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Interstitial photodynamic laser therapy in interventional oncology

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Abstract Photodynamic therapy (PDT) is a well-investigated locoregional cancer treatment in which a systemically administered photosensitizer is activated locally by illuminating the diseased tissue with light of a suitable wavelength. PDT offers various treatment strategies in oncology, especially palliative ones. This article focuses on the development and evaluation of interstitial PDT for the treatment of solid tumors, particularly liver tumors. The PDT is mostly used for superficial and endoluminal lesions like skin or bladder malignancies and also more frequently applied for the treatment of lung, esophageal, and head and neck cancer. With the help of specially designed application systems, PDT is now becoming a practicable option

for solid lesions, including those in parenchymal organs such as the liver. After intravenous treatment with the photosensitizer followed by interstitial light activation, contrast-enhanced computed tomography shows the development of therapy-induced necrosis around the light-guiding device. With the use of multiple devices, ablation of liver tumors seems to be possible, and no severe side effects or toxicities related to the treatment are reported. PDT can become a clinically relevant adjunct in the locoregional therapy strategies.

Keywords Interstitial photodynamic therapy · Interventional radiology · Local ablative treatment · Liver malignancies

Introduction

Unsuccessful control of locoregional malignancy remains a major problem causing morbidity and mortality in cancer. The main focus in the management of patients with incurable disease is the relief of symptoms and the delay of consequences caused by the advanced tumor load. Locoregional treatment strategies have shown to be beneficial for these patients. If tumor burden is not advanced, ablative options like laser-induced interstitial thermotherapy (LITT) or radiofrequency ablation (RF) can even be curative [1, 2]. Photodynamic therapy (PDT) is another minimally invasive treatment strategy for the ablation of tumorous masses. Over the past few decades, PDT has been applied to treat a number of oncological diseases. To date, it has mainly been used to treat super-

ficial malignant or premalignant skin lesions and mucosal lesions accessible via endoscope or bare fibers such as carcinoma in situ of the urinary bladder, endoluminal tumors of the esophagus or the bronchus, or tumors in the head and neck region. Except for bladder lesions, where treatment can be curative, the main intention is palliation. The therapeutic options are limited by the modest tissue penetration of the light that is necessary to activate the sensitizer locally.

In combination with special catheter systems, fibers, and the development of new photosensitizers, interstitial PDT can be a feasible treatment option for patients with solid tumors and especially with liver metastases. In phase I multicenter studies, PDT was shown to be feasible and effective in the treatment of liver metastases [3]; further studies are continuing. Other solid tumor masses,

however, can also potentially be treated with PDT as well as with LITT, such as those in the head and neck region or the breast [4, 5].

Principles of photodynamic therapy

The primary mechanism of the photodynamic reaction is the local generation of an active and cytotoxic form of molecular oxygen, singlet oxygen, which causes destruction of tumor tissue and vascular damage. Therefore the photosensitizer is usually applied systemically and is activated locally by suitable light after a given period of time that varies with the photosensitizer. The optimal drug–light interval is the time at which there is a maximum difference between photosensitizer retention in the tumor and the surrounding normal tissue. Light sources are mainly lasers, and the light is guided to the tumor by fibers and endoscopic instruments. The energy of the visible light with the appropriate wavelength can be transferred to the sensitizer, so that the drug reaches a higher energy level. This energy is transferred to molecular oxygen producing singlet oxygen (see Fig. 1). This active form of molecular oxygen has various cytotoxic effects: a vascular stasis of tumor vessels, followed by vascular collapse and the escape of vascular liquid and blood cells [6]. Some authors suggest that the vascular reactions are more important for the PDT effect than generally expected [7]. Release of immunomodulators or cytokines, such as interleukin, prostaglandin, or eicosanoids seems to mediate the cytotoxic effect [8, 9]. Going back to its ground state the photosensitizer emits energy as fluorescence or heat. This phenomenon can additionally be used for tumor detection. Within the first 24 h, the treated area shows evidence of swelling, infiltration of inflammatory cells, and tissue breakdown [10].

Dougherty et al. performed the first systematic studies in 1978 using PDT in superficial lesions in humans [11]. Clinically, the photosensitizer is normally applied intra-

venously and is supposed to accumulate in tissue with rapidly dividing cells [12, 13]. Other studies, however, did not show preferential accumulation [14]. After a specific drug–light interval of some hours up to several days, the light treatment of the target volume follows. The light is guided to the lesion via fibers, endoscopic instruments, or lamps. Without activation neither the sensitizers nor light treatment alone has pharmacologic effects. It is important to realize that in the initial stages (days/weeks) the patient is sensitive to many kinds of light, especially to sunlight.

For useful tumor tissue destruction the following parameters must be carefully selected: type and dose of photosensitizer, drug–light interval (time between drug application and light therapy), irradiance (mW), light dose (J), and wavelength (nm).

Photosensitizers

There are a large number of photosensitizers undergoing various stages of clinical trials. Most are porphyrin derivatives, phthalocyanines, and chlorins. All show a large absorption band between 400 and 430 nm and smaller bands above 550 nm. Bands above 600 nm are normally targeted for PDT treatment [15]. An overview of the main photosensitizers is shown in Table 1.

Photofrin

A first-generation sensitizer, Photofrin (Porfimer sodium, Axcan Pharma Inc., QC, Canada) is probably the best evaluated sensitizer, and is a mixture of oligomer porphyrins. It is activated at a wavelength of 632 nm. In the cell these are taken up by mitochondrial membranes. Clinical treatment uses doses between 0.8 and 2.5 mg/kg body weight and a relatively long drug–light interval of 24–72 h [16]. Tissue penetration at 632 nm is relatively poor (5–10 mm) and thus clinical use is limited. Cutaneous tumors seem to accumulate the drug, as 5–10 times higher drug concentrations were found in comparison to normal skin. However, no general accumulation in tumor cells was observed *in vitro*. The retention of Photofrin in some solid tumors could be caused by poor lymph drainage and fragile vessels within the tumor [6]. It is approved for esophageal and lung cancer in the United States, for bladder, gastric, and cervical cancer in other countries and is under investigation for other applications [16, 17].

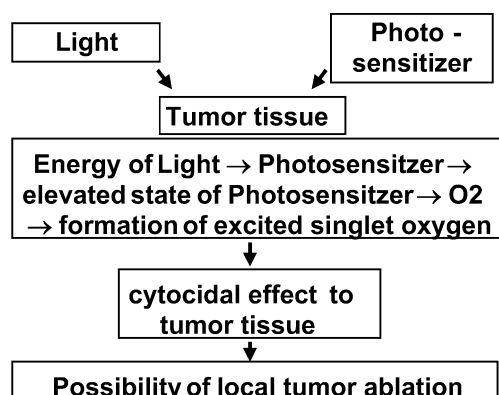


Fig. 1 Principles of photodynamic therapy

Table 1 Photosensitizers mainly used (modified after Sibata [16]; *ca.* cancer, *clin.* clinical)

Name	Wavelength	Description	Indication, <i>advantage/disadvantage</i>
Porphyrins			
Photofrin (porfirmer sodium)	630 nm penetration 5–10 mm	Hematoporphyrin monomers/di-, oligomers	FDA approved for lung and advanced esophageal ca., in Canada for bladder ca. <i>clin. trials:</i> dysplasia in Barrett's esophagus, head and neck, breast ca., pleural mesothelioma, brain, Bowen's disease, cutaneous Kaposi's sarcoma. At 400 nm: photodetection <i>Prolonged photosensitivity</i>
Verteporfin	690 nm	Benzoporphyrin derivative monoacid ring A	Skin ca., choroidal melanoma, prostate ca. (tumor bed sterilization) <i>Short drug–light interval (to 6 h), short skin photosensitivity</i>
Foscan	652 nm	m-THPC, <i>Tetra(m-hydroxyphenyl)chlorin</i>	<i>Clin. trials:</i> head and neck cancer, mesothelioma, bronchial and prostate ca.
Levulan	630 nm	Δ -aminolevulinic acid (Δ -ALA), precursor of endogenous porphyrins	Topical for malignant skin tumors; GI tumors; actinic keratoses at 400 nm: photodetection
Purpurin	660 nm	SnET2, Tin ethyl etiopurpurin	Cutaneous Kaposi's sarcoma (Phase I/II) Preclinical: prostate <i>Transient skin sensitivity to sunlight</i>
Texaphyrins			
Lutrin	732 nm	Lutetium texaphyrin, synthetic porphyrin analogue	<i>Clin. trials:</i> recurrent breast ca. <i>Short drug–light intervals (2–4 h)</i>
Chlorin			
Npe6	660 nm	Mono-L-aspartyl chlorin e6	<i>Clin. trials:</i> superficial/internal tumors <i>Short drug–light interval</i>
Phthalocyanine			
Pcs	660–700 nm	Synthetic porphyrin-like dyes	Phase I trials in dermal ca. <i>Efficient sensitizer, large extinction coefficient in the far red Rapid clearance from skin</i>
Photofrin	Axcan Pharma Inc., QC, Canada		
Verteporfin	Visudyne (QLT Inc.)		
Foscan	Temoporfin (Biolitec)		
Levulan	DUSA Pharmaceuticals, Toronto, ON, Canada		
Purpurin	Miravant Inc.		
Lutrin	Pharmecyclics Inc., Sunnyvale, Calif.		
Npe6	Light Sciences Corporation, Meji Seika, Japan; Snoqualmie, Wash.		

Chlorins

*mTHPBC (5,10,15,20-tetrakis(m-hydroxyphenyl)chlorin)**mTHPC (meta-tetra(hydroxyphenyl)chlorin)*

Foscan (Biolitec, Netherlands) is a synthetic porphyrin derivative with an absorption wavelength of 652 nm. mTHPC has shown to be an effective photosensitizer in various tumor models and in clinical studies [18–20]. There is possible preferential uptake in colon carcinoma in mice [21]. In a rat model, promising results for the treatment of liver metastases of colorectal carcinoma were demonstrated [22]. mTHPC is one of the most potent photosensitizers currently available for clinical use and it is the predecessor of mTHPBC.

SNQ 400 (mTHPBC, Biolitec, Netherlands) is a newly developed second-generation photosensitizer with a maximum absorption at a wavelength of 740 nm that enables a better tissue penetration of light, which is especially helpful in liver lesions. SNQ 400 was used in a phase I study for the treatment of colorectal liver metastases discussed later in this article.

LS11 (*Npe6* or *ME2906*)

The peak absorption of LS11, which is also a monoaspartyl derivative of chlorin e6, is at 664 nm. Clinical phase I and phase II studies show good response rates for cutaneous and early endobronchial tumors. The first results of a clinical phase I study are presented in this article (study 2).

Phthalocyanines (*Pcs*)

Phthalocyanines are synthetic porphyrin-like dyes with a large extinction coefficient at 660–700 nm. Pc6 has its absorption peak at 670 nm and shows a rapid clearance from skin and a good efficacy [23].

Recently developed second-generation sensitizers show a quicker clearance from skin and other normal tissue and therefore a shorter interval of skin photosensitivity than first-generation ones.

Lasers and nonlaser light sources

PDT is dependent on the local light delivery. Therefore, light source and delivery are fundamental aspects of the treatment procedure. Lasers have become the standard light source because of their monochromatic character, high power output, and compatibility with fiber optics. In the past dye lasers with a wavelength of 630 nm were used to activate Photofrin. The light was directly guided to the tumor via quartz fibers. The use of light with a higher wavelength can improve the tissue penetration [6]. In most tissues, light in the 600–700-nm region of the spectrum penetrates 50–200% more than light in the 400–500-nm region [15]. Dye lasers like Nd:YAG and Coherent Lambda-Plus dye lasers are FDA approved for PDT. New developments in diode laser technology achieved adequate power and provided a much higher grade of efficacy [24], while this new technology promises cheaper performance and a wider range of clinical use and compatible photosensitizers.

Relatively new light sources consist of arrays of light-emitting diodes (LED) for surface irradiation but now are also feasible for interstitial irradiation [25]. We used these diodes in study 2.

PDT: clinical use in liver lesions

The use of PDT in the liver has been limited so far for several reasons. Some photosensitizers show more accumulation in normal liver tissue than in liver malignancies. Moreover, light penetration in the highly pigmented liver tissue is limited and extremely dependent on the wavelength; generally, higher wavelengths show better

penetration. Light penetration decreases exponentially as a function of distance. Thus, photosensitizers that require higher wavelengths and an interstitially located light source appear useful in PDT of the liver. Interstitial irradiation of m-THPBC (activated at 740 nm)-sensitized liver tissue resulted in significantly greater necrosis than that of Photofrin- (activated at 632 nm) and mTHPC (activated at 652 nm)-sensitized livers [26]. This illustrates the advantage of near-infrared photosensitizer activation and a specific role for mTHPBC in interstitial PDT of liver tumors.

However, preclinical studies also showed an efficacy of PDT using first-generation photosensitizers in the liver. Purkiss has already reported clinical experiences with HpD (hematoporphyrin derivative) for interstitial PDT in liver tumors. He observed reduced tumor growth compared with nontreated tumors [27]. Rovers et al. showed a complete tumor remission in 87% of cases using mTHPC in a rat model ($n=31$) for the treatment of colorectal liver metastases. The dose of the sensitizer was 0.1–0.3 mg/kg body weight, the light (wavelength 652 nm) was guided via quartz fibers with 100 mW/fiber, applied energy per tumor was 15 J. The mean necrosis per fiber measured 13 mm; the treated tumors, however, were relatively small (24.7 ± 9.4 mm²). Different kinetics for tumor and liver tissue were also demonstrated. While mTHPC concentration decreased quickly in liver tissue it remained high in tumor tissue up to 48 h after administration [22]. These data show the potential of PDT in the treatment of liver malignancies demanding for the development of new sensitizers activated at higher wavelengths, achieving a better tumor-to-tissue ratio and less accumulation in the skin.

Clinical phase I studies

Promising results with interstitial PDT in liver metastases can be reported from two clinical, multicenter phase I studies in our department. In these interventional studies nine patients with ten liver metastases have been treated to date. All patients suffered from recurrent inoperable progressive metastatic cancer after various chemotherapeutic regimens. All patients signed informed consent that was approved by the local ethics committee explaining the nature of the procedure.

Study 1. Five patients with six liver metastases of colorectal carcinoma, four women and one man, were treated. The photosensitizer used was SQN 400 (mTHPBC, Biolitec, Netherlands). It was applied intravenously at a dose of 6 mg/kg body weight in three patients and 3 mg/kg BW in two further patients. The photoactivation followed 120 h later with a diode laser (Ceram Optec, Bonn, Germany), with a wavelength of 740 nm and a fluence of 60 J/cm. For interstitial photoactivation spe-

cial catheter systems (Somatex, Berlin, Germany) were implanted in the liver tumors under CT guidance (Somatom Plus 4, Siemens, Erlangen, Germany) and under local anesthesia (see Fig. 2). Via the catheters, cylindrical diffuser fibers (Ceram Optec, Bonn, Germany) were inserted. There is no development of heat during photoactivation, thus direct therapy control with MR thermometry [28] is not yet possible.

Depending on tumor size and geometry, we used four ($n=2$), five ($n=1$), or seven ($n=2$) catheters and fibers to treat one and in one case two tumors. Contrast-enhanced CT scans (Somatom Plus 4) were performed at 1 week, 1 month, 3, 6, and 12 months after photoactivation. Necrosis was defined as nonenhancing sharply defined

areas. Therapy-induced necrosis was proven in all cases, the diameter around every catheter was 1.5 cm on average (see Fig. 3). After six months, 50% of the treated lesions showed no signs of activity, no contrast enhancement, no further growth but decrease in necrosis. In 60% of the patients the treated lesions were successfully ablated. However, this statement has to be qualified as two patients received chemotherapy 3 and 4 months after PDT. One of these is a responder, the other a nonresponder to PDT. All patients tolerated the treatment well; no major adverse events were observed. We saw one case of a minor burning in the face after sunlight through the shutters and one on the finger after application of a saturation probe (see Fig. 4). Patients carried a luxmeter to measure the light intensity. Other minor complications were minor local burning during injection and a slight thrombophlebitis at the injection site, which did not require specific treatment. Reactions such as local pain and pain in the right shoulder were due to the injection



Fig. 2 Intratumorally positioned applicator system (study 1)



Fig. 4 Local burning on fingertip after oximeter use (study 1)

Fig. 3 Case presentation for study 1 (treatment with SQN400). Liver metastasis of a colorectal carcinoma in segment 8

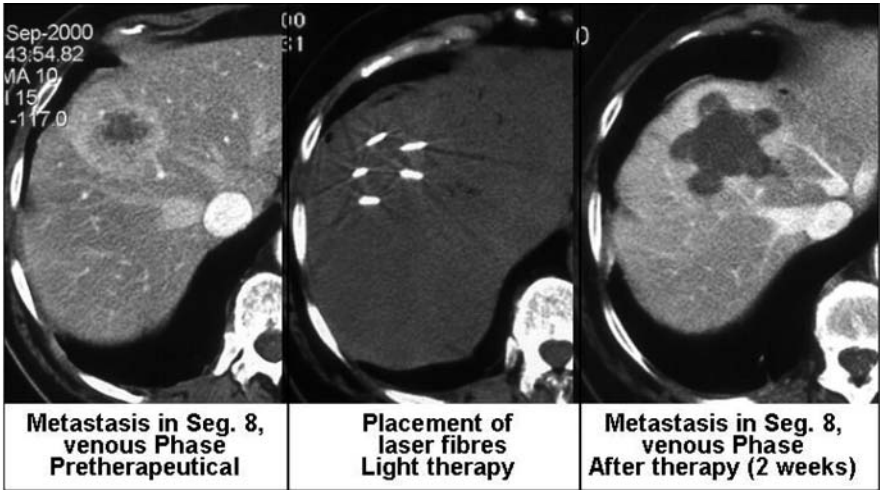


Fig. 5 Procedure of CT-guided placement of Lumatron light device (study 2)

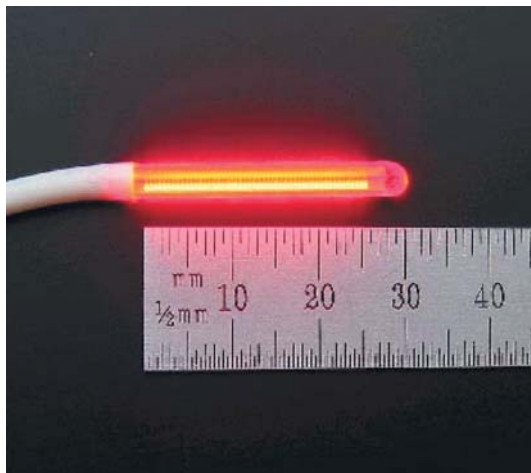
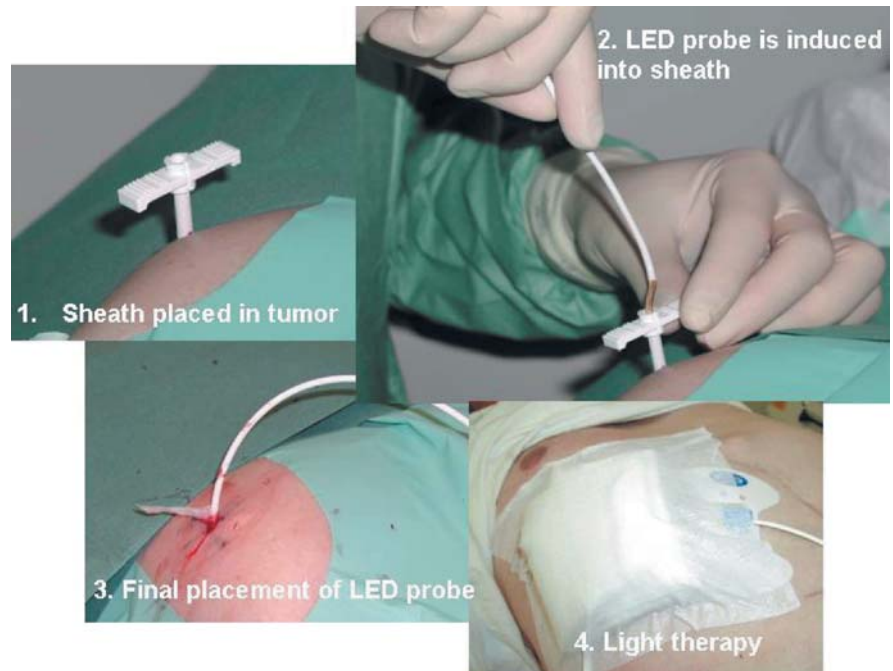


Fig. 6 LED light device (study 2)



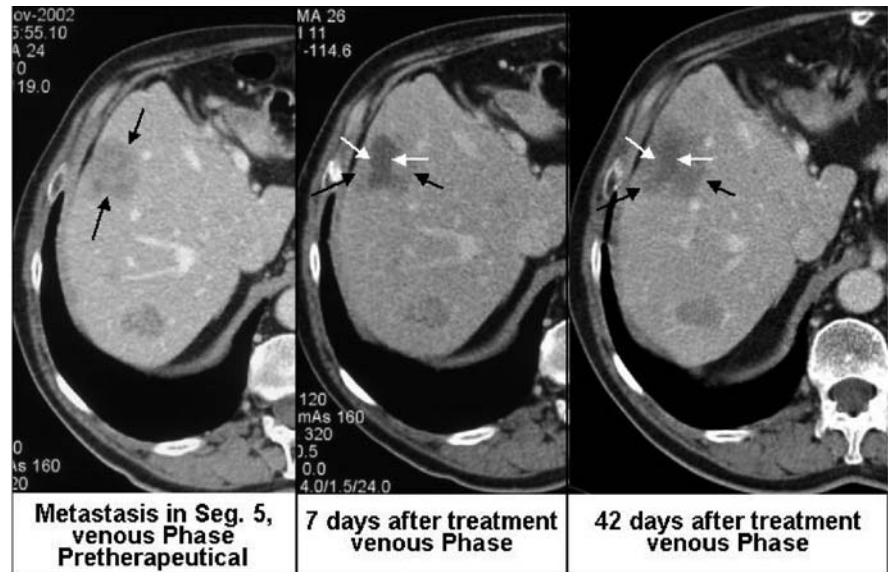
Fig. 7 Implanted Lumatron light device in the liver MPR (multiplanar reconstruction of plain CT scan). Arrows tumor, curved arrow light device

procedure. Systemic changes, especially alterations of laboratory parameters, were not observed.

Study 2. In study 2, four liver metastases in four patients were treated. The study, however, was open to solid tumors in various regions. Primary tumors were colorectal carcinoma ($n=3$) and melanoma ($n=1$). The photosensitizer used was LS 11 (talaporfin sodium, applied dose

40 mg/m^2 , Light Sciences Corporation, Snoqualmie, Wash., USA), which was activated via CT-guided percutaneously inserted intratumoral Lumaflex Light Sources (Light Sciences Corporation; see Figs. 5, 6, 7). These contain a linear flexible 25-mm-long array of LEDs in the distal end. In two metastases one LED device was used, and in another two lesions two devices were used. One hour after a dose of LS 11, light therapy with a

Fig. 8 Case presentation for study 2 (treatment with LS11). Liver metastasis of colorectal carcinoma in segment 5 (*black arrows*), therapy-induced necrosis (*white arrows*)



wavelength of 664 nm and a dose of 100 J/cm² started. In all cases a PDT-induced necrosis around the LED was detected. The mean diameter of necrosis per device on contrast-enhanced CT scans (Somatom Plus 4 Volume Zoom) was shown to be 14 mm (range 13–17 mm). After 6 weeks, partial response/progressive disease were seen in one case each, while in two cases complete response was observed (see Fig. 8 for the example of a partial response). After 3 months, one of the latter cases showed a local recurrence. No cutaneous phototoxicity was observed. The only adverse event observed was a cholalic fistula which was successfully treated with percutaneous drainage applied over a period of 1 week.

Other clinical applications

As mentioned above, PDT is already part of the clinical routine for special indications in mainly endoluminal tumors. Further applications are part of clinical studies.

Esophagus

Since the diagnosis of esophageal malignancies is normally late, PDT is used as a palliative option to improve dysphagia. Here, improvement of clinical signs of up to 9.5 months has been reported. In a randomized trial in patients with obstructive esophageal cancer, the objective tumor response lasted longer after PDT (2.0 mg/kg Photofrin, 300–400 J/cm², wavelength 630 nm, drug–light interval 40–50 h) than after laser treatment with an Nd:YAG laser, perforations were seen less often (1% vs 7%), and the treatment was more comfortable for

the patients [29]. Promising results were recently published for the adjuvant treatment of high-grade dysplasia in Barrett's esophagus in a clinical phase III–IV study. Up to 70% of the patients did not show high-grade dysplasia 2 years after treatment [30].

Urologic

Safe treatment of mucosal or submucosal malignancies of the bladder with PDT is possible. It is also approved as an adjuvant prior to resection of papillary tumors. Light doses for focal treatment are 100–200 J/cm² and around 15 J/cm² for irradiation of the whole bladder [31]. Dysuria, polyuria, and bladder shrinkage can be complications after therapy. The results for appropriate indications are good. In bladder tumors, superficial irradiation seems to be satisfying.

Endobronchial tumors (NSCLC)

PDT is possible in patients who are not candidates for standard resection either with early non-small cell lung cancer (NSCLC) or for palliative treatment in obstructive advanced NSCLC. A Japanese study reported PDT to be superior to Nd:YAG laser ablation in advanced NSCLC for relief of dyspnea, cough, and hemoptysis [32].

The first results of PDT of lung metastases with interstitially inserted diffuser fibers derive from a study in pigs. Up to four fibers were inserted (100 mW/cm). The necrosis of a single fiber measured between 0.7 and 2.2 cm. In contrast to Nd:YAG laser treatment, the tissue

architecture and collagenous structures of the lung parenchyma in the PDT lesions were preserved.

Head and neck cancer

PDT is becoming a successful treatment option in head and neck tumors. Initially used in advanced cancer, it is reported to be used more successfully in the treatment of early-stage cancers in the oral cavity. Biel reported on 107 patients who were treated with interstitial PDT using Photofrin for cancers of the larynx, pharynx, and oral cavity. Some T2 or T3 tumors were treated with a combination of interstitial and surface irradiation. Treatments consist of 2 mg/kg Photofrin, laser activation 2 days later (wavelength 630 nm) with light doses between 50–75 J/cm² for smaller lesions and 80 J/cm² for bigger lesions in the larynx. All 20 patients with T1 tumors of the tongue and floor of the mouth and 23 patients with laryngeal T1 and T2 tumors responded completely (follow-up 40 months). In 13 patients with combined treatment of T2 or T3 tumors, 8 were still disease-free after 3 years [33].

A small Japanese study used rotating optical fibers for interstitial PDT of squamous cell carcinoma of the tongue. The necrosis measured up to 2.4 cm around a single fiber. In two of three treated patients complete remission was achieved [5]. A German pilot study using Foscan (m-THPC) for interstitial PDT in head and neck cancers reported development of a significant necrosis and improvement of the tumor-related symptoms in 11 of the 12 patients treated. However, one severe adverse event was reported; a major bleeding occurred due to erosion of the carotid artery [34].

Skin indications

These indications should be mentioned for the sake of completeness. PDT has already been used in dermatology since the early 1900s [35]. Today it is mainly used to treat cutaneous T-cell lymphoma and cavitory tumors with a psoralen derivative and long-wavelength ultraviolet radiation (PUVA) or porphyrin-based and non-porphyrin-based PDT [36].

Discussion

PDT seems to have the potential to contribute to palliative treatment in oncologic patients. In special indications there might even be a curative option. PDT will not replace surgery, chemotherapy, or other standard therapies, instead, at the moment, it is an adjuvant to these treatment strategies. It is not only well tolerated but also simple. A better healing in comparison to most other lo-

cal treatments seems to be characteristic. It can be performed within a short hospitalization period or even on an outpatient basis and can be ranked in the group of local (ablative) treatments. The most important modalities are LITT and RF, as well as transarterial chemoembolization (TACE) or chemoperfusion, percutaneous ethanol injections (PEI), or local application of chemotherapeutic agents.

LITT of liver lesions of up to 5 cm reaches a high security of tumor ablation with a local control rate of more than 95% after 6 months [37]. The principle is the creation of coagulation necrosis by the thermal effect of the laser. A condition for a good result is the complete destruction of the tumorous lesion not only tumor mass reduction. The long-time survival is comparable to that after surgical resection. A mean survival period of 40.9 months in 606 patients is reported [38]. The lasers used are ND:YAG lasers, the diffuser fibers are inserted via saline-perfused catheters for cooling. In our first study we also used diffuser fibers and similar catheter systems (Somatex, Berlin, Germany). Due to the missing induction of heat during PDT, neither this system nor the LED devices required cooling.

A further ablative procedure is RF ablation. It also develops a coagulation zone by inserting the RF probes percutaneously into the tumor. The size of the coagulation necrosis was still increased by the application of cooled-tip electrodes [39]. In the treatment of small hepatocellular carcinoma (HCC) lesions, a complete necrosis was obtained in 90% of the lesions [40].

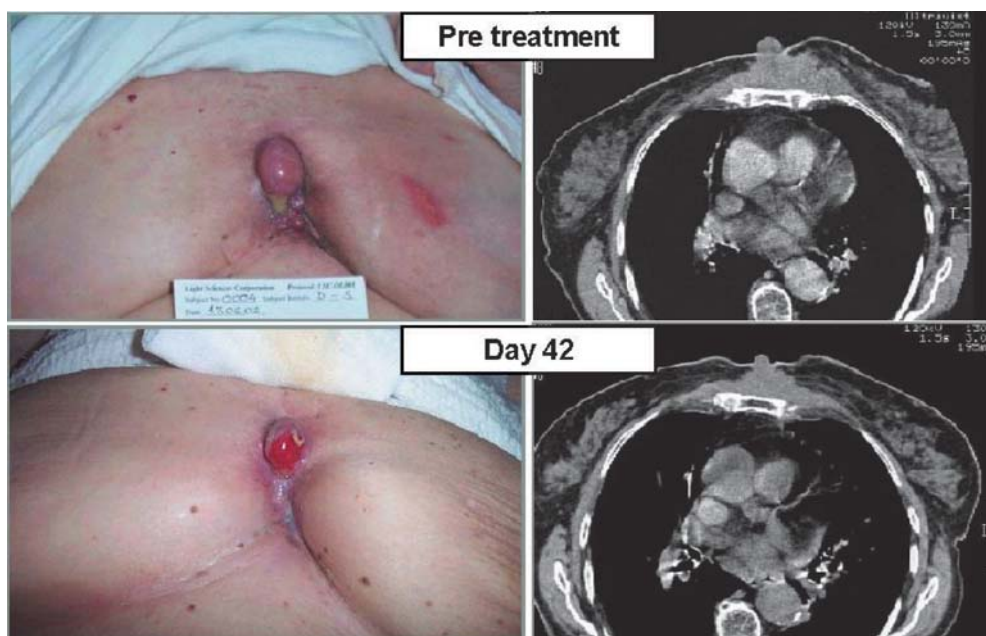
LITT and RF ablative techniques are superior to the other procedures mentioned above in local tumor therapy, if the treated lesions are focal. However, TACE and PEI can be effectively used in some cases. With both techniques very good results can be obtained, particularly in the therapy of HCC, so that these procedures can be indicated when other therapy options are lacking, or when puncture is risky due to present liver cirrhosis or ascites [41, 42].

PDT appears to have a similar potential to local therapy. Reproducible necroses are seen along the fibers. A review of the various studies mostly using second-generation photosensitizers shows development of a comparable diameter of necrosis around a single light source that measures between 0.7 and a maximum of 2 cm, which is still relatively small; LITT and RF produce clearly larger necroses.

Further studies are necessary for the optimization of the necrosis. Variables are dose and drug–light interval. In addition, drugs with a selectivity for tumor tissue and absorption peaks at longer wavelengths are desirable.

The dose difference in our first study does not seem to cause a substantial difference in the size of the necrosis. However, no statistics statement is possible due to the small study population. A recent study from the Netherlands using Foscan demonstrated a disassociation

Fig. 9 Interstitial treatment of a sternal adenocarcinoma with LS 11



between tumor drug levels and optimum drug–light intervals for PDT response in a mouse model. However, there was a good correlation between plasma drug levels and tumor or skin response reported. Thus the authors suggest that the PDT effect is largely mediated via vascular damage and that the selectivity of PDT is not only based on differential tumor drug uptake [7].

The main motivation for the continuing development of PDT is the selectivity of this treatment for tumorous tissue. Preclinical models using interstitial PDT showed stronger effects in development of necrosis in tumor tissue than in muscle tissue [43]. As expected, studies also reveal that damage to a safety margin of adjacent normal tissue is necessary for local control [44]. As another approach to improve selectivity for tumor tissue in the liver, a US and Italian group tried to use antibody-targeted photosensitizers in a model of hepatic metastasis of colorectal cancer in mice. The photoimmunoconjugates with a tumor-normal liver ratio up to 2.5 shows an advantage over literature reports of other photosensitizers, which results in ratios of less than 1 [45]. Based on these data, a further study was initiated to test the efficacy of selective interstitial treatment of hepatic metastases from colorectal cancer with a 17.1A chlorin e6 immunoconjugate in mice. There was a highly significant reduction in the tumor weight after photodynamic therapy and an increase in survival. In contrast, PDT with free chlorin e6 showed smaller nonsignificant decrease in tumor weight and extension in survival [46].

Interstitial PDT using LS11 is reported to be effective also in solid tumor in other locations than the liver, such as the head and neck region or skin metastases of adenocarcinoma (see Fig. 9).

In both of our studies the therapy-induced necrosis around the LED was relatively small with a mean diameter of about 1–1.5 cm. Therefore, confluence of the necroses and total tumor ablation can be a problem. The use of the LED devices was based on the results of a preclinical study in prolonged PDT in normal rat livers, which revealed a significant increase of the necrosis with longer photoactivation. The photosensitizer used was MACE (Mono-L-aspartyl chlorine 6), the light source was an implanted LED device [25]. Another sensitive factor in PDT seems to be the drug–light interval. Preclinical data suggest that for each sensitizer and indication, the suitable dose, drug–light interval, and illumination duration have to be titrated. As mentioned above, it was recently published that the PDT effect with Foscan depends more on the plasma level than on the tumor tissue level. Since Foscan is the predecessor of SQN 400, the same might be the case in our study, and 120 h could be too long for the largest necrosis zone, although another existing study showed a bigger necrosis with longer drug–light intervals.

A review of the volume of necrosis in the literature and our data with a comparable diameter between around 1 and 2 cm (despite different drug–dose intervals, light sources and different PS) suggests that the main limiting factor for a bigger necrosis might be the tissue penetration of light, especially in the liver.

The regional effects of PDT are controllable and the lack of systemic side effects makes interstitial PDT a potential treatment modality for liver metastases. Additionally, PDT is not cell cycle dependent and does not have the problem of multidrug resistance, probably because of

the similarity of the molecular structure with normal cell molecules [47]. As it is a tissue-sparing method, retreatments and multiple insertions are simultaneously possible.

In conclusion, current data show that complete tumor ablation of liver tumors with PDT is possible if complete necrosis of the whole lesion including a safety margin can be achieved. With a multiapplicator technique, the geometry of the tumor must be taken into account and

confluence of necrosis must result. Advantages of this technique are the low rate of side effects and the painless character of the treatment with high patient acceptance, as well as the possible use in an outpatient setting.

Further developments are directed towards the development of PDT systems for a wider range of oncological indications. A phase II study using LS11 with multiple light devices for the treatment of colorectal liver metastases is ongoing.

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