi.ru">www.gpi.ru</a>

Table 1: Commercially available photosensitizers

Photosensitizer	Type of diseases	Country
(5-ALA)	Actinic keratosis,	U.S., EU
5-aminolevulinate	Basal cell carcinoma	
Photofrin	Barrett’s displasia	U.S., Canada, EU, UK
Photofrin	Cervical cancer	Japan
Photofrin	Endobronchial cancer	Canada, Most EU Countries, Japan, U.S.
Photofrin	Esophageal cancer	Canada, Most EU Countries, Japan, U.S.
Photofrin	Gastric cancer	Japan
Photofrin	Papillary bladder cancer	Canada
Foscan	Head and neck cancer	EU, Norway, Iceland
Verteporfin	Age-related Macular Degeneration	Canada, Most EU Countries, Japan, U.S.

Table 2: Photosensitizers approved for therapy

The following photosensitizers are the most promising ones right now as they fulfill much better the specificity quality criteria.

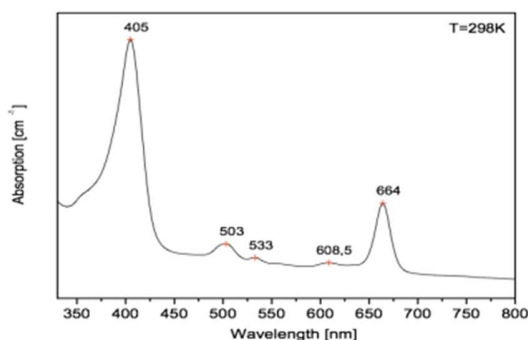
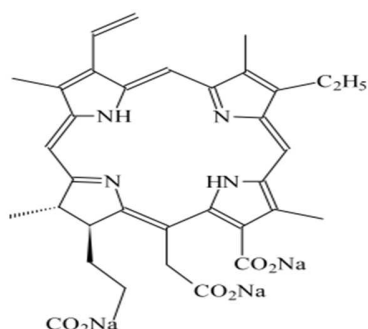
### 3.2) Chlorin E6

Chlorin E6 plays a crucial role in photodynamic tumor therapy. It is a natural derivative from chlorophyll and gained by extraction from green plants such as chlorella alga. The chemical structure is changed by three attached carboxyl groups as Trisodium salt which makes the molecule soluble in water or saline solution for infusion (16). It is particularly attractive because it

- is more than 99% pure
- has a very high absorption rate in the red light spectrum (around 660nm) and
- binds to tumor cells with extremely high selectivity so that there is nearly no collateral damage of surrounding healthy cells as a result from the treatment.

In addition, Chlorin E6 has special photo-physical properties which are advantageous for PDT:

- the configuration of Chlorin E6 stays in the triplet state for a prolonged time and it accumulates selectively in tumor cells just 3-4 hours after it has been infused.
- Chlorine E6 is also completely removed from the body after 48 hours, which reduces the time significantly during which patients have to avoid sunlight because of light sensitivity.
- tumor necrosis and apoptosis can be demonstrated within only a few hours.
- blue light with a wavelength of 405nm can also be used for photodynamic diagnostics (PDD). The tumor area that is irradiated with blue light before PDT irradiation will show red fluorescence and in this way the tumor size can be determined exactly.(16).



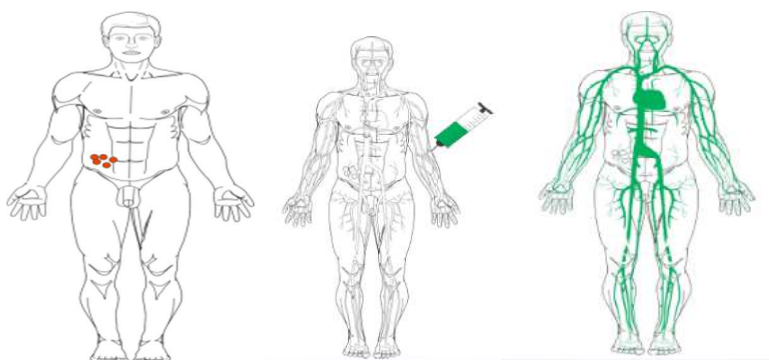
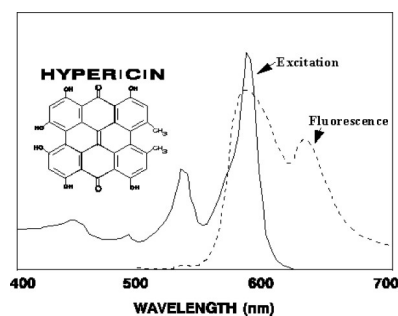
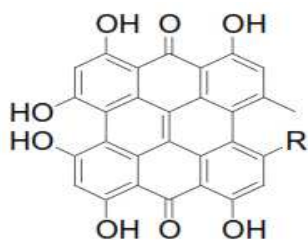


Figure 7-9: Structure, absorption spectrum and application of Chlorin E6

### 3.3) Hypericin

Hypericin is a red Anthrachinone derivative and one of the main components of St. John's wort from which it is extracted. It has its absorption maximum at approximately 589nm (yellow light) (17). In photodynamic therapy, it is not only used in tumor therapy, but also for treatment of depression and treatment of viral and chronic bacterial infections (18). Already in 2002, Liu et al. could prove the anti-tumoral effects of Hypericin in combination with photodynamic interstitial laser stimulation in vitro and in vivo for pancreatic carcinoma in animal trials (19). (J. Surg Res. 2000 Sep;93(1):137-43). A plant extract consists of a mixture of hypericin, pseudohypericin and hyperforin. Only very recently, a pure pharmaceutical grade Hypericin solution has become available, which can be used for intravenous infusion. The normally hydrophobic substance can be bound to albumin and so dissolved in physiological saline solution.



Figures 10-12: St. John's wort, structure formula of Hypericin and absorption spectrum.

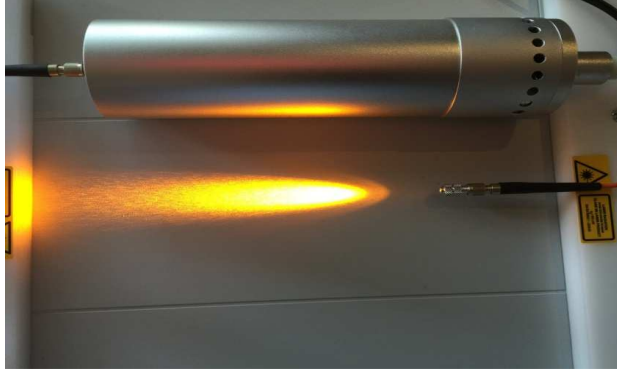


Figure 13: New yellow laser for Stimulation of Hypericin.

### 3.4) Curcumin

Curcumin is another highly effective and selective natural photosensitizer. It can be extracted from curcuma (*Curcuma longa*), but can also be produced synthetically. It consists of three main components, the so-called curcuminoids:

- Curcumin I = Diferuloylmethane, appr. 77 % share
- Curcumin II = Demethoxycurcumin, appr. 17 % share
- Curcumin III = Bisdemethoxycurcum. appr. 3 % share.

Curcumin has a long history in medical applications and has already shown its potency in slowing down tumor growth and protection against metastasizing of cancers (20,21).

The absorption maximum of Curcumin is at 445nm (blue light). Similar to Hypericin, it can not only be used in tumor therapy, but also for treatment of viral and chronic bacterial infections.

In 2005, Bruzell et al. published a study that proofed the photo- induced cytotoxicity of Curcumin (22).

Only very recently has a 150 mg pure substance become available to produce an infusion solution. The normally hydrophobic substance is bound to human albumin and can so be dissolved in physiological sodium chloride solution for infusion (23).





Figure 14-16: Curcuma longa plant, curcuma powder, absorption spectrum of Curcumin and chemical structure.



Figure 17: The new blue laser 447 nm for stimulation of Curcumin.

A broad range of studies exists both for Hypericin and for Curcumin that has demonstrated the efficacy of these substances (24,25). Up to now they could hardly be used in clinical trials as a blue laser able to activate Curcumin has only become available in the past 2 years; a yellow laser able to activate Hypericin is available only since 2014.

### 3.5) Epigallocatechingallate (EGCG)

Epigallocatechingallate (EGCG) (Polyphenol EGCG from green tea) can be used in PDT as well.

In 2014, Mun et al. showed its anti- tumoral effects for various cancers after activation with light (26).

It is of special interest as it can be activated by infrared light which has the best ability to penetrate bones / the skull. It can accordingly potentially be used to treat brain tumors.

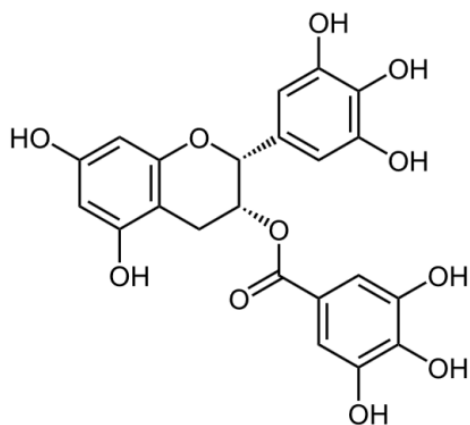


Figure 18: Structure formula of Epigallocatechingallate

### 3.5 Indocyanine green

**Indocyanine green (ICG)** is a cyanine fluorescent dye used in medical diagnostics. It is used for determining cardiac output, hepatic function, and liver blood flow, and for ophthalmic angiography.<sup>[2]</sup> It has a peak spectral absorption at about 800 nm.<sup>[3]</sup> These infrared frequencies penetrate retinal layers, allowing ICG angiography to image deeper patterns of circulation than fluorescein angiography.<sup>[4]</sup> ICG binds tightly to plasma proteins and becomes confined to the vascular system.<sup>[2]</sup> ICG has a half-life of 150 to 180 seconds and is removed from circulation exclusively by the liver to bile juice.<sup>[2]</sup>

ICG is administered intravenously and, depending on liver performance, is eliminated from the body with a half life of approx. 3–4 minutes.<sup>[6]</sup> ICG sodium salt is normally available in powder form and can be dissolved in various solvents; 5% (<5% depending on batch) sodium iodide is usually added to ensure better solubility.<sup>[7]</sup> The sterile lyophilisate of a water-ICG solution is approved many European countries and the United States under the names ICG-Pulsion and IC-Green as a diagnostic for intravenous use.

ICG was developed in the Second World War as a dye in photography and tested in 1957 at the Mayo Clinic for use in human medicine. After being granted FDA approval in 1959, ICG was initially used primarily in hepatic function diagnostics and later in cardiology. In 1964, S. Schilling was able to determine renal blood flow using ICG. From 1969, ICG was also used in the research and diagnosis of subretinal processes in the eye (in the choroid). In the years since 1980, the development of new types of cameras and better film material or new photometric measuring devices has cleared away many technical difficulties. In the mean time, the use of

ICG in medicine (and especially in fluorescent angiography in ophthalmology) has become established as standard. A distinction is therefore also made, when describing fluorescent angiography, between NA fluorescent angiography and ICGA / ICG fluorescent angiography. Around 3,000 scientific papers on ICG have now been published worldwide.<sup>[8]</sup>

The absorption and fluorescence spectrum of ICG is in the near infrared region (see figure 19). Both depend largely on the solvent used and the concentration.<sup>[9]</sup> ICG absorbs mainly between 600 nm and 900 nm and emits fluorescence between 750 nm and 950 nm. The large overlapping of the absorption and fluorescence spectra leads to a marked reabsorption of the fluorescence by ICG itself. The fluorescence spectrum is very wide. Its maximum values are approx. 810 nm in water and approx. 830 nm in blood. For medical applications based on absorption, the maximum absorption at approx. 800 nm (in blood plasma at low concentrations) is important. In combination with fluorescence detection, lasers with a wavelength

of around 780 nm are used. At this wavelength, it is still possible to detect the fluorescence of ICG by filtering out scattered light from the excitation beam.<sup>l</sup>

The intravenous LD<sub>50</sub> values measured in animals are 60 mg/kg in mice<sup>[10]</sup> and 87 mg/kg in rats. Occasionally – in one out of 42,000 cases – slight side-effects occur in humans such as sore throats and hot flushes. Effects such as anaphylactic shock, hypotension, tachycardia, dyspnea and urticaria only occurred in individual cases; the risk of severe side-effects rises in patients with chronic kidney impairment.<sup>[11]</sup> The frequencies of mild, moderate and severe side-effects were only 0.15%, 0.2% and 0.05%

### **Selectively over-heating cells (especially cancer)**

ICG absorbs near infra-red, especially light with a wavelength of about 805 nanometers. A laser of that wavelength can penetrate tissue.<sup>[19]</sup> That means, dying tissue with injected ICG allows an 800 nm-810 nm laser to heat or overheat the dyed tissue without harming the surrounding tissue.<sup>[20][21]</sup> Although overheating is the main mechanism for it to kill cells, a small amount of the laser energy absorbed by the ICG releases free radicals such as singlet oxygen that also damage target cells.

That works particularly well on cancer tumors, because tumors naturally absorb more ICG than other tissue. When ICG is injected near tumors, tumors react to the laser 2.5 times as much as the surrounding tissue does.<sup>[22]</sup> It's also possible to target specific cells by conjugating the ICG to antibodies such as daclizumab (Dac), trastuzumab (Tra), or panitumumab (Pan).<sup>[23]</sup>

Studies have been done,<sup>[21]</sup> and are currently being done, on using this method to destroy cancer tumors without surgery. Early experiments on mice managed to slow tumor growth with a single laser treatment.

Studies are currently examining the combination of ICG laser therapy with a triggered immune response for tumor destruction. This method is similar to cancer vaccine),<sup>[24]</sup> where the immune system is trained to target future recurrences of cancer. Glycated Chitosan is currently undergoing trials for this purpose.<sup>[citation needed]</sup>

ICG and laser therapy has been shown to kill human pancreatic cancer cells (MIA PaCa-2, PANC-1, and BxPC-3) in vitro.<sup>[25]</sup>

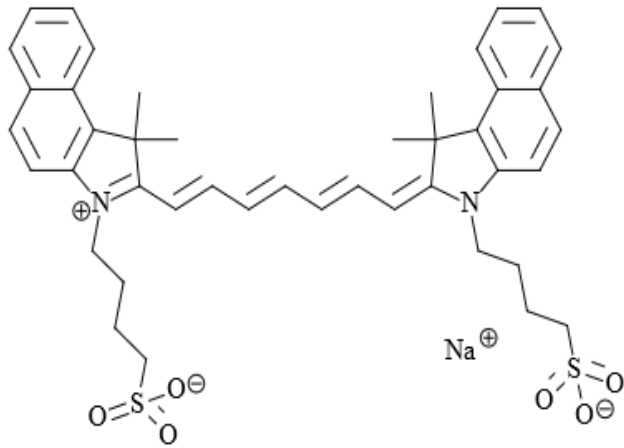


Fig. 18 Molecular structure of Indocyanine green

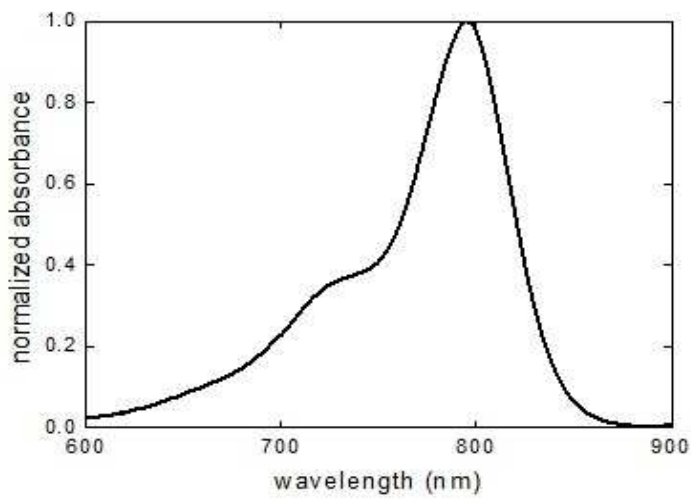


Fig. 19: Indocyanine green Absorption spectrum

A new technology for improved „Tumortargeting“ is the application of ICG in nanoparticles or liposomes.

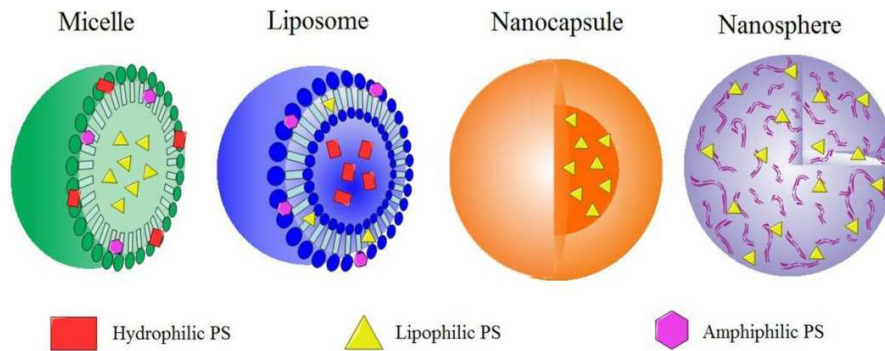


Fig. 20: Different nanoparticles for transport, targeting and delivery of photosensitizers

Liposomes and Micelles were the first investigated nanosystems for improved and more targeted introduction of photosensitizers into tumor cells (Fig.20). They have similar structures characterized by a core/shell model and are so able to incorporate hydrophilic, hydrophobic and amphiphilic substances for delivery into cancer cells ( Fig. 21). So a considerable improved and selective uptake into tumor cells can be achieved combined with an extended retention time of the photosensitizer in the cells. The great advantage is the possibility of several irradiation treatments after a single application of the drug.

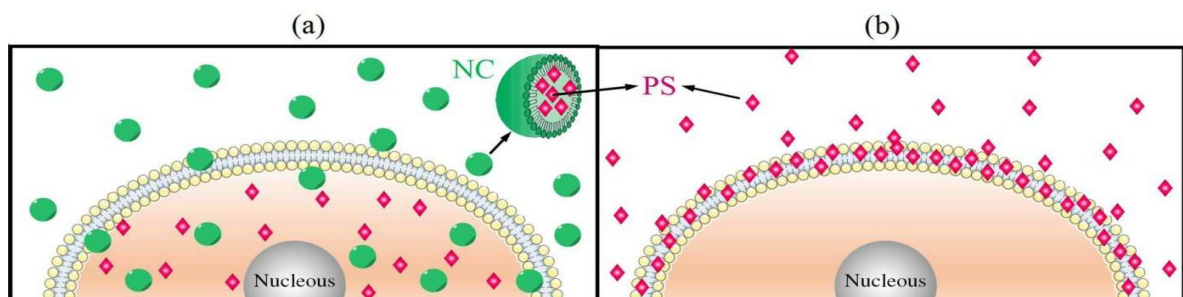


Fig. 21: Illustration of the difference of cell targeting and drug delivery of a lipophilic photosensitizer like Porphyrins (PS) in tumor cells. Photosensitizer (a)

encapsulated in in Polymere Nanokapsules (NC) and (b) non encapsulated (free Porphyrin).

Using the new liposomal/nanosomal technology and improved drug delivery treatment conditions of cancer patients and success rates are much more promising. Prolonged retention time of the photosensitizer allows several laser irradiations with near infrared light (810 nm ). Irradiation of more superficial tumors on or below the skin can be performed externally without penetration of the skin.

Deeper tumors like pancreatic cancer or liver metastases should be treated using the Weber interstitial technology. Fiberoptic canulas of different legths ( available from 2 – 12 cm ) can be placed ultrasound guided on the surface of the liver casule in case of liver metastases or the peritoneum in case of peritoneal cancer. The skin is still a great barrier for laser penetration, even for strong infrared light and absorbs nonspecifically already 80 – 90 % in the first 5 mm. After skin penetration light penetration of deeper layers of the tissue is a lot better. Special fiberoptic catheters with circular or spheric irradiation can also be placed into peritoneal or pleural effusions. The fiberoptic catheter technology can also be used in all urological problems like prostate and bladder cancer.

Infrared laser is able to penetrate the bone quite well so now for first time there is an option for photodynamic treatment of brain tumors and bone metastases.

2 mechanisms are responsible for the improved photodynamic effect of liposomal Indocyanine green

- an overheating hyperthermia effect
- the photodynamic effect creating singlet oxygen radicals

Combination of both effects can be described as “Photothermodynamic Therapy (PTDT) or “Photothermoablation” of tumor tissue.

Liposomal Indocyanine green is now available in 75 mg ampouls and can be ordered from Webermedical GmbH, Germany. Recommende dosage is 1 – 1,5 mg/kg body weight and can be in fused in 30 minutes in 250 ml saline solution.

New possibilities for better and more specific targeting of liposomal Indocyanine gree are now under investigation. Conjugation with different antibodies or hormones are some of the new options.

Combination with Chlorin E6 and other plant derived photosensitizers described above are possible and can improve the therapeutic results. Combination with laser stimulated low dose chemotherapy is another promising option.

#### 4) Immunological effects of photodynamic therapy

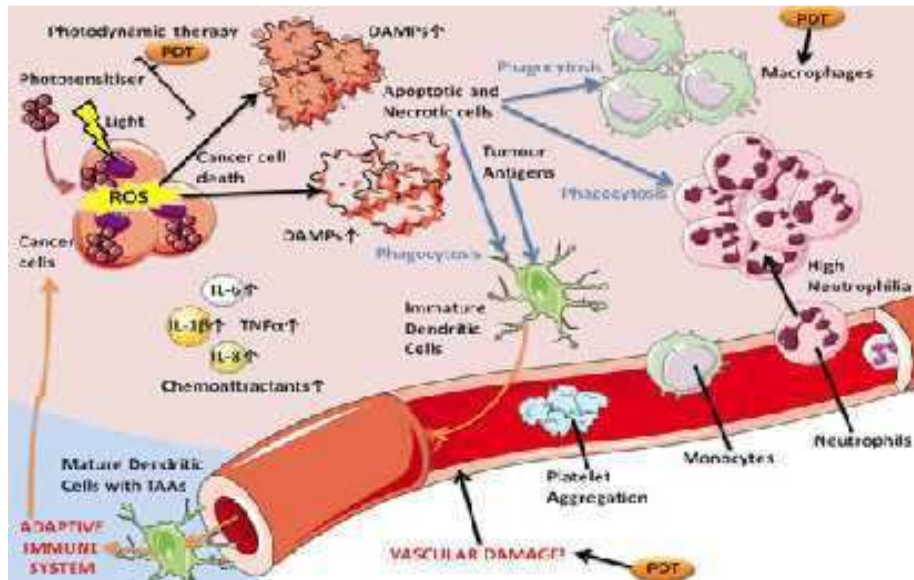


Figure 25: Different reactions within the irradiated PDT area

Contrary to conventional chemotherapy, photodynamic cancer therapy leads to the destruction of tumor cells with a following cascade of immune processes:

- Production of reactive oxygen species and cell necrosis and apoptosis
- Production of DAMP's (damaged molecular patterns)
- Vascular shut-down with tumor starvation
- Increase of neutrophiles and dendritic cells, phagocytosis of tumor debris with immune stimulation
- Dendritic cells take up tumor antigenes, become mature and initiate
- anti-tumor immune response
- Immune reaction by production of different cytokines and chemokines in the tumor micro-environment.

On the one hand, tumor cell necrosis and apoptosis through reactive oxygen species (ROS) leads to the formation of various products (e.g. tumor debris, various breakdown products), but now specific immune reactions follow as a result of these products.



The tumor vessels supplying the tumors will be capped (vascular shut-down of neo-angiogenesis) and tumor tissue is being starved. Proliferation and activation of macrophages takes place as well, together with maturation of dendritic cells. The latter will absorb the tumor antigens and produce a specific immune response with production of cytokines and chemokines both in direct proximity to the tumor tissue and circulating in the rest of the body.

## **5) Combination of PDT with other methods**

The literature shows different options to combine PDT with other treatment regimes:

- Combination with traditional chemotherapy (27)
- Combination with light sensitive chemo drugs (using chemotherapeutic drugs as photosensitizers) (28)
- Combination with antioxidants (29)
- Combination with antiangiogenesis inhibitors (30)
- Combination with Cox-2 inhibitors (31)
- Combination with antibodies (32)
- Combination with different natural compounds
- Combination with immunotherapy (33)

In the following, only combinations with low-dose chemotherapeutic drugs and immunotherapy are presented as their potential to improve the results of PDT is mostly significant.

### **5.1 Combination with traditional chemotherapy: Chemotherapeutic drugs used as photosensitizers in low dose**

In case of big tumor masses or multiple metastases even the described new methods of PDT are often not effective enough. The author's own experience has shown that tumors or metastases larger than 3-4 cm mostly cannot be destroyed by PDT alone or maybe only with multiple follow-up treatments.

The conventional procedures in such cases are well known: If possible, tumor mass has

to be reduced by surgical procedures. In many cases, especially for diagnosed multiple metastases, chemotherapy has to be used as well. However, the side effects of high dose chemotherapy are well known. In this context, a new approach can contribute to the alleviation of the destructive and immune suppressing effects of traditional chemotherapy.

Like the above described natural derived photosensitizers also the different chemotherapeutic drugs have a specific light absorption spectrum and their efficacy can be enhanced by stimulation with appropriate laser light (using chemotherapeutic drugs as photosensitizers). As a consequence, the drug's dose can be reduced significantly and the well known side effects are alleviated. Studies show that chemo drugs in a low dose even have the potential to enhance the immune system in combination with PDT (34).

### 5- FU

A first report in the literature showed that light stimulation increased the efficacy of 5-FU by up to 100 times. The mechanism was described in a shift from the chemical lactam- into the lactim form (35).

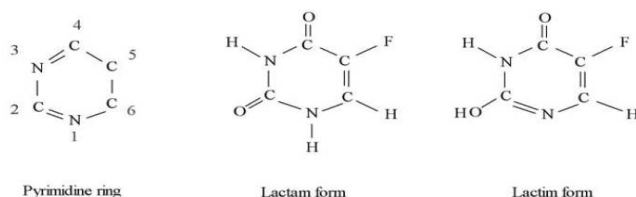


Figure 1. The pyrimidine ring and the two 5-FU tautomers: lactam and lactim forms.

Fig.19-21: The tautomeric forms of 5-FU

### Cis- Platin

For Cis-Platin, an enhancement of the therapeutic efficacy up to 20 times could be shown as well (35). However, the usage of 5-FU and Cis-Platin as photosensitizers is still difficult because the substances absorb ultraviolet light which is only delivered by relatively cost- intensive ultraviolet lasers. From economic points of view, colored chemotherapeutic drugs which absorb in the visible spectrum between 400 and 750 nm are the most interesting ones.

## Mitoxantron

One of them is Mitoxantron, a blue substance in solution, which can be activated by yellow and red light. It has already been shown in earlier publications that it can be used successfully as a strong photosensitizer for breast cancer or malignant melanoma (37,38).

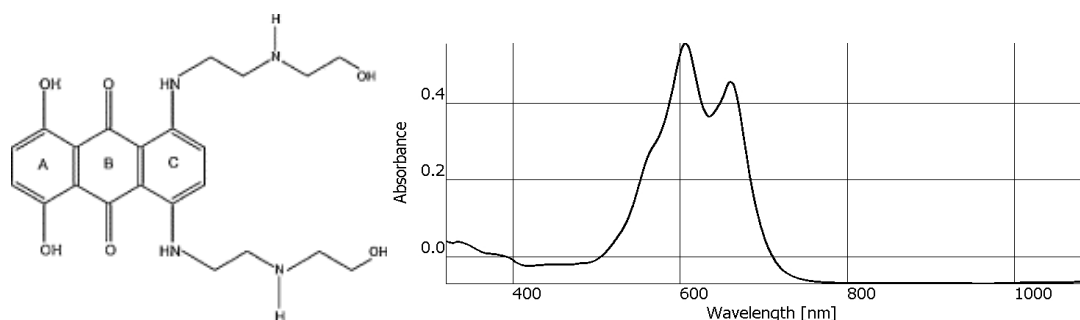


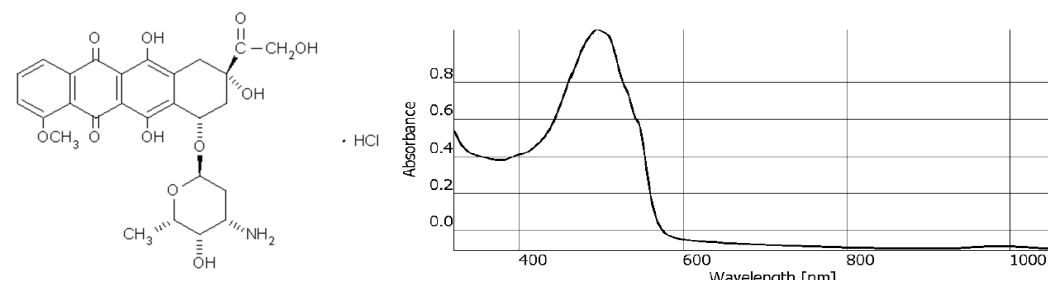
Fig.22: Chemical structure and absorption spectrum of Mitoxantrone

The displayed absorption spectrum of Mitoxantrone was determined in the author's own laboratory using the Photolab 7000 device. Thereby, the absorption spectrum was measured in the exact defined conditions in which it was applied to the patient with intravenous infusion.

More targeted drug delivery to the tumor tissue can even be enhanced by application of liposomal Mitoxantrone (36).

## Doxorubicin

Doxorubicin and other anthracycline antibiotics are widely used for many different cancers. Although they are regarded as very effective against many cancers they have a lot of side effects. Doxorubicin is an orange solution and is stimulated by blue and green laser light. It is already available in a liposomal delivery form (38). In different publications it was shown that Doxorubicin can be used as a strong photosensitizer (39).



24: Chemical structure and absorption spectrum of Doxorubicin

Fig.23-

## 5.2 Hyperbaric oxygenation

The success of photodynamic tumor therapies ultimately depends on the availability of tissue oxygen as the final tumor toxicity is triggered by oxygen radicals.

Unfortunately, tumor tissue is often poor in tissue oxygen. PDT very soon expends the available oxygen. Additive oxygen therapies that increase the amount of available oxygen can thus improve the success of photodynamic tumor therapies.

Therefore, oxygen devices by Regelsberger can be used for intravenous oxygen therapies (..).

However, the optimal solution is the utilization of hyperbaric oxygen chambers (hyperbaric oxygenation). With this method, the concentration of tissue oxygen can be increased up to 20 times.

Already in 2000, Meier et al. reported that hyperbaric oxygenation led to improved results of photodynamic treatments of oesophageal cancer (Meier et al.: 2000).



Figure 26: Hyperbaric oxygen chamber

### 5.3) GcMAF

Another recommendation to support immune reactions after PDT is immunization with macrophage activating substances, e.g. GcMAF from Japan. It can be injected subcutaneously for several months after the PDT treatment. It also can be injected directly into the treated tumor area to enhance the immunological effect of the PDT.

Macrophage activation factor (MAF) are glycoproteins that increase macrophage activity and transform them into natural killer (NK) cells. Vitamin DBP (Gc Protein) is the primary MAF. The glycosylated Gc Protein is the best MAF. Unfortunately, tumor cells produce an enzyme which destroys the body's own GcMAF by a specific enzyme named Nagalase.

Nagalase is an enzyme produced in small amount by liver cells but in large amounts by cancer cells. Nagalase deglycosylates the Gc-protein and so has an immunosuppressive effect. Nagalase is also produced by different viruses, bacteria and fungi. GcMAF macrophage activation therapy is useful in the treatment of many diseases, such as cancer, HIV AIDS, Hepatitis B virus (HBV), Hepatitis C virus (HCV), Herpes Simplex virus (HSV), Tuberculosis, Pneumonia infection, Epstein-Barr virus (EBV), cystitis/urinary tract infection. The therapeutic effects of GcMAF were first described by Nobuto Yamoto from Japan.

#### **General goals of GcMAF therapy are to:**

- Improve well-being and quality of life (QOL)
- Return the patient to good health so that they are able to participate in regular lifestyle activities
- Achieve long term survival
- Enhance the effect of other therapies
- Repair the immune system
- Increase the number of monocytes (macrophages) and activate them to destroy cancer cells, viruses, bacteria and other pathogens in the body
- Increase the rate of maturation of dendritic cells (DCs)

Different sources of GcMAF are available today. There are many claims for GcMAF therapy in the literature, especially cancer, autoimmune diseases and autism. However more research is necessary to approve the therapeutic effects.

## 6) Treatment examples

### 6.1) Treatment of metastasizing small intestine cancer with Chlorin E6

In a first pilot study, the author of this article employed the combination of “systemic PDT” via intravenously applied photosensitizers and subsequent intravenous irradiation as one component and interstitial PDT with fiber optic laser catheters and direct laser activation as the other component to treat a patient with small intestine cancer and 4 liver metastases from May 2010 to May 2011.

The small intestine cancer had been removed operationally in 2009, but 2 new liver metastases developed soon.

The patient had received chemotherapy with different chemotherapeutical agents, but the treatments did not lead to significant improvements and had strong side effects.

A first systemic PDT was given in May 2010 that led to a surprising improvement of life quality and after a second treatment course in June 2010 both metastases were no longer visible in a July 2010 MRI. However, in December 2010 the liver metastases reappeared. In January 2011 the patient was treated with 3 sessions of systemic PDT. Despite this the metastases were still growing slowly.

In February 2011 the patient received a combination of systemic PDT with Chlorin E6 and interstitial laser therapy to treat the metastases. Interstitial therapy was achieved by puncturing the skin with 4 needles and inserting fiber optic catheters to a depth of about 2 cm in the direction of the metastases. This overcame the significant reduction of laser energy by the skin barrier. The needles were not placed directly into the metastases. Red light at 50 mW and 658nm was used to stimulate the injected Chlorin E6 with a power density of 10 W/cm<sup>2</sup> for 20 min. Two weeks after the therapy the metastases changed showing evidence of becoming necrotic.

The combined treatment protocol of systemic and interstitial therapy led to an impressive recovery of the patient (including 5 kg weight gain). She was successfully operated on by partial liver resection at the University Clinic of Göttingen. It was possible to surgically remove all of the remaining liver metastases. Tumor markers had sunk to normal values by 6 weeks following the surgical procedure.

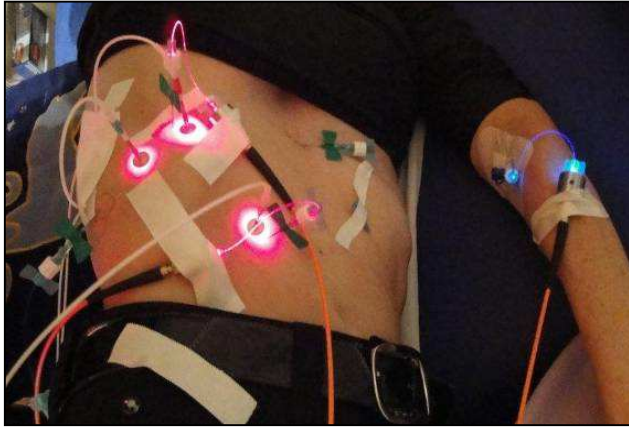


Figure 27: First pilot study with combination of systemic and interstitial PDT

## 6.2) Treatment of metastasizing pancreas cancer

Another patient (76 years) had been suffering from a cancer in the head of the pancreas and that was operated on in August 2012. Only a few months after the cancer reoccurred in the form of malignant ascites. Chemotherapy with Gemzar (Gemcitabine) had to be abandoned due to intolerance to the side effects by the patient. At this point the ascites was out of control, malignant pleural effusions developed as well and a secondary tumor-related anemia set in that required ongoing blood transfusions.

Despite the negative outlook a combination of systemic and interstitial PDT was started. The patient as treated twice and Chlorin E6 was used as a photosensitizer. Treatment was given directly to the ascites through interstitial intra-abdominal applicators.

In addition, the patient received low-dose-chemotherapy with 2x1000 mg Xeloda (Capecitabine) orally. The 5-FU that was released from this pro-drug was stimulated by laser blood irradiation (functioning as a chemo-photosensitizer) as it is known that blue-violet-irradiation increases the tumor toxicity of 5-FU approximately 100 times. After three months, the ascites had completely receded, the secondary tumor anemia had disappeared and MRI examinations showed no recurrence of the tumor and no more sign of peritoneal effusions. Histological studies were entirely normal (tumor free).

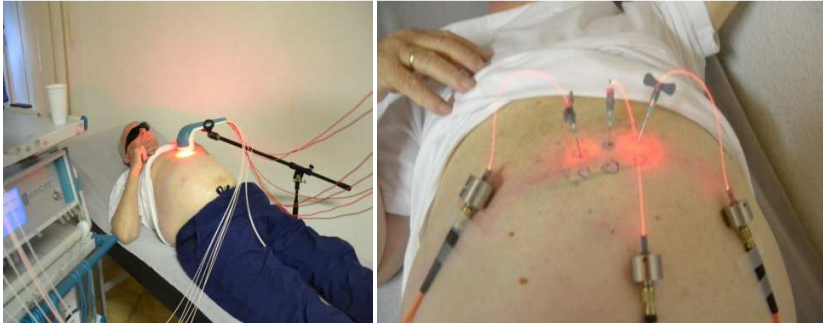


Figure 28: PDT for treatment of pancreatic cancer with malignant ascites, local and intra-peritoneal irradiation.



Figure 29: MRI in the beginning with malignant ascites and 4 months after 2-times PDT.

### **6.3) Treatment of a patient with mediastinal and lumbar metastases after breast cancer**

A 50- years old patient developed mediastinal metastases and lumbar- metastases after an initial breast cancer had already been operated successfully. Both areas were treated interstitially with PDT.

A checkup one year later showed that all metastases had completely disappeared and the lumbar vertebrae were completely stabile.



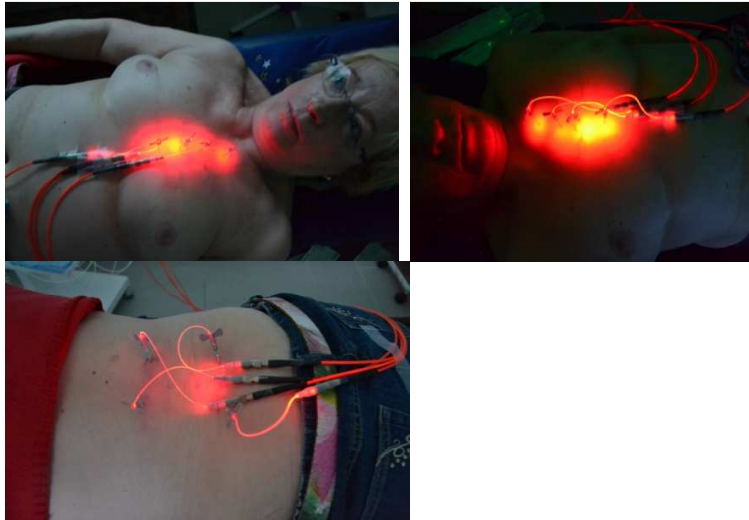


Figure 30: Interstitial PDT of mediastinal and lumbar metastases in breast cancer

#### 6.4) Interstitial PDT of Breast cancer

A patient with recrudescence of operated breast cancer was treated interstitially with Chlorin E6, Hypericin and Curcumin. Afterwards, no signs of tumor growth were visible anymore.

This and many comparable cases showed that direct puncture of breast cancer are often unnecessary - in many cases peritumoral or interstitial irradiation is sufficient. However, the success of this approach decreases with increasing tumor size – it should not be bigger than 3-4 cm.

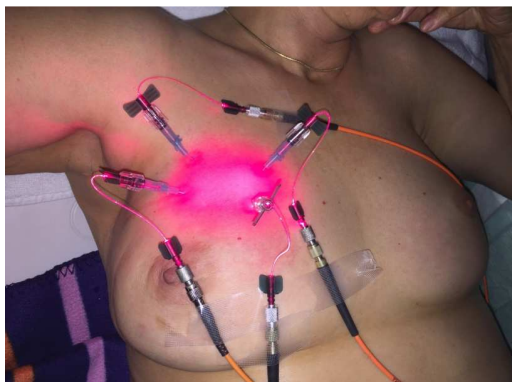


Figure 31: Interstitial PDT of breast cancer

Another patient from New York was treated as explained above. She refused conventional treatments. At the time of treatment the tumor had a size of 5 cm, but no metastases were evident. 6 weeks after the treatment no sign of cancer was evident.

### **6.5) Interstitial PDT of lung carcinoma**

A patient from Tucson, Arizona/ USA, developed a 4,5cm lung tumor in the left upper lobe, located between A. pulmonalis and aorta. It was thus inoperable. Also in this case, an interstitial PDT was conducted with multiple fibre-optic canulas that were applied at the pleura without puncturing the lung. As the evidence suggests, this method brings sufficient amounts of light in the lung to irradiate it deep and effectively. Once again it was shown that overcoming the skin barrier with interstitial technology is the key to successful photodynamic tumor treatments.

8 months after irradiation the tumor had degenerated significantly and the patient felt well.

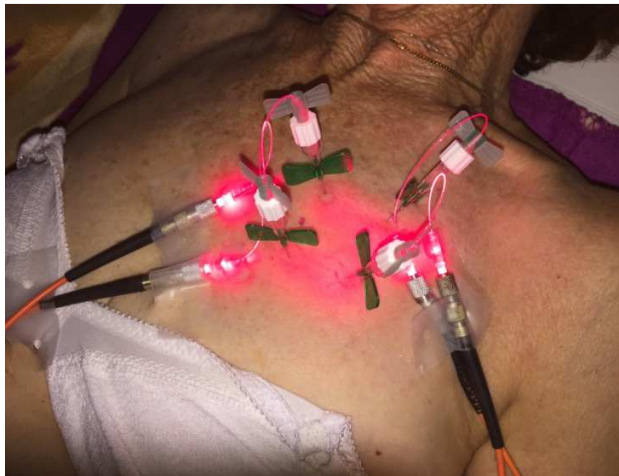


Figure 32: interstitial PDT of lung cancer

### 6.6) PDT for urological cases

It is well known that prostate cancer is one of the most frequent malignancies in men. Conventional treatments consist of operations and/or radiation with severe side effects. In addition, there are thousands of patients who undergo disputable biopsies because of borderline of high PSA levels that are done for screening of prostate cancer. These patients live in permanent fear of prostate cancer.

For treatment of prostate cancer with photodynamic therapy a special catheter system with integrated fiber optic technology has been developed. A thin fiber optic that is attached to a transparent permanent catheter emits radiation in the area of the prostate that penetrates the whole organ. Apart from its usage for prostate cancer, the treatment is also suitable for chronic prostatitis.

Whether an improvement can also be achieved in treatments of benign prostate enlargement is not clarified yet, but previous positive experiences with cases like this raise hopes that good results can also be achieved in this field of application. The new catheter-facilitated fiber optic procedure can also be used for the treatment of bladder cancer in a similar manner. In this case a ball-shaped steel fiber optic is inserted in the catheter.

#### Procedure:

Patients receive the following infusions: 90mg Chlorin E6, 10mg Hypericin and 150mg Curcumin. 3 hours later, the photodynamic intra-prostatic irradiation therapy is given. For 20 minutes irradiation with red light (658nm), yellow light (589nm) and blue light (447nm) is given each for a total of 60 minutes. It is applied through a ball-shaped radiating probe that is attached to a transparent silicon catheter. It leads to the spherical irradiation of the bladder from inside.



Figure 33: Spherically radiating probe for intravesical irradiation of bladder cancer

The treatment is completed after only one session. No side-effects apart from temporary pain are expected.

Bladder cancer is treated in a similar manner, but the urinary bladder has to be flushed thoroughly before the treatment starts. The therapy is also very well suited to treat chronic interstitial cystitis.



Figure 34: Fiber optic for intra-prostatic PDTs for prostate cancer

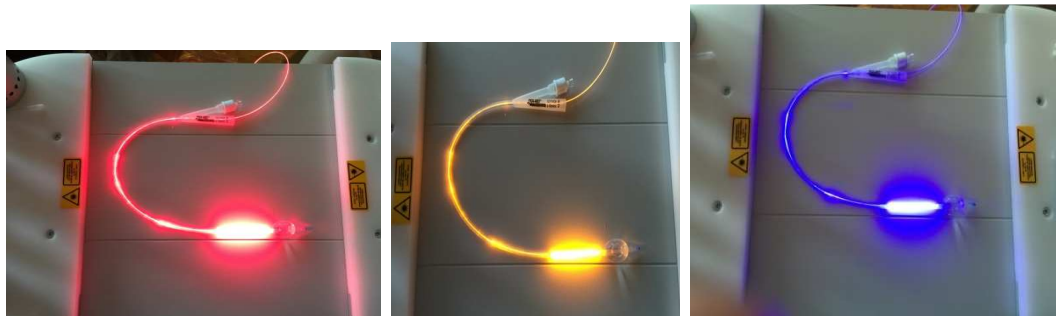


Figure 35: Catheter system for intraprostatic PDT



Figure 36: Spherically irradiating probe for PDT of bladder cancer



Figure 37: Treatment of bladder cancer

### Case studies:

#### 1: Bladder cancer

In October 2014, a patient with bladder cancer was treated accordingly to the technology described above. In February 2015 a PET-CT showed that the treatment had led to complete remission.

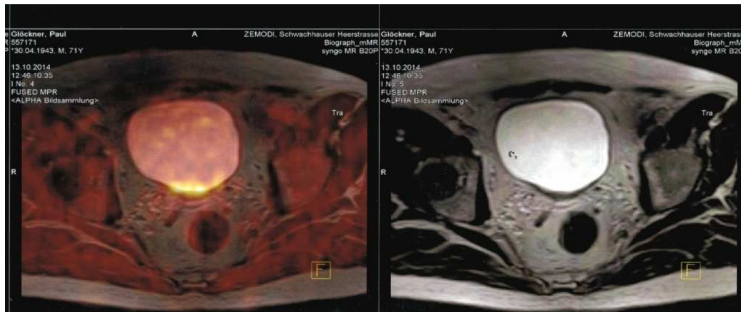


Figure 38: Bladder cancer before PDT

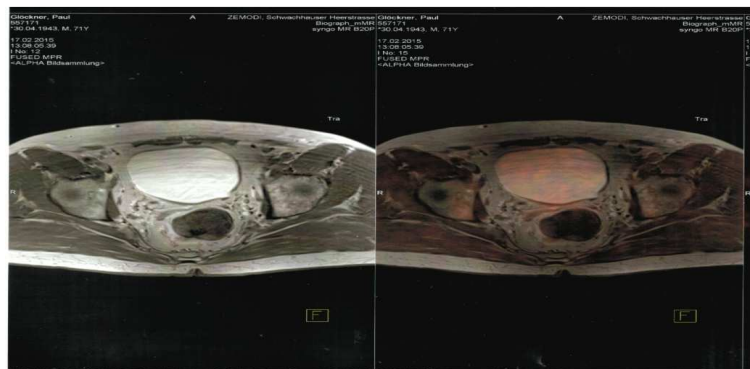


Figure 39: Bladder cancer 5 months after PDT

## 2: Bladder cancer

Another patient from Boston/ USA was treated according to the same scheme and was completely tumor- free after 2 treatments.



Figure 40: Patient with successful bladder cancer treatment

## Prostate cancer: A first study

From May to September 2014, 20 patients with prostate cancer were treated. In 4 cases, a complete remission was achieved. In 7 cases, the treatment resulted in a partial remission. In 7 other cases there was no further cancer progression and in 2 cases progression continued. Many benefits from PDT do not occur immediately, one can expect further improvements in individual cases within the next weeks and months. 8 more patients were treated for chronic prostatitis. 6 of them were free of complaints immediately. In 2 cases a chronic prostatitis reoccurred after several weeks and the treatment will have to be repeated.

## **7) Summary**

An effective photodynamic therapy has to fulfill two criteria:

A highly selective photosensitizer needs to be used and a sufficient dosage of laser light has to be applied at the tumor area to induce necrosis and apoptosis of tumor cells. Until recently, a lack of appropriate photosensitizers and the missing technology to apply light in the depth of the tumor tissue limited photodynamic therapy to dermatological applications.

Today, a number of highly selective photosensitizers (e.g. Chlorin E6, Hypericin, Curcumin and Epigallocatechingallate) and a new fiber- optic catheter technology that facilitates the application of laser light deep in the tissue (by interstitial therapy) set the stage for the establishment of PDT as a new treatment option in oncology.

WeberMedical, a German company, manufactures the laser system that is used with the new fiber optic catheter technology. Many immune reactions go hand in hand with the primary effect of the introduced treatment regime, the destruction of tumor cells:

Through intravenous blood irradiation circulating tumor cells and tumor stem cells can be destroyed and concomitant infections are treated after a photosensitizer has been administered intravenously.

Even though the results of PDT are very promising by itself, the therapy should be regarded as a complementary approach to traditional chemo therapy, not only as an alternative therapy. PDT contributes to lessen the side effects of chemotherapies. Additionally, many chemotherapeutic agents have an absorption spectrum that allows laser treatments to stimulate them as well. In the above mentioned cases where low-dose chemotherapy was used with Capecitabine or Cis-Platin both chemotherapeutics were used as photosensitizers. If they are used in low dosages and in combination with light they can even have immune- stimulating effects.

PDT is a very promising new treatment option in oncology; it is easy to apply and had only been limited due to technological reasons in the past. As shown in this article, these limitations have now been overcome and PDT will in all probability be established as a mainstream treatment for cancer soon.

**Address of the author:**

Dr. med. Dipl. Chem. Michael Weber, Sohnreystrasse 4 37697 Lauenförde

Email: [weber@webermedical.com](mailto:weber@webermedical.com)

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