# Intravenous and interstitial photodynamic lasertherapy: New options in oncology

By Dr. M. WEBER

Summary

**Objective:** Application of different new photosensitizers and new laser technology facilitating photodynamic treatments of oncological patients.
**Method:** A combination of the photosensitizers (Chlorin E6, Hypericin and Curcumin) with intravenous laser therapy (systemic PDT) and interstitial PDT using laser catheter technique.
**Results:** First results are reported on different case reports.
**Conclusion:** The combination of a modern highly specific photosensitizer in combination with intravenous laser blood irradiation (systemic PDT) and interstitial PDT using fibre-optic catheter techniques seems to be a promising new treatment in future oncology and should be investigated in further studies.

**Keywords:** PDT, photodynamic therapy, laser therapy, intravascular laser therapy, interstitial lasertherapy

**Introduction**

Photodynamic therapy is one of the most interesting and promising approaches in the treatment of different cancers. The therapy is easy to perform and – in contrast to chemotherapy – normally without severe side effects.
The principle is the stimulation of a light-sensitive drug which is injected into the blood. Through endocytosis, the so-called photosensitizer binds with high specificity to tumour cells anywhere in the body. The process takes several hours and tumour cells will have become lightsensitive at its end. Tumour tissue can then be destroyed by irradiation with light of appropriate wavelength according to the absorption spectra of the various photosensitizers. The basic principle behind this mechanism is the development of radical oxygen species. Photosensitizers are mostly porphyrin molecules and derivatives either from the human haem (without iron atom) or plant-derived chlorophyll (without magnesium atom). Accordingly, they are called haematoporphyrines or chlorines. Some are already approved and used in therapy, e.g. Photofrin for treatment of early stage bronchial and gastric cancer.

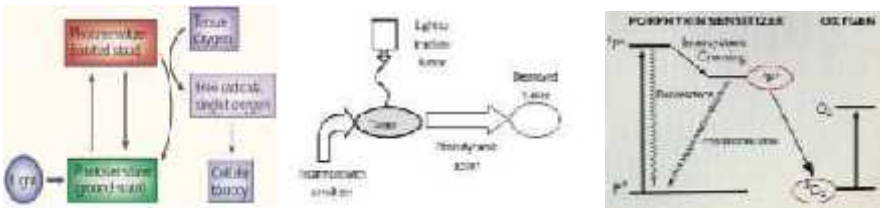

Figure 1: Principle of photodynamic therapy

Red (in most cases), blue or yellow light is used for light activation of photosensitizers either from outside or through an endoscope. Due to the limited penetration depth of light effective photosensitizer stimulation and tumour destruction can only be achieved at the surface of the skin or within only a few cm in the depth of the tissue. An effective treatment of deep tumours or metastases (e.g. liver cancer or lymph nodes) is thus normally not possible and therapeutic applications have so far been primarily used to treat dermatological tumours. Due to this limitation, progress has been slow until recently.

Today, new technological developments that facilitate "systemic photodynamic therapies" and interstitial laser therapies overcome this barrier and constitute the basis for massive growth in the field.

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. In their study, the authors tried to overcome the problem of limited penetration depth by using fibre-optic laser catheters that have been directly inserted in tumour tissue or metastases. With this method, they were able to document an effective and controlled necrosis and were convinced to be able to treat liver metastases as well. They further mentioned that one of the key advantages of the therapy is that it goes almost without side-effects and pain. This leads to a great acceptance by patients. Another advantage is that the therapy can be conducted ambulant.

The idea of treating cancer patients with intravenous laser irradiation („systemic PDT") was first introduced by Kaplan et al in 2008. They ran a study with 76 patients with metastasized malignant melanoma which they treated with intravenously applied Chlorin E6 and 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 arrested for 6 – 12 months. Besides a general boost of the immune system the authors further assumed that freely circulating tumour cells and tumour stem cells had been destroyed by the therapy. This leads to an additional immunisation through tumour decay products. Lastly, the elimination of micro organisms in the blood stream can prevent patients from contracting concomitant infections.

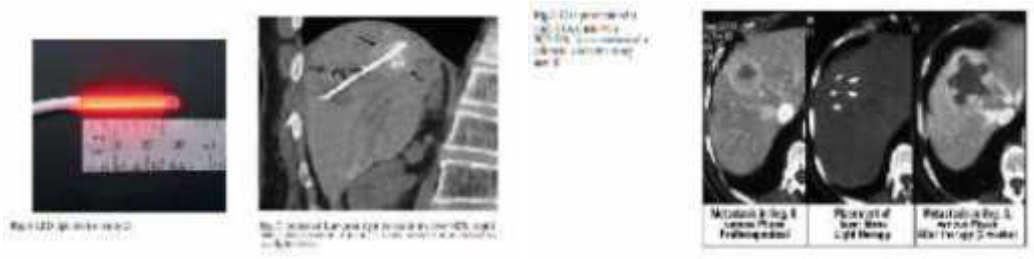

Figure 2: Interstitial PDT of liver metastasis (Vogl. Et al. )

Putting these results together, a combination of "systemic PDT" via intravenously applied photosensitizers and subsequent intravenous irradiation as one component and interstitial PDT with fibre optic laser catheters and direct laser activation as the other component might be established as a new treatment regime for various types of cancer.

**Photosensitizers**

**Overview**

Various photosensitizers are commercially available and therapeutically used over a couple of years but most of them do not fulfil important quality criteria such as sufficient specificity. Photofrin can be regarded as the mother substance but leads to increased light sensitiveness of healthy tissue as well as it does not bind exclusively to tumour cells with sufficient specificity. Its usage might thus lead to damage of healthy tissue as well. It furthermore has to be infused two days in advance and patients will have to avoid sunlight for several weeks after their treatment.
Another general disadvantage of many photosensitizers is that they are relatively expensive.

Table 1 Currently available photosensitizers.

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

Figure 3: Commercially available photosensitizers

The following three photosensitizers are the most promising ones right now as they best meet quality criteria:

**Chlorin E6**

Chlorin E6 plays a crucial role in photodynamic tumour therapy. It is a naturally occurring molecular structure that can be extracted from green plants such as chlorella- alga. It is particularly attractive because it 1) has a very high absorption rate in the red light spectrum (around 660nm) and 2) binds to tumour cells with extremely high selectivity so that practically no collateral damage results from the treatment. It furthermore has photophysical features which are of advantage for PDT: For example, it has a long lifetime in the triplet state and will have selectively accumulated at tumour cells already 3 – 4 hours after it has been infused. It will also have been completely removed from the body after 48 hours which significantly reduces the time in which patients have to avoid sunlight due to their light sensitivity. Already after few hours, tumour necrosis and apoptosis can be demonstrated.

Using blue light with a wavelength of 405nm it can also be used as a drug for photodynamic diagnostic (PDD). The tumour area that is irradiated with blue light hereby gleams red (fluorescence) and the tumour circumference can be determined.

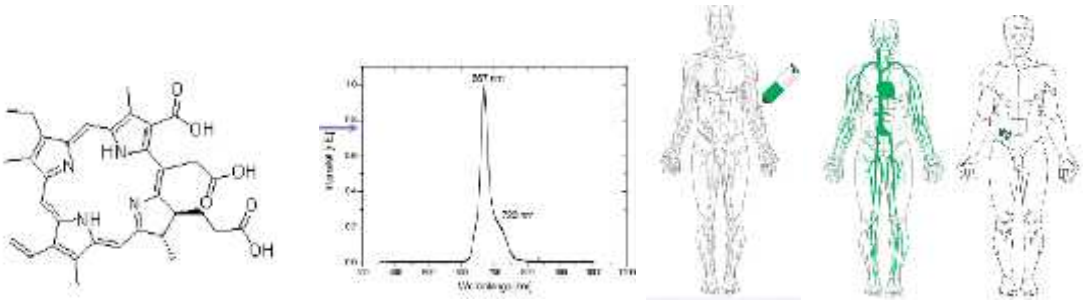

Figure 4: Structure and absorption spectrum of Chlorin E6, therapeutic application

**Hypericin**

Hypericin is a red Anthrachinon-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). In photodynamic therapy, it is not only used in tumour therapy, but also for depression treatments and for treatments of viral and chronic bacterial infections.

A plant extract consists of a mixture of hypericin, pseudohypericin and hyperforin. Since very recently, a 10 mg pure substance is available to produce an infusion solution. The normally hydrophobic substance can be dissolved in physiological common salt solution by binding to human albumin.

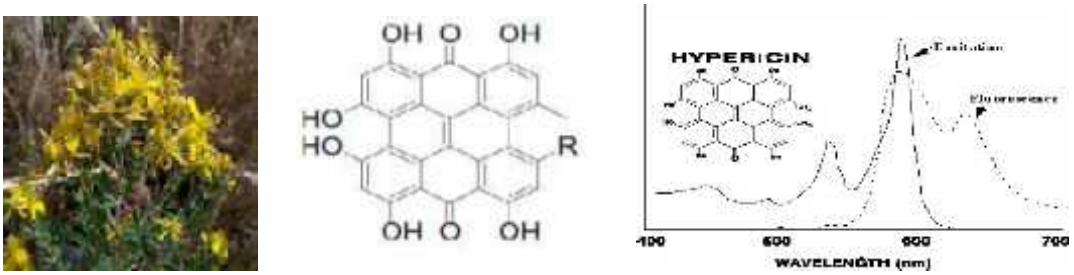


Figure 5: St. Johns Wort, structure formula of Hypericin and absorption spectrum

**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 = Diferulolylmethan, appr. 77 % share
- Curcumin II = Demethoxycurcumin, appr. 17 % share
- Curcumin III = Bisdemethoxycurcumin, appr. 3 % share.

The absorption maximum of curcumin is at 405nm (blue light).

Similar to Hypericin, it can not only be used in tumour therapy, but also for depression treatments and for treatments of viral and chronic bacterial infections.

Since very recently, a 150 mg pure substance is available to produce an infusion solution. The normally hydrophobic substance can be dissolved in physiological common salt solution by binding to human albumin.

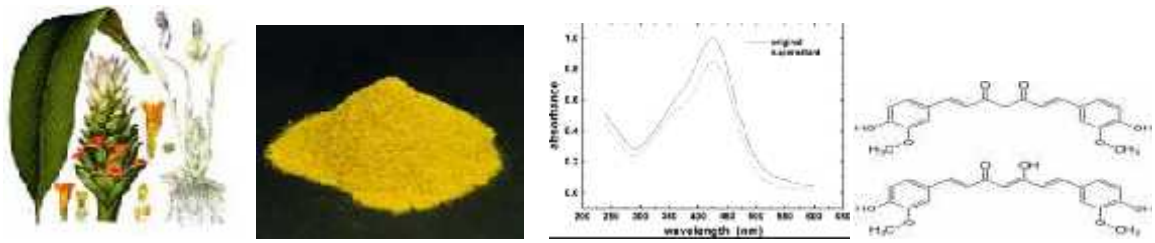

Figure 6: Curcuma longa plant, curcuma powder, absorption spectrum of curcumin and structure formula.

A broad range of studies exists both for Hypericin and for Curcumin that proves the efficacy of these substances. Though they could hardly be used in clinical trials so far as a blue laser that is able to activate Curcumin has been available only for three years and a yellow laser that is able to activate Hypericin has been available only since 2013.

**Immunological effects of photodynamic therapy**

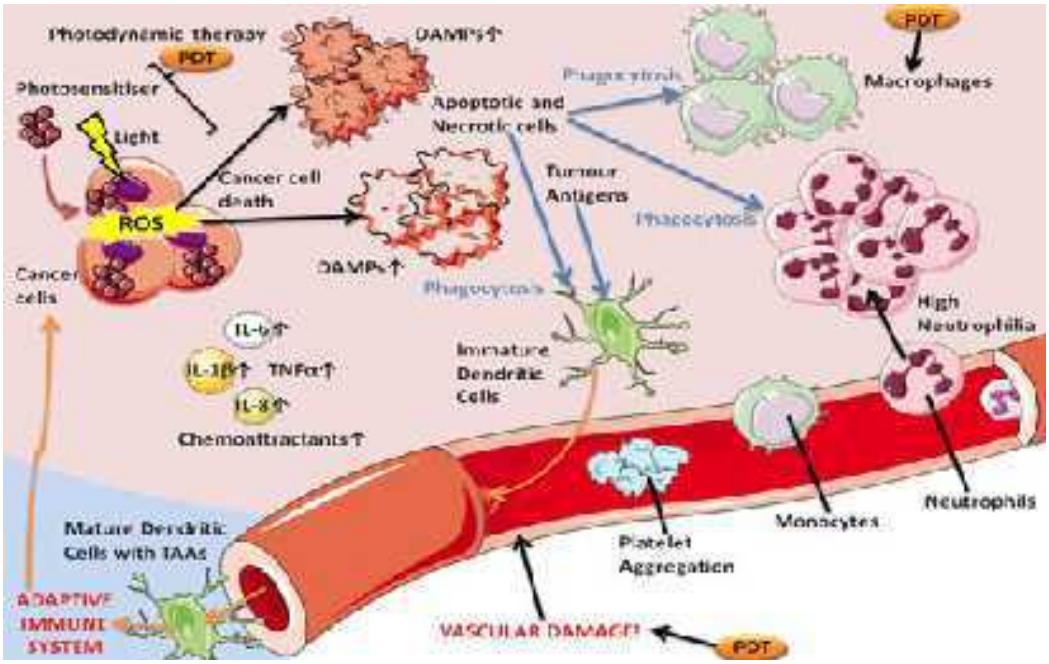


Figure . 7: Different reactions in irradiated PDT area

In contrast to conventional chemo therapies, photodynamic cancer therapies not only lead to the destruction of tumour cells through development of radical oxygen species but also to a variety of subsequent reactions that together lead to significant stimulation of the immune system (PDT- immunisation).
On the one hand, tumour cell necrosis and apoptosis through reactive oxygen species (ROS) lead to the formation of various decay products (e.g. tumour debris, damaged molecular patterns). A specific immunisation derived from these products is possible.

On the other hand, those vessels that nourish the tumours will be capped (vascular shut-down of neoangiogenesis) and tumour tissue will be starved out.
It furthermore causes proliferation and activation of macrophages and to the maturing of dendritic cells. The latter will absorb the tumour antigenes and produce a specific immune response with production of cytokines and chemokines both in direct proximity to the tumour tissue and in the whole organism.

**Treatment examples**

**1. Treatment of metastasizing small intestine carcinoma 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 fibre-optic laser catheters and direct laser activation as the other component to treat a patient with small intestine carcinoma and 4 liver metastases from May 2010 to May 2011.

Previously, the patient had received chemotherapy with different chemotherapeutics but the therapy did not lead to significant improvements and had strong side-effects. Also, the small intestine carcinoma had been removed operationally in 2009 but 2 new liver metastases developed soon after.

A first systemic PDT in May 2010 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 MRT. However, in December 2010 metastases reappeared and in January 2011 the patient was treated with 3 sessions of systemic PDT. But the metastases were still growing slowly. In February 2011 the patient received a combination of systemic PDT with Chlorin E6 and interstitial laser therapy of the metastases. For interstitial therapy, the skin was punctured with 4 needles and fibre optic catheters were inserted to a depth of about 2 cm in the direction of the metastases to overcome the significant laser energy reduction by the skin. The needles were not placed directly in the metastases. Red light at 50 mW and 658nm was used for stimulation of the applied Chlorin with a power density of 10 W/cm2 for 20 min. Two weeks after the therapy the metastases changed and showed 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) so that she could be successfully operated by partial liver resection in the University Clinic of Göttingen. All remaining liver metastases could be removed and tumour markers had sunk to normal values 6 weeks afterwards.

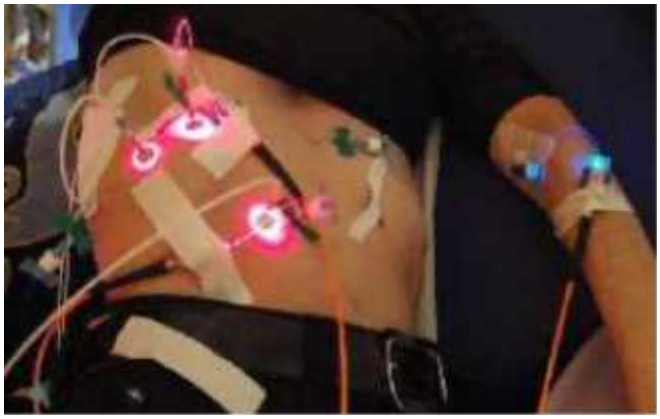

Figure 7: First pilot study with combination of systemic and interstital PDT

**2. Treatment of metastasizing pancreas- cancer**

Another patient (76 years) had been suffering from a pancreas head carcinoma and was operated in August 2012. Only a few months afterwards a recrudescence with malignant ascites developed. A chemo therapy with Gemzar (Gemcitabine) had to be terminated off due to intolerance by the patient. At this moment, the ascites was hardly controllable and malignant pleural effusions and a tumour anaemia that permanently required transfusions occurred as well.
Despite the negative prognosis a combination of systemic and interstitial PDT was instituted. The treatment was conducted two times and Chlorin E6 was used as photosensitizer. Thereby, the treatment was applied directly in the ascites through interstitial intra-abdominal application.
In addition, the patient received low- dose- chemotherapy with 2*1000 mg Xeloda (Capezitabine) orally. The 5- FU that was released from this prodrug was stimulated by laser blood irradiation (thereby functioning as a chemophotosensitizer) as it is by now known that blue- violet- irradiation increases the tumour toxicity of 5- FU approx. 100 times.
After three months, the ascites had been degenerated, the tumour anaemia had disappeared and MRT examinations showed no recrudescence and no peritoneal carcinosis. Control examinations were without pathological findings.

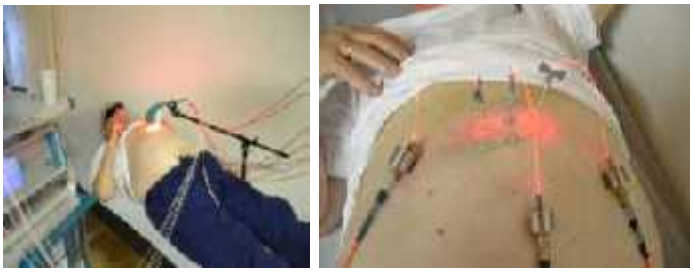

Figure 8: PDT for treatment of pancreas-carcinoma with peritoneal carcinosis, local and intra- peritoneal irradiation.

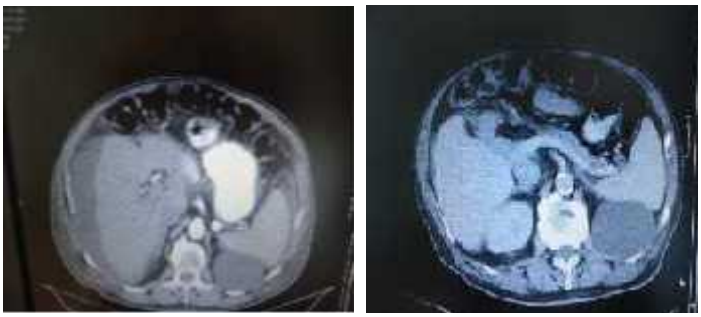

Figure 9: MRT at beginning with ascites and peritoneal carcinosis and 4 months after 2-times PDT.

**3. Treatment of a metastasizing mamma carcinoma**

A 40- years old patient was diagnosed with a mamma carcinoma with a size of 3,5 cm with affection of axillary lymph nodes. The patient refused all kinds of surgical or oncologically established therapies. She received Chlorin E6 with systemic and interstitial PDT. Already after few days a clearly visible necrosis could be observed. After 6 weeks the area was healed and no tumour was detectable anymore.

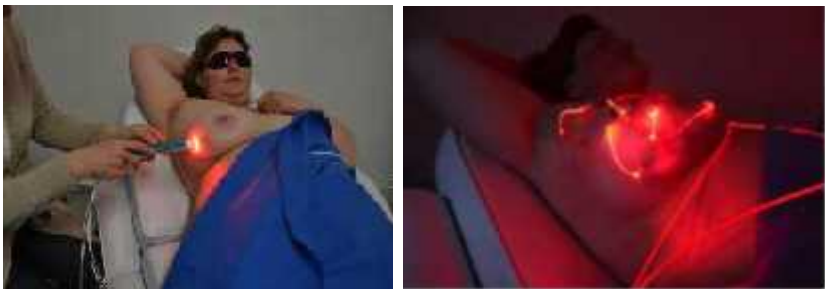

Figure 10: Local and interstitial lasertherapy with Chlorin E6.

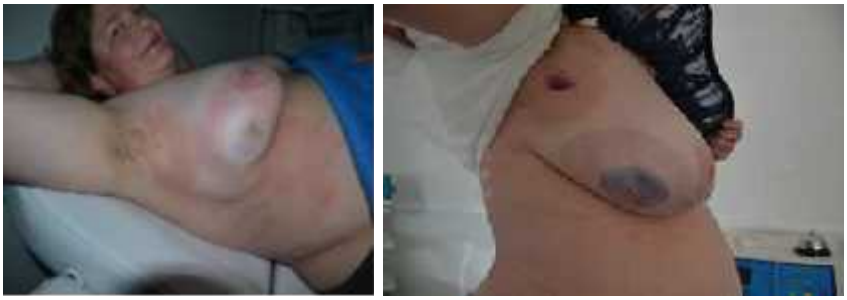

Figure 11: First reaction and beginning necrosis.

Figure 12: Necrosis and healing after 6 weeks

**4. Treatment of another mamma carcinoma**

A patient was treated as explained in example 3. She also refused traditional treatments.
At the time of therapy, the tumour had a size of 5 cm but no metastases could be detected.
6 weeks after the treatment, no tumour could be detected anymore.

**5. PDT for urologic clinical pictures**

As it is well- known prostate carcinoma are the most frequent malignant growths of men. Established therapeutic interventions are operations and/ or radiation therapies with severe side- effects. In addition, there are thousands of patients who undergo disputable biopsies in reaction of results from PSA screenings. These patients live in permanent fear of cancer.
To employ photodynamic therapies to treat prostate carcinoma, a special catheter system with integrated fibre optic has been developed. Thereby, a thin fibre optic that is attached to a transparent permanent catheter emits radiation in the area of the prostate that penetrates the whole organ. Besides its usage for prostate carcinoma, the therapy is also suitable for chronic prostatitis.
Whether an improvement can also be achieved in treatments of benign enlargements is not clarified yet but previous results raise hope that good results can also be achieved in this field of application.
The new catheter- facilitated fibre optic procedure can be employed for the treatment of bladder carcinoma in similar manner. Hereby, a ball- shaped steel fibre-optic is inserted in the catheter.

**Procedure:**

Patients receive the following infusions: 80mg Chlorin E6, 10mg Hypericin and 150mg Curcumin. 3 hours later, the photodynamic intra- prostatic irradiation therapy is conducted with 20 minutes irradiation each with red light (658nm), yellow light (589nm) and blue light (405nm). The therapy is finished after only one session. No side- effects besides temporary pain can be expected.
Bladder carcinomas are treated in equal manner but the urinary bladder has to be rinsed thoroughly with an aliquot before the treatment starts.
The therapy is also very well suited to treat chronic interstitial cystitis.

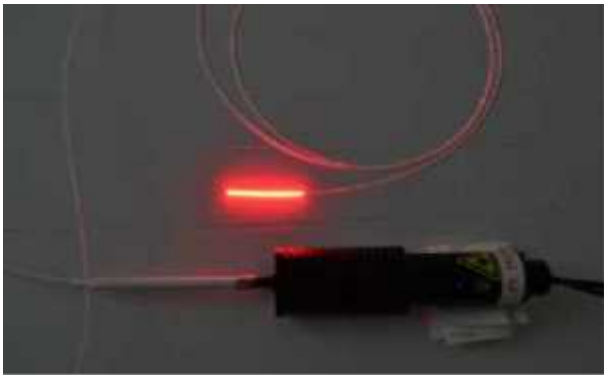

Figure 13: Fibre optic intra- prostatic PDT of prostate carcinomas

Figure 14: Catheter system for intra- vesical PDT of bladder carcinomas

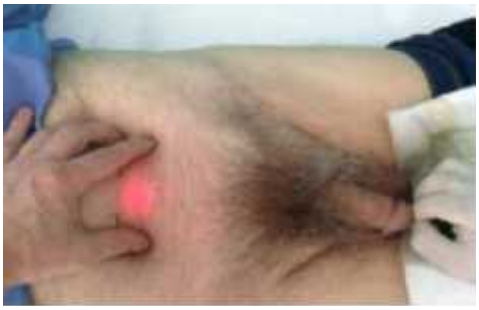

Abb.15: PDT of urinary bladder carcinoma

First results:

From May to September 2014, 20 patients with prostate carcinomas were treated.
In 4 cases, a complete remission was achieved. In 7 cases, the treatment resulted in a partial remission. In 7 other cases, the progression was suspended and in 2 cases progression continued. As many benefits from PDT do not occur immediately one can expect further improvements of the 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 recrudescence occurred after several weeks and the treatment has probably to be repeated.

**Summary:**

An effective photodynamic therapy has to meet two conditions:
A highly selective photosensitizer needs to be employed and a sufficient dosage of laser light has to be applied at the tumour area to induce necrosis and apoptosis of tumour cells. Until recently, a lack of appropriate photosensitizers and the missing technology to apply light in the depth of the tumour tissue limited photodynamic therapy to dermatological applications.
Today, three highly selective photosensitizers (Chlorin E6, Hypericin and Curcumin) and a new fibre-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. The laser system that is used with the new fibre-optic catheter technology is manufactured by WeberMedical, a German company.
Many immune reactions go hand in hand with the primary effect of the introduced treatment regime, the destruction of tumour cells: Through intravenous blood irradiation circulating tumour cells and tumour stem cells can be destroyed and concomitant infections can be treated after a photosensitizer has been given to the body.
In addition, an oxygenation system can be employed as well to improve the micro circulation and oxygen supply. All above mentioned treatments have been conducted with an add- on oxygenation therapy with the oxygenation system of company Oxyven, Germany.
Another recommendation to support immune reactions after PDT is a immunisation therapy with macrophage activating substances, e.g. GcMAF from Japan. It can be injected subcutaneously for several months after the PDT treatment.
Even though the results of PDT are very promising by itself, the therapy should be regarded as a complementary approach to traditional chemotherapy, not as an alternative therapy. It can for example contribute to lessen the side- effects of chemo therapies. Additionally, many chemo therapeutics have an absorption spectrum that allows to use them as photosensitizers their selves. Also in the above mentioned cases where low- dose chemo therapies with Capezitabine or Cis- Platin have been conducted both chemotherapeutics were used as photosensitizers as well.
Another option to optimize the post PDT immune reaction is the direct injection of immune therapeutics in the irradiated PDT area. First results of this approach are expected to be available soon.
All researchers agree that PDT is a promising new treatment option in oncology that is easy to administer and had only been limited due to technological limitations so far. As has been shown in this article, these limitations have now been overcome and PDT will hopefully be established as a mainstream treatment for cancer soon.

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