Photodynamic Therapy in Cancer Treatment

RCT summary for professionals

1. Abstract ........................................................................................................................................... 3

2. What is it? ....................................................................................................................................... 4
  2.1 Introduction ................................................................................................................................. 4
  2.2 Principles of photodynamic therapy ........................................................................................ 5
    2.2.1 Biological mechanisms of PDT ......................................................................................... 5
    2.2.2 Basic components of PDT ................................................................................................. 7
      2.2.2.1 Photosensitizers ........................................................................................................ 7
      2.2.2.2 Light sources and delivery ......................................................................................... 9
    2.2.3 Treatment monitoring ......................................................................................................... 10
      2.2.3.1 Dosimetry .............................................................................................................. 10
      2.2.3.2 Optical imaging ...................................................................................................... 11
  2.3 Advantages and limitations of photodynamic therapy ............................................................. 11
  2.4 Mechanisms of synergies ......................................................................................................... 13
    2.4.1 Combinations of photodynamic therapy with standard therapies ................................. 13
    2.4.2 Novel strategies in photodynamic therapy ...................................................................... 14
      2.4.2.1 Nanotechnology in PDT ......................................................................................... 14
      2.4.2.2 PDT-mediated immune response .......................................................................... 16

3. Does it work? ................................................................................................................................. 17
  3.1 Introduction ............................................................................................................................... 17
  3.2 Clinical applications of photodynamic therapy per anatomical location .............................. 18
    3.2.1 Anal cancer ....................................................................................................................... 18
    3.2.2 Barrett’s esophagus ......................................................................................................... 18
    3.2.3 Bile duct cancer ............................................................................................................. 19
    3.2.4 Bladder cancer .................................................................................................................. 20
    3.2.5 Brain cancer ...................................................................................................................... 21
    3.2.6 Cancer of the lower genital tract .................................................................................... 22
    3.2.7 Esophageal cancer ........................................................................................................... 23
    3.2.8 Eye cancer ....................................................................................................................... 25
    3.2.9 Head and neck cancer ..................................................................................................... 25
    3.2.10 Lung cancer ..................................................................................................................... 27
      3.2.10.1 PDT in early stage lung cancer ................................................................................. 27
      3.2.10.2 PDT in advanced lung cancer ............................................................................... 28
      3.2.10.3 PDT in other lung cancer indications ................................................................... 29
    3.2.11 Prostate cancer ................................................................................................................. 30
    3.2.12 Skin cancer ...................................................................................................................... 30
      3.2.12.1 Actinic keratosis .................................................................................................... 31
      3.2.12.2 Bowen’s disease ................................................................................................. 32
      3.2.12.3 Basal cell carcinoma ............................................................................................ 33
4. Is it safe? .................................................................................................................................................. 34
  4.1 Does photodynamic therapy have any complications or side effects? .................................. 34
  4.2 Contraindications for using photodynamic therapy ................................................................. 35

5. Conclusions ......................................................................................................................................... 35

6. References ............................................................................................................................................. 36
  6.1 Scientific publications .................................................................................................................... 37
  6.2 Books ............................................................................................................................................. 53
  6.3 Professional Societies/Organizations ........................................................................................ 54
1. Abstract

Photodynamic therapy (PDT) is a medical treatment that uses the combination of a drug, a photosensitive molecule called a photosensitizer, and visible light of an appropriate wavelength (generally in the red to deep red, between 600-800 nm) to activate the drug. PDT involves a two-step procedure that consists of administering either locally or systemically the photosensitizer, which is retained selectively by malignant tissue, followed by local irradiation of the tissue which eventually results in a series of photochemical reactions forming high-energy oxygen molecules. These reactions occurring in the immediate locale of the light-absorbing photosensitizers mediate cellular toxicity in the tumor and associated vasculature and induction of a local inflammatory reaction. PDT has been under study for several decades and is now an emerging treatment modality for a range of primarily malignant conditions. It is generally used as either a primary treatment or as an adjunctive treatment alongside surgery or chemotherapy. PDT is under clinical investigation for the treatment of cancers of mainly head and neck, skin, esophagus, lung, gastrointestinal and genital tract, bladder, prostate and brain. Recent systematic reviews revealed that PDT can be considered as an option in the treatment of malignant and premalignant non-melanoma skin lesions. It is also useful in the treatment of Barrett’s esophagus and unresectable cholangiocarcinoma. In general, the advantages of PDT over classical chemotherapy or radiotherapy rely on lower long-term morbidity, improved functional and cosmetic outcome, the possibility of repeated treatments either alone or as adjuvant therapy. A perceived limitation of PDT, however, is that it is a localized therapy and has little benefit in widespread disease. Current research is focused on the development of photosensitizers that would be more powerful and more specifically target cancer cells. Ongoing research exploiting the property of PDT to stimulate the host’s anti-tumor immunity might expand the rather selective therapeutic applications of PDT to disseminated disease. This review will address the basic principles of PDT and summarizes its current clinical status.

Keywords: photodynamic therapy, PDT

This text is written by Erik Cabuy (RCT) and reviewed by Prof. Patrizia Agostinis (Cell Death Research and Therapy Unit, Department of Cellular and Molecular Medicine KU Leuven, KU Leuven, Leuven, Belgium) and by Prof. Peter de Witte (Laboratory of Pharmaceutical Biology, KU Leuven, Leuven, Belgium).
2. What is it?

2.1 Introduction

The first attempts to use photosensitizing drugs dates back to ancient Egypt, India, and Greece, where psoralen-containing plant extracts and light were applied to treat psoriasis and vitiligo (Daniell and Hill, 1991). The concept of photodynamic therapy dates from the early days of the twentieth century. The use of an applied photosensitizing agent in combination with light to treat disease may be attributed to Raab who as a medical student unintentionally destroyed paramecia that had been incubated in a fluorescent dye when strong light was introduced (Raab, 1900). The term photodynamic effect was coined by Von Tappeiner in 1904 to describe oxygen-dependent chemical reactions induced by photosensitization and eventually, by the early 1900s brought photodynamic therapy to the clinic (Jodlbauer and Von Tappeiner, 1904; Jesionek and Von Tappeiner, 1905). The modern explosion of interest in PDT dates from the discovery of hematoporphyrin derivative (HpD) by Lipson and Baldes (Lipson and Baldes, 1960), and was fueled by pioneering studies in both basic science and clinical application by Dougherty (1974) and co-workers (1978; 1979). Although the application of the principles of photodynamic effect to patients’ treatment and what became photodynamic therapy (PDT) was practiced in 1960s and 1970s, clinical trials were only started in the 1980s, following successful synthesis of clinically usable photosensitizers (drugs) and the manufacturing of light sources (Mitton and Ackroyd, 2008).

PDT belongs to the light induced therapies. Unlike other phototherapies, PDT employs a sensitizing agent that when activated by an appropriate wavelength and intensity of light, in the presence of oxygen, will lead to toxic photodynamic reactions that may cause direct cancer cell killing and disrupt of the tumor vasculature (Allison et al., 2004). On the other hand, the use of light to cause damage to diseased cells through localized heat generation is referred to as photothermal therapy (PTT). PTT including derivatives hereof such as laser immunotherapy will not be covered in this review. Phototherapy thus distinguishes itself from PDT by lack of oxygen dependence. From the point of view of biological response, PDT is fundamentally different from other cancer therapies. Unlike ionizing radiation, PDT achieves its cytotoxic effects primarily though damage to molecular targets other than DNA. The specific subcellular targets damaged by PDT depend on the photosensitizer’s localization within the cell, which varies among photosensitizers and cell types. PDT can be ranked among cancer therapies (including cryotherapy, hyperthermia, and focused ultrasound ablation) producing a chemical and physical insult in tumor tissue perceived by the host as localized acute trauma. PDT in particular is a promising approach to cancer treatment because of the absence of systemic toxicity of the drug in the absence of light irradiation, the possibility to irradiate the tumor selectively, the opportunity of treating multiple lesions simultaneously, and the ability to retreat a tumor to improve the response. It has particular appeal in oncology because the use of chemotherapy, ionizing radiation, or surgery does not preclude the use of PDT, and all of these approaches can be used in a patient who has received PDT. Despite these advantages PDT remains unknown to many oncologists.

PDT has been investigated most extensively in disorders for which standard treatment has low efficacy or unacceptable side-effects. Examples include premalignant conditions and
tumors that are inaccessible by surgery or would be associated with unacceptably high morbidity. PDT is approved for clinical use in a number of countries worldwide for the elimination of early stage malignancies, palliation of symptoms, and reduction of obstruction in patients with late stage tumors. Researchers continue to study ways to improve the effectiveness of PDT and expand it to other cancers. Clinical trials are under way to evaluate the use of PDT for cancers of the skin, cervix, head and neck, esophagus, lung, gastrointestinal and genital tract, bladder, prostate, and brain. Other research is focused on the development of photosensitizers that are more powerful, more specifically target cancer cells, and are activated by light that can penetrate tissue and treat deep or large tumors. Researchers are also investigating ways to improve equipment and the delivery of the activating light. The purpose of this review is to outline the principles by which PDT ablates tumor tissue within the human body, including limitations, mechanisms of synergies, and patient outcomes are presented.

2.2 Principles of photodynamic therapy

2.2.1 Biological mechanisms of PDT

PDT is a treatment modality involving the topical or systemic administration of a photosensitizing compound. Currently, it is believed that most photosensitizers (PSs) travel intravenously as complexes of serum proteins (Allison et al., 2008). At this small size they may not generally be recognized by the reticulo-endothelial system, though PS may still undergo uptake by the Kupfer cells of the liver. The PSs are then taken up preferentially by rapidly proliferating tissue, such as tumor tissue, although the mechanisms of this phenomenon are not well understood (Nowis et al., 2005a). This may be through a mechanism similar or identical to the low-density lipoprotein receptor. Leaky neovascularity will also allow for enhanced permeability and accumulation of the PS in the tumor region (Allison et al., 2010). PDT drugs in their free state need to be lipophilic to pass through cellular membranes and reach subcellular sites sensitive to the initial oxidative damage that will subsequently destroy cells (Wang et al., 2011). The PS can be localized in various organelles such as mitochondria, lysosomes, endoplasmic reticulum, Golgi apparatus and plasma membranes and this sub-cellular location governs much of the signaling that occurs after PDT (Mroz et al., 2011a). A period of time is required to permit photosensitizer uptake ranging from a few minutes up to several days. The PS is then activated at a specific wavelength of non-thermal monochromatic light and in the presence of oxygen, produces reactive oxygen species (ROS). The accumulative presence of these cytotoxic photoproducts starts a cascade of molecular and biochemical events resulting in cell death via apoptotic or necrotic mechanisms (Dougherty et al., 1998; Buytaert et al. 2007). The use of a focused non-ionizing light beam for drug activation instigates selective killing of tumor cells. Sometimes the destruction of tumor cells is manifested as swelling and formation of necrotic tissue. The damaged/killed tissue eventually sloughs away (or is resorbed), and there is normal healing of the treated site. The antitumor effects of PDT derives from 3 inter-related mechanisms: direct cytotoxic effects on tumor cells, damage to the tumor vasculature, and induction of a robust inflammatory reaction that can lead to the development of systemic immunity (Olivo et al., 2010). Each of these mechanisms will be described briefly.
Unique to PDT is the generation of an oxygen dependent photodynamic reaction. Following the absorption of light (photons), the sensitizer is transformed from its ground state (singlet state) into a relatively long-lived electronically excited state (triplet state) via a short-lived excited singlet state (Henderson and Dougherty, 1992). The triplet state can undergo two different reactions. First it can undergo electron transfer to form radicals that interact with oxygen to produce oxygenated products, which effectively oxidize the cellular components at locations where they have been produced (Calzavara-Pinton et al., 2007). Alternatively, it transfers its energy directly to ground-state triplet oxygen to form singlet oxygen ($^1O_2$), thought to be the main mediator of PDT. The first alternative is called type I reaction, the second type II reaction. PDT-generated reactive oxygen species (ROS) subsequently lead to severe oxidative stress causing damage to different intracellular membranes/organelles in the treated cells and consequently lead to cell death. The lifetime of singlet oxygen is on the order of microseconds and is limited to approximately 200 nm in diffusional range (Hopper, 2000). Consequently, $^1O_2$-mediated oxidative damage will occur in the immediate vicinity of the subcellular site of photosensitizing molecule localization during light exposure. Tissue damage is therefore restricted to the penetration depth of the light used to activate the photosensitizer. Different cell death modalities activated by PDT have been described such as those involved in apoptosis (self-killing), cell death associated with autophagy (i.e. self-eating) and necrosis (Nowis et al., 2005b; Garg et al., 2010; Mroz et al., 2011a). To achieve the desired therapeutic effect, this procedure should leave the surrounding healthy tissue unharmed, and thus production of ROS should be spatially limited to the tumor tissue.

PDT also damages the tumor-associated vasculature. The shutdown of tumor vessels may lead to local depletion of nutrients and oxygen and therefore trigger secondary PDT related necrosis. Apart from direct cell killing and damage to the tumor vasculature, PDT can also activate the host’s immune response against the tumors (Korbelik, 1996; Dougherty et al., 1998; Dolmans et al., 2003; Korbelik et al., 2005; Castano et al., 2006; Gollnick and Brackett, 2010; Mroz et al., 2010; Mroz et al., 2011b). Numerous preclinical and clinical observation studies have demonstrated the immuno-stimulatory capability of PDT, however, the precise molecular mechanisms underlying PDT-induced antitumor immunity are not well defined. PDT would alter the tumor microenvironment by stimulating the release or expression of various pro-inflammatory and acute phase response mediators from the PDT-treated site (Cecic and Korbelik, 2002; Gollnick et al., 2003; Cecic et al., 2006; Korbelik et al., 2008). PDT thereby prompts a powerful acute inflammatory response, causing accumulation of neutrophils and other inflammatory cells in large numbers at the treated site and attack tumor cells (Krosl et al., 1995; Cecic et al. 2006). Studies reported infiltration of lymphocytes, leukocytes and macrophages into PDT-treated tissue, indicating that PDT has the capability to activate the immune response. Several preclinical studies demonstrated that PDT is able to control the growth of tumors present outside the treatment field (e.g. Kabingu et al., 2007), although others have failed to demonstrate control of distant disease after PDT (e.g. Thong et al., 2008). While it is possible that the intracellular site of action of the photosensitizer and type of cell death that ensues following its light-activation may influence the immunogenic properties of the target cells (Garg et al., 2012), different studies highlighted that compromising the host immune system has a negative impact on tumor cure rates (Korbelik, 2006).
PDT-mediated anti-tumor immune responses are reviewed in Agostinis et al. (2011) and Mroz et al. (2011b).

The combination of all three PDT mechanisms may lead to long-term tumor control via anti-tumor action against both the primary and metastatic tumors (Dolmans et al., 2003; Castano et al., 2006; Gollnick and Brackett, 2010). The relative contribution of these mechanisms depends to a large extent on the type and dose of PS used, the time between PS administration and light exposure, total light dose and its fluence rate, tumor oxygen concentration, and perhaps other still poorly recognized variables (Agostinis et al., 2011). All of these factors are interdependent (Dolmans et al., 2003). Thus the choice of optimal combinations of these parameters is crucial for successful PDT.

2.2.2 Basic components of PDT

While clinically relatively simple to perform, in reality PDT is a complex interaction requiring numerous components to be available both in time and space. Here we will review the key components of current PDT i.e. the photosensitizers and light sources.

2.2.2.1 Photosensitizers

Photosensitizers (PSs) are critical to the successful eradication of malignant cells and numerous first and second-generation photosensitizers have been tested both clinically and *in vitro* over the past years. The properties of an ideal photosensitizer should include (Moan, 1990b): a minimal dark toxicity, selective accumulation in target tissue, a short time interval between administration and maximal accumulation in target tissue, rapid excretion from the body to give minimal systemic toxicity, a high quantum yield of ROS production, which is often mediated by singlet oxygen and a high extinction coefficient in the 600-800 nm range, where light penetration into tissue is maximal, and where the photons still have enough energy to produce $^{1}\text{O}_2$. However, such an ideal photosensitizer has not been found yet. To date, several PSs are commercially available and some of them are approved for the treatment for oncologic indications. Most of the PSs used in cancer therapy are based on a tetrapyrrole structure, similar to that of the protoporphyrin contained in hemoglobin, and are derivatives of porphyrins, chlorines and bacteriochlorins (Allison and Sibata, 2010a). Photosensitizers are generally classified as porphyrins and non-porphyrins. Porphyrin-based photosensitizers are also often classified as a first, second, and third generation PS.

The first PS used clinically in PDT was hematoporphyrin derivative (HpD). Its purified fraction porfimer sodium later became known as Photofrin. Photofrin and HpD are first-generation photosensitizers. They are known to have two major drawbacks. One is the time taken (typically 48 hours) for tissues to accumulate sufficient levels of PS to allow irradiation. The second is the time taken for PS concentration to fall below clinically active levels. Persistent levels will typically last for many weeks, causing photosensitivity of the skin. Photofrin, however, does not appear to concentrate in connective tissue, allowing for superior tissue healing even in heavily pretreated anatomy (Allison and Sibata, 2010a).
Many of the limitations of first generation PSs have been at least partially overcome by the development of second generation photosensitizers. These second generation PSs have various structures including porphyrins, expanded porphyrins, chlorophyll derivatives and dyes (Allison and Sibata, 2010a). They demonstrate higher absorption in the 650-800 nm range where tissue penetration is optimal and have higher extinction coefficients of absorption in the red than the first generation compounds, shorter tissue accumulation time and lower toxicity. Prolonged skin photosensitization, a problem that essentially hampered the broad implementation of PDT, has been nearly eliminated by the development of second generation PSs. The two main compounds in use are 5-aminolaevulinic acid (ALA) and its methyl ester (MAL). Both are precursors of an endogenous photosensitizer, protoporphyrin IX (PpIX), which is expressed in all nucleated mammalian cells but at very low level, below those which would cause photosensitivity. After application of ALA or MAL to a skin tumor or lesion the pro-drug is taken up into abnormal cells and converted via the heme cycle to PpIX. The rate limiting step of ferrochelatase results in accumulation of PpIX in abnormal cells, with relatively less accumulation in surrounding normal skin (Ibbotso, 2010). Administration of sufficient ALA or MAL results in a rapid elevation (for a few hours) of PpIX levels, meaning that illumination can take place. Following this there is also rapid systemic clearance of ALA-induced PpIX, within 24 hours. Tetra (m-hydroxyphenyl) chlorin (mTHPC, Foscan) is another second generation photosensitizer, a pure synthetic chlorin compound, which is activated by 652 nm light. The major advantages of mTHPC are a short duration of skin photosensitivity (15 days), a high quantum yield for singlet oxygen, and depth of tumor necrosis of up to 10 mm in preclinical models. PSs such as Indocyanine green (ICG) are being explored as an alternative PDT agent for melanoma (Mamoon et al., 2009).

In recent times much work has been done on developing new PS, and at the present time there is such a great number of potential PSs for PDT that it is difficult to decide which ones are suitable for which particular disease or application. Side effects of the present PSs and their specificities are the main reasons for designing new drugs for specific neoplastic conditions. Also, PSs require amphiphility, the ability both to travel unhindered through the blood system and then to localize and be introduced into the target tissue. Most of the second generation PSs are hydrophobic and can aggregate very easily in aqueous media which can affect their photophysical, chemical and biological properties. Therefore, third generation photosensitizers are mainly characterized by the drug delivery approach, by conjugation to carrier molecules to target the PS to the target cells, resulting in minimized accumulation in healthy tissues (Josefsen and Boyle, 2008). To obtain higher tumor localization, several tumor-targeting molecule photosensitizer conjugates were developed such as a monoclonal antibody directed against tumor-associated antigens (Ogura et al., 2012), oligonucleotides (Chernonosov, 2005), proteins (Huang et al., 2006), peptides (Sibrian-Vazquez et al., 2007), cyclodextrins (Kralova et al., 2006), and epidermal growth factors (Savitsky et al., 2000). Other means such as encapsulation of PSs in liposomes (Guelluy et al., 2010) to enhance specificity are currently in research. A particularly promising conjugate is based on a PS attached to a chemotherapeutic agent. The PS and chemotherapeutic agents accumulate in the tumor membrane and via illumination lead to PDT as well as release (photolysis) of the chemotherapeutic agent (Bednarski et al., 2007; Noguchi et al., 2008). The conjugates might be an antibody, imaging agent, or perhaps a biodegradable nanoparticle (see 2.4.2.1).
The PS can be administered systemically, locally, or topically to a patient bearing a lesion, followed after some time by the illumination of the lesion with visible light. The mechanisms involved in the selective uptake and retention of photosensitizers by tumor cells are not yet fully understood. The specific subcellular targets damaged by PDT depend on the PS's localization within the cell, which varies among photosensitizers and cell lines. Very few PSs have been rigorously tested for clinical application and only a handful have passed clinical trials to allow for regulatory approval for patient treatment. Furthermore, some PSs have passed regulatory approval in some countries, but not others, and are therefore unavailable for patients (Allison et al., 2010). For an overview of photosensitizers see the clinical review of Allison and Sibata (2010a).

2.2.2.2 Light sources and delivery

The primary requirement for the light source and delivery devices for photodynamic therapy is to achieve adequate light illumination throughout the target tissue volume. This means having the total optical power at the appropriate wavelength for activation of the photosensitizer and optimum penetration into the target tissue and the corresponding diffusion of the spatial distribution of that power with the size and shape of the tumor or illumination volume (Mang, 2008). PDT became popular after the invention of the laser, which allowed the production of monochromatic and coherent light that could be easily coupled into optical fibers. An advantage of using lasers is that their light can be focused into fiber systems and led to otherwise inaccessible locations, such as urinary bladder, digestive tract or brain. Larger lesions can be treated with interstitial therapy, in which case multiple laser fibers are inserted directly into the depth of the tumor through needles positioned under image guidance. In addition to facilitating the treatment of thick and deeply lying tumors, interstitial light delivery via multiple fibers allows for the treatment of irregularly shaped lesions while sparing normal surrounding tissue. However, sometimes PDT demands a homogeneous light distribution over an extensive surface area such as when treating Barrett’s esophagus. In recent years, LED technology has come to the forefront of PDT. These tiny light sources can now easily fit through scopes and biopsy channels for deep tissue illumination. They can also be designed for easy surface illumination such as for skin cancer through various arrays. The advance here is the highly portable energy source, for example, battery power, which is self-contained. Now the patient can be mobile during illumination. This allows for the realization of prolonged outpatient illumination as well as metronomic repeated illumination (Bisland et al., 2004). However, the wavelength generated is not amiable to manipulation and therefore have to be matched for a chosen photosensitizer.

Currently, most PDT procedures are performed with optical fibers which allow light to be directed easily to deliver irradiation to desired regions without the requirement of a straight light path. By attaching diffuse scattering tips of various geometrical shapes at the exit end of the fiber, point, linear, and planar light sources can be produced. The wavelength of light used for PDT is typically in the wavelength range between 600-800 nm, the so called therapeutic window. In this wavelength range, the energy of each photon is high enough to excite the photosensitizer and yet is low enough so that the light has sufficient penetration into the tissue (Zu and Finlay, 2008). The interaction of light with tissue is incompletely
understood but in theory, wavelengths approaching 700-800 nm will penetrate tissue to about 1 cm while wavelength closer to 600 nm penetrate to about 0.5 cm (Plaetzer et al., 2009). Blue light thus penetrates least efficiently through tissue, whereas red and deep red radiations penetrate more deeply. The interval between the sensitizer administration and light exposure is also another key factor in determining PDT efficacy. Fractionated drug-dose PDT regimens (i.e. metronomic PDT) were reported to result in a superior therapeutic effect compared to single-dose regimens and were able to induce long-term tumor growth control (Dolmans et al., 2002). For instance, light fractionation using a 2 hour dark interval significantly enhanced the clinical response of superficial basal cell carcinoma to ALA PDT (de Haas et al., 2006). For non-cutaneous lesions light is generally delivered in a single curative fraction due to the technical difficulties in delivering low dose and prolonged or intermittent (metronomic) illumination with commercially available light sources (Wilson and Patterson, 2008).

2.2.3 Treatment monitoring

2.2.3.1 Dosimetry

To successfully ablate lesions without undue normal tissue injury is the goal of PDT dosimetry (Allison and Sibata, 2010a). To achieve this reliably and consistently requires reproducible dose parameters. A myriad of variables affects the clinical outcome of PDT and many attempts have been made to create a real time system of dosimetry that evaluates these variables and generates appropriate treatment parameters (Allison and Sibata, 2010a). The primary requirement when treating lesions with PDT is to ensure that sufficient, homogenous light is delivered to the target tissue in the presence of an optimal tissue concentration of photosensitizer. This is referred to as the photodynamic dose. The light dose to a particular patient will depend on type of tissue (e.g. vascularity), applicator and on the number of sequential fiber placements needed to treat the entire volume of the target tissue. Since PDT works via the interaction between a photosensitizing drug, PS-activating light and tissue oxygen, the outcome following PDT is dependent on the parameters used during the treatment. Parameters that can affect the outcome include the intracellular distribution of the PS, the PS and light doses, the time interval between PS administration and light activation, the light fluence rate and the duration of light treatment (Olivo et al., 2010). The fluence rate (the rate at which the PS-activating light is delivered) is known to be one of the key parameters in PDT that can be varied to modulate the PDT outcome (Olivo et al., 2010). Given the enormous challenge of measuring these factors and including them in the practice of dosimetry for each patient, in the clinical setting the physician treating the patient can, in practice, ignore all of these factors to save two critical therapeutic components; the administered drug dose and the total light dose delivered. The physician must ensure that the appropriate amount of light is delivered to the target site and that the energy and time that light is delivered exceeds a value which has been determined by prior clinical trials and is in accordance with standard approved light doses (Mang, 2008). Currently, the use of drug dose and light dose as well as Drug application to Illumination Interval (DLI) are the crude means employed to optimize therapy (Allison and Sibata, 2010a; Olivo et al., 2010).
2.2.3.2 Optical imaging

Often, it is difficult to clinically discriminate neoplastic regions from normal tissue by appearance in microsurgeries, irrespective of the cancer type. However some of the light absorbed by photosensitizers is re-emitted at a different wavelength, a process known as fluorescence. The fact that most photosensitizers are also fluorescent as well as photochemically active means that imaging and detection strategies can be applied in PDT protocols. These techniques are known as photo(dynamic) detection or diagnosis and may be used alongside PDT. The technique of photodiagnosis (PD) relies on this differential accumulation of photosensitizer within abnormal tissues. PD may thus be carried out to detect otherwise hidden disease such as dysplasia, to delineate tumor borders, or to visualize disease in inaccessible areas. This phenomenon has been clinically applied in detecting neoplasms in the brain, esophagus, bladder, uterus, and skin. This technique exploits PS-induced differences in fluorescent signatures between normal and tumor tissues (Krammer and Plaetzer, 2008). Numerous studies show an improved ability to accurately remove the tumor and conserve normal tissue (Allison and Sibata, 2008). This has already been demonstrated to be feasible for cutaneous tumors and bladder cancer (Berger et al., 2003; Szeimies et al., 2008). Analyzing the fluorescence region aids in estimating preoperative states or postoperative residual tumor. Changes in fluorescence may be a part of an accurate real time PDT dosimetry system that allows the operator to determine if treatment was sufficient for lesion destruction during therapy (Wilson and Patterson, 2008). Further, fluorescent signatures of malignant or premalignant lesions may be distinct enough to allow for optical diagnosis instead of histological diagnosis (Brown et al., 2004).

2.3 Advantages and limitations of photodynamic therapy

PDT has the advantage of dual selectivity, due to the preferential localization of the photosensitizer by the malignant tissue and restriction of photoactivation to the tumor site due to localized light irradiation. In addition, the evident advantage of PDT over other conventional cancer treatments such as chemotherapy and radiotherapy is its minimal side effects, no drug resistance and reduced toxicity that allows for repeated treatment (Dolmans et al., 2003; Wang et al., 2011a). Another benefit of PDT as compared to chemotherapy or radiation therapy is that PDT does not seem to be carcinogenic (Allison and Sibata, 2010a); mutations that confer resistance to chemotherapy or radiation therapy do not limit the efficacy of PDT. None of the clinically approved PSs accumulate in cell nuclei, limiting DNA damage that could be carcinogenic or lead to the development of resistant clones. An additional advantage of PDT is that it can induce a form of programmed cell death called apoptosis, which is not associated with the destructive effects of necrotic cell death. This means that cancer cells dying in response to PDT by apoptosis, do not spill out their intracellular content, thereby preventing major inflammatory reactions and damage to the surrounding stromal components. Scar formation is minimal and the native tissue that replaces the cancer cells maintains its normal functions limiting the functional loss significantly (Karakullukcu et al., 2011). PDT thus has the ability to preserve the anatomic and functional integrity of many organs such as the tongue, bladder or larynx (Dolmans et al., 2003). PDT also offers the ability to treat diseased tissue not reachable by surgery. As has been shown by many clinical studies PDT delivers excellent cosmetic results, scarring being...
Excellent cosmetic outcomes make PDT suitable in particular for patients with skin cancers (especially non-melanoma skin cancer). There are no significant changes in tissue temperature, and the preservation of connective tissue leads to minimal fibrosis, allowing retention of functional anatomy and mechanical integrity of hollow organs undergoing PDT. Selected patients with inoperable tumors, who have exhausted other treatment options, can also achieve improvement in quality of life with PDT. The fact that a rapid cyto- and vasculotoxic reaction ensues with visible tumor destruction and sparing of normal tissue makes this therapy appealing to both patient and clinician. Moreover, PDT can be applied alone or in combination as an adjuvant therapeutic modality with chemotherapy, surgery, radiotherapy and immunotherapy (Juarranz et al., 2008; Ortel et al., 2009) (see 2.4). Finally, many PDT procedures can be performed in an outpatient or ambulatory setting, thereby not only alleviating costs, but also making the treatment patient-friendly. All of these properties have led to PDT receiving increased support from preclinical research although PDT is not widely available as compared to operating rooms and radiation centers.

However, as often discussed, disadvantages of PDT do exist. The majority of currently approved photosensitizing agents lack a complete selectivity and localization of the photosensitizer in tumors vs. normal tissue (Mang, 2008). In this respect, PDT has also been criticized by proponents of near infrared photo-immunotherapy (e.g. Mitsunaga et al., 2011) for that the PS accumulation and selective recognition of target tissue is still not high enough for many clinical applications. PDT is also less effective in treating poorly oxygenated large tumors. Most wavelengths of light cannot penetrate through more than 1-2 cm of tissue using standard laser and LED technology, thus limiting application of PDT to the treatment of tumors on or under the skin, or on the lining of some internal organs or cavities. One way around this limitation is to use hollow needles to get the light into deeper tissues. High-powered LED technology combined with photosensitizers which excites at 750-800 nm would await further development to achieve a greater depth of light penetration. Paradoxically, the highly localized nature of PDT is also one of its current limitations, because the treatment is ineffective against metastatic lesions, which are the most frequent cause of death in cancer patients. Another limitation of PDT is the variability of photosensitizer concentration observed in systemically photosensitized tissues, mainly due to differences of the tissue architecture, cell lines, and pharmacokinetics (Vollet-Filho et al., 2010). If the local concentration is lower than estimated for the application, only an insufficient photodynamic effect will be achieved, and the targeted lesion will not be completely treated. This is a relevant issue when dealing with malignant lesions because recurrence frequently worsens a patient’s clinical condition (Vollet-Filho et al., 2010). Another parameter that can limit direct tumor-cell destruction is the availability of oxygen within the tissue that is targeted by PDT. It is known that most solid tumors contain regions with low oxygen concentration due to poor vasculature and this may lead to low PDT efficiency. Systemic administration of the photosensitizer leads to a period of unwanted residual photosensitivity that must be managed until the drug is eliminated.
2.4 Mechanisms of synergies

2.4.1 Combinations of photodynamic therapy with standard therapies

One approach which is being explored for the enhancement of the effectiveness of PDT involves the combination of a different therapeutic modality such as surgery, chemotherapy and radiotherapy (Luksiene et al., 2006; Khdair et al., 2009; Postiglione et al., 2011). Combinations of various therapeutic modalities with non-overlapping toxicities are among the commonly used strategies to improve the therapeutic index of treatments in modern oncology. However, there have been few recent studies on combinations of PDT with standard antitumor regimens published to date. PDT can be used in combination with surgery as a neoadjuvant, adjuvant, or repetitive adjuvant treatment, preferably fluorescence image-guided (see 2.2.3.2) to confine illumination to the most suspicious lesions. For instance, curettage of the hyperkeratotic or crusty surface or debulking of a nodular basal cell carcinoma could be regarded as surgical approaches that can be combined with subsequent PDT very well. Also the reduction of tumor size by PDT to simplify surgical removal is a useful approach in specific cases (Sidoroff and Thaler, 2010).

PDT has been successfully combined with radiotherapy and chemotherapy (see ref. in Agostinis et al., 2011). During the last twenty years of research, radiotherapy has been combined with PDT, although conflicting results have been reported (Berg et al., 1995; Luksiene et al., 1999; Takahashi and Misawa, 2008; 2009). PDT does not interfere with radiotherapy which means for example that radiotherapy can still be used if PDT was ineffective in a given patient (Sidoroff and Thaler, 2010). More recently, Weinberg et al. (2010) reviewed the outcome of combined PDT and high dose rate brachytherapy (HDR) for patients with symptomatic obstruction from endobronchial non-small cell lung cancer. The authors concluded that combined HDR/PDT treatment for endobronchial tumors is well tolerated and can achieve prolonged local control with acceptable morbidity when PDT follows HDR and when the spacing between treatments is 1 month or less.

Several recent studies have examined the usefulness of PDT combination with local chemotherapy. Zhang et al. (2007) conducted a pilot study in 140 patients to evaluate the efficacy of PDT combined with local chemotherapy using 5-fluorouracil (5-FU) for the palliative treatment of advanced esophagocardiac cancer. Long-term follow-up (up to 36 months) showed that the mean survival time of combined treatment group was longer than that of the PDT group. Local administration of 5-FU can improve PDT efficacy and prolong survival according to these authors. A study by Li et al. (2010) investigated the effect of Photofrin PDT combined with chemotherapy (5-FU and DDP) on advanced esophageal cancer, compared with PDT or chemotherapy alone. All the 90 patients were followed up for 2 years. It was concluded that PDT combined with chemotherapy for advanced esophageal cancer is superior to PDT alone and chemotherapy alone. Another example of combined therapy use is topical imiquimod or topical 5-FU; both have been shown to be effective in non-melanoma skin cancer (Sidoroff and Thaler, 2010). In general, PDT can be used either before or after surgery, ionizing radiation, or chemotherapy without compromising these treatments or being compromised itself (Hopper, 2000; Agostinis et al., 2011). As yet these combinations have not been studied much in patients.
2.4.2 Novel strategies in photodynamic therapy

As most current photosensitizers used in PDT do not display significant tumor tissue selectivity, there is a need for designing improved targeted delivery as we have seen in 2.2.2.1. To enhance selectivity and overall efficacy of PDT, third-generation photosensitizers are being designed and developed (Josefsen and Boyle, 2008), by improving the existing photosensitizers, adding specific moieties and using delivery vehicles to specifically target these compounds (Sharman et al., 2004). Targeted-PDT via receptor specific synthetic peptides has been researched in the recent years to achieve a certain degree of selectivity by site-specifically confining the PS, and thereby increasing the efficacy of PDT (Olivo et al., 2010). Several other approaches to improve PDT outcome are currently under preclinical investigation such as nanoparticle based drug delivery; vascular and anti-angiogenesis targeted PDT and PDT-mediated immune response are in preclinical research. In addition, molecular beacons as fluorescent probes with target specificity and 2-photon PDT are interesting developments. In 2-photon PDT, short (approximately 100 femtosecond) laser pulses with very high peak power are used, so that 2 light photons are absorbed simultaneously by the PS. Because each photon only contributes one-half of the excitation energy, near-infrared light can be used to achieve deeper tissue penetration (Agostinis et al., 2011). Also, certain compounds activated by low-intensity ultrasound (sonosensitizers) have been combined with PDT which is named sonodynamic photodynamic therapy (SPDT) (Wang et al., 2011b). However, only two major developments in PDT will be discussed hereafter.

2.4.2.1 Nanotechnology in PDT

Nanoparticles (NPs) may offer a versatile platform for PDT drug delivery by targeting and with additional advantages such as enhanced light penetration.

For PDT drug delivery, a photosensitizer is encapsulated or immobilized on the nanoparticle surface using covalent or non-covalent interactions. The use of nanoparticles for molecular transport is advantageous for providing an inert environment which protects the drug from recognition and clearance before reaching the target. The same argument has been used for the development of other transport vectors (including micelles, liposomes, dendrimers, and polymer based NPs) for drug stabilization until reaching the tumor target (Doane and Burda, 2012). In addition, the advantage of this approach would be the targeted delivery of the photosensitizer to the tumor site in a more selective manner and with low toxicity, rendering minimal damage to the normal tissues (Bechet et al., 2008). In this approach, NPs can be used as drug carriers where the drug is either dissolved in the matrices or adsorbed on the surface of the cell. This approach has been gaining attention in recent years because of the tunability of size, surface characteristics and high drug loading capability of the nanoparticles. NPs can increase the solubility of hydrophobic drugs and offer the benefits of hydrophilicity and proper size to accumulate in the tumor tissue. Selective accumulation may be improved by the modification of the surface area using other ligands, which offers an attractive strategy to increase drug delivery to cancer cells and thereby keeping them away from healthy tissue sensitive to the toxic effect (Chatterjee et al., 2008; Kozlowska et al., 2009). NP encapsulated photosensitive drugs have a variety of advantages. Due to their small sizes they are not removed from the body by the reticulo-endothelial system which
leads to longer half-life times. They have a strong ability to protect encapsulated agents, are compatible with biological systems, and their surface can easily be modified with functional groups such as antibodies or other ligands to improve selectivity (Roy et al., 2003; Kateb et al. 2011). Several types of nanomaterials for encapsulating PS have now been studied for drug delivery. Such nanomaterials are: lipids, polymers, protein, dendrimers, metallic or silicon nanoparticles, quantum dots (Oba, 2007; Dhandhkar et al., 2010), and upconversion nanoparticles (Wang et al., 2011a). Also, the use of carbon nanotubes as a new photosensitizer for PDT is another area of research currently under investigation. NPs can be biodegradable polymer based, such as chitosan (Lee et al., 2009) and poly lactic acid derived (Zeisser-Labouebe et al., 2009) or inorganic particles such as silica (Roy et al., 2003) or gold (Wieder et al., 2006) and quantum dots (Yaghini et al., 2009).

In addition to targeting, a nanoparticle based approach can have advantages such as, increasing light penetration which is crucial for an effective PDT. To overcome this limitation, NPs for 2-photon PDT (Gao et al., 2006) have been developed. Two-photon absorption induced excitation uses two photons of lower energy (red shift, IR region) to produce an excitation that would otherwise be produced by the absorption of single photon of high energy (blue shift). Hence this method facilitates deeper penetration of light into tumor tissues compared to the single photon PDT drugs. This feature has been used in the treatment of gliomas as these tissues need higher penetration power. In another approach, up-conversion phosphors for the ceramic-based NPs have been utilized by Ungun et al. (2009) for PDT. Up-conversion phosphors are ceramic materials with a rare earth atom in the crystalline matrix. These absorb light in the near IR region and up convert to emit shorter wavelength light that activates the attached PS (Chatterjee et al., 2008). Advantages are that the power required to excite these particles is 107 times less than the intensities needed for two photon excitation of conventional organic dyes and they are resistant to photobleaching. Another example is the combined use of PDT and magneto-hyperthermia using magnetic nanoparticles (Gu et al., 2005; Primo et al., 2008). This is related to a hyperthermia approach that combines PDT and photothermal therapy (PTT) (Kah et al., 2008), in which photothermal agents can selectively heat the local environment (Barakat, 2009). This relies on materials where, after light absorption of the photothermal agent, mainly non-radiative decay channels are used, which results in overheating of the area around the light absorbing species. A typical example is the use of gold nanoshells conjugated to anti-epidermal growth factor receptor as a photothermal agent and PDT using hypericin as the photosensitizer, which proved to be an effective treatment strategy compared to conventional PDT or PTT alone (Kah et al., 2008). A combination nanoparticle for both PDT and chemotherapy (based on doxorubicin and methylene blue bound to aerosol OT alginate nanoparticles) was used to overcome drug resistance problems in chemotherapy (Khdair et al., 2009). Likewise, approaches for a combination of radiotherapy and nanoparticle PDT have been developed. Here, scintillation or persistent luminescence nanoparticles with bound PS are used. Upon exposure to ionizing radiation such as X-rays, the nanoparticles emit scintillation or persistent luminescence, which, in turn, activates the photosensitizers (Zhao et al., 2009).

However, also attention has to be given to the potential drawbacks of such systems. These may include prolonged tissue exposure, yet unknown long term effects, stability (Muthu and
Feng, 2009), alteration of the photophysical properties of the PS. In fact, many toxic effects of nanoparticles have been noted. These ranges from increased inflammation, to lung tumor induction, impairment of cardiac function, higher levels of oxidative stress, platelet aggregations and others (Radomski et al., 2005; Medina et al., 2007).

2.4.2.2 PDT-mediated immune response

A large body of evidence suggests that PDT-induced inflammatory reaction is a critical factor for activating host anti-tumor immunity. It is reported that during and after PDT, pro-inflammatory damage formed in cellular membranes and the blood vessel walls of treated tumors start to recruit neutrophils, mast cells, monocytes and macrophages (Chen and Huang, 2006). In addition to its direct photo-cytotoxicity, PDT seems to induce a variety of host immune responses under certain doses and treatment conditions (reviewed in Castano et al., 2006; Gollnick and Brackett, 2010). While immune responses may be seen as a secondary effect of PDT in cancer treatment, an active immunological stimulation can produce synergistic effects and further enhance overall therapeutic efficacy. Recent studies have further delineated the mechanisms of PDT-induced immune responses and the rationale of combining PDT and immunotherapy to achieve better therapeutic effects.

It is now widely accepted that there is a pronounced activation of the immune system after PDT for cancer in both animal models and also in patients. Both experimental and clinical studies suggest that anti-tumor immunity may be responsible for eliminating minimal residual tumors and preventing metastases (Chen and Huang, 2006). Several studies have shown that local PDT treatment can lead to the induction of systemic anti-tumor immunity (Castano et al., 2006; Gollnick and Brackett, 2010) and an ability to combat distant disease (Kabingu et al., 2007; Thong et al., 2007; 2008). In a recent clinical study, it was reported that basal cell carcinoma (BCC) patients who underwent PDT showed an increased systemic immune response to a BCC associated tumor antigen compared to patients who underwent surgical removal of the tumors (Kabingu et al., 2009). Garg et al. (2012) found that after PDT, dying cancer cells undergo immunogenic apoptosis characterized by phenotypic maturation and functional stimulation of dendritic cells as well as induction of a protective antitumor immune response. It is possible that the activation of a specific and systemic host immune response could result not only in further destruction of remaining tumor cells but also in the control of metastases. For instance, Thong et al. (2007) reported clinical observation of a PDT-activated immune response against distant untreated angiosarcoma lesions. Following PDT of lesions in the head and neck region, new lesions appeared on both upper limbs, whereas the main cluster of lesions on the right upper limb were treated with PDT. The untreated lesions on the right and left upper limbs underwent spontaneous remission 2 months and 4 months after PDT, respectively. This was the first clinical case in which untreated distant tumors were observed to regress following PDT. Thus a local treatment of tumors may lead to a systemic immune response against tumors outside of the treatment field. In recent years, there has been a growing interest on this aspect of PDT-mediated tumor destruction (Dolmans et al., 2003; Castano et al., 2005; Gollnick and Brackett, 2010).

There is at present a rather optimistic view on the possibility of developing effective anti-tumor immunotherapy, although only very little has yet reached the stage of clinically
proven efficacy. However, there is no agreement on the molecular and cellular determinants of the effect and more importantly on how to improve it. Because of the infrequency and generally unsatisfactory nature of the observable immune response after PDT, a considerable amount of work has gone into testing strategies designed to administer some sort of immunostimulant or adjuvant in combination with PDT to increase the frequency or strength of the anti-tumor immune response. Large and diverse arrays of therapies that combine PDT and an immunostimulant have been tested but there is no agreement on which is best and which could be clinically applied. Many new studies show that immunoadjuvants such as e.g. glycated chitosan (GC) can facilitate leukocyte infiltration. Experimental data indicated that the combination of PDT and immunoadjuvants, such as GC, could significantly increase the survival of tumor-bearing animals. T-cell responses (CD4 and CD8) have been observed and these have been shown to be tumor specific and to lead to memory immunity. Other reports have demonstrated the activation of neutrophils, NK cells and macrophages after PDT (Mroz et al., 2011b). It would be safe to conclude that photo-immunotherapy awaits further evaluation and despite significant advances in specific delivery of photosensitizer, still remains an experimental approach.

3. Does it work?

3.1 Introduction

This section highlights recent outcomes of photodynamic therapy (PDT). The purpose is to summarize the clinical feasibility and efficacy of PDT for each anatomical tumor location. Evidence for its efficacy comes from published research studies and clinical trials. Main focus is on phase 2 and 3 randomized controlled clinical trials if available. Over 140 clinical trials are registered in the ClinicalTrials.gov (access May 2012, conditions: the different cancer types; interventions: photodynamic or PDT). An electronic search of the Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken between February 2012 and May 2012. Two sets of keywords were used for the search strategy. One was for the PDT interventions, the other set was for each cancer type per anatomical location. In vitro and animal studies, as well as case reports and abstracts have been omitted, including studies published before 2005, however, review studies generally go further back in time. Case reports have been mostly omitted mainly because they are based on an individual patients profile hence results cannot be generalized. PDT applications in experimental research of breast, liver, ovarian, cutaneous T-cell lymphoma, bone or rectal cancer and in the treatment of vascular malformations (e.g. Jerjes et al., 2011d) will not be covered either. Thus these selection criteria would benefit the rationale for rating the efficacy of PDT based on what is available in clinical practice today.

A systematic review of PDT in the treatment of pre-cancerous skin conditions, Barrett’s esophagus and cancers of the biliary tract, brain, head and neck, lung, esophagus and skin was conducted by Fayter et al. (2010). This review presents data till May 2009. More recently, an eloquent general overview was given by Agostinis et al. (2011). A systematic analysis of the literature per anatomical cancer location, however, is limited due to lack of optimal PDT parameters (illumination conditions or PS dose) that could be comparable among these studies as well as variation in PDT technique including photosensitizer choice.
which makes comparison difficult. There is also considerable heterogeneity among the studies with regard to both outcome measurements used and follow-up times reported. The major endpoint of these studies though, has been response rates. Cosmetic outcome, tolerability (pain) and patient’s preferences have been secondary endpoints in some of these trials. Only a few adequately powered randomized controlled trials have been performed to date. The clinical trials mentioned hereafter have tended to focus on patients who have not responded to the usual treatment, but more recent research is now assessing the effectiveness of PDT as a first-line intervention. PDT has been approved by several authorities such as the National Institute for Clinical Excellence (NICE).

3.2 Clinical applications of photodynamic therapy per anatomical location

3.2.1 Anal cancer

There are only a small number of clinical reports on PDT for the treatment of cancer in the anal region. Most recently, Allison et al. (2010d) examined the treatment and outcome of Photofrin based PDT in a cohort of patients with anal cancer who failed locally despite chemoradiation (n=6) and two patients with positive margins of resection after excision of small T(1) squamous cell anal cancers who refused further surgery or chemoradiation. At the drug dose and light dose employed lesion ablation is possible as is retention of a functioning sphincter. All patients completed PDT without incident and all have maintained local control of disease in the anal region for the length of follow-up (18-48 months). Photofrin Given the good outcomes presented the authors suggested that PDT may be an option for sphincter sparing salvage therapy and perhaps an upfront treatment for early stage disease.

3.2.2 Barrett’s esophagus

The application of PDT in the gastrointestinal tract has been divided into 2 groups: PDT of the esophagus (see 3.2.7) and beyond i.e. Barrett’s esophagus. PDT has been used to treat high grade dysplasia (HGD) in Barrett’s epithelium, and both early and advanced esophageal carcinomas (Gray and Fullarton, 2007). A randomized, phase 3 trial of porfimer sodium-mediated PDT for Barrett’s esophagus and high-grade dysplasia has been performed by the International Photodynamic Group for High-Grade Dysplasia in Barrett’s Esophagus (Overholt et al., 2007). Patients were randomized to treatment with omeprazole (70 patients) or omeprazole with PDT (138 patients). At 5 years, PDT was significantly more effective than omeprazole alone in eliminating high-grade dysplasia (77% vs. 39%). A secondary endpoint of preventing progression to cancer showed a significant difference with approximately one-half the likelihood of cancer occurring in the PDT arm (15% vs. 29%). There was also a significantly longer time to progression to cancer favoring PDT. On the basis of this trial, it appears that PDT with porfimer sodium in addition to omeprazole is more effective than omeprazole alone at producing long-term ablation of HGD and slowing/preventing progression to cancer. It is based upon these data that the US FDA approved porfimer sodium-mediated PDT for patients with Barrett’s esophagus and high-grade dysplasia who do not undergo surgery. PDT using 5-aminolaevulinic acid (ALA PDT) may be a more attractive alternative to PDT with porfimer sodium for the treatment of HGD in Barrett’s esophagus because of the shorter
duration of light photosensitivity and low risk of esophageal stricture formation. Published results, however, show marked variation in its efficacy, and optimum treatment parameters have not been defined. One trial found that patients with HGD receiving high-dose ALA PDT (60 mg/kg) and high-dose red light (1,000 J/cm) had a significant decrease in cancer risk compared with treatment groups with lower doses of photosensitizer and/or lower light doses at 36 months (3% risk vs. 24% risk). Red light was associated with lower rates of adenocarcinoma than green light (8% vs. 45%) (MacKenzie et al., 2007). Also, Mackenzie et al. (2009) investigated how the dose of ALA and the color of the illuminating light influenced the biological effect. Twenty-seven patients were enrolled into a randomized controlled trial of red versus green (635 nm or 512 nm) laser light activation for the eradication of HGD with ALA PDT in Barrett’s esophagus. A further 21 patients were subsequently treated with the most effective regimen. Patient’s receiving ALA at 30 mg/kg relapsed to HGD more than those receiving 60 mg/kg. Additionally, for those treated with ALA 60 mg/kg, red laser light was more effective than green laser light. 21 patients who were subsequently treated with this optimal regimen demonstrated an eradication rate of 89% for HGD and a cancer-free proportion of 96% at 36 months’ follow-up. Using an ALA dose of 60 mg/kg activated by 1,000 J/cm red laser light, the authors found that ALA PDT was an effective treatment for HGD in Barrett’s esophagus.

NICE reported in 2010 that current evidence on the efficacy of PDT for patients with Barrett’s esophagus with HGD is adequate, provided that patients are followed up in the long term. There are no major safety concerns, although there is a risk of esophageal stricture, and photosensitivity reactions are common. This procedure may be used in patients with Barrett’s esophagus with HGD provided that normal arrangements are in place for clinical governance, consent and audit (NICE, 2010). A Cochrane review, however, concluded that radiofrequency ablation has significantly fewer complications than PDT and is efficacious at eradicating both dysplasia and Barrett esophagus (Rees et al., 2010).

### 3.2.3 Bile duct cancer

Bile duct cancer or cholangiocarcinoma (CC) is emerging as an important treatment indication for PDT (Allison et al., 2009a). Intervention is aimed at tumor removal if possible, but mainly at biliary drainage. The majority of patients with hilar CC has irresectable disease and requires palliation to alleviate symptoms and prevent biliary sepsis. Chemotherapy and radiotherapy have proven to be ineffective. Palliative biliary drainage by either percutaneous or endoscopic insertion of endoprosthese improves quality-of-life by reducing pruritus, cholangitis, and pain, but has been reported to improve survival time only slightly (Tomizawa and Tian, 2012). NICE reported in 2005 that current evidence on the safety and efficacy of PDT for bile duct cancer does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research (NICE, 2005). More recently, there have been several promising reports of the outcomes of PDT as an advanced palliative strategy for CC, which have noted significant improvements in quality of life and survival after PDT and stenting. PDT is usually given alongside biliary stenting following endoscopic retrograde cholangiopancreatography (ERCP) rather than as a stand-alone treatment (Fayter et al., 2010).
In a large study of 184 patients with hilar CC, Witzigmann et al. (2006) concluded that PDT plus stenting, employed in a subset of 68 patients, was superior to stenting alone with survival nearly doubling to 12 months. Successful drainage was achieved in 75% of PDT plus stent patients versus 39% receiving stents alone. Similarly, Kahaleh et al. (2008) reported that the addition of Photofrin PDT to stenting alone achieved a 16.2 month vs. 7.4 month survival advantage. Oral ALA has been tried for CC as well. A small phase 1/2 study of Foscan for non-resectable biliary strictures from CC or recurrent stent occlusion achieved a median survival of 8 months (Pereira et al., 2007). However, Foscan with the applied drug dose/light dose combination appears to have significant acute morbidity and mortality.

Fuks et al. (2009) aimed to assess the accuracy of PDT in a single center. Fourteen selected patients, with jaundice related to unresectable CC, underwent Photofrin PDT and biliary stenting (with or without chemotherapy). No severe toxicity was noted. PDT improved the Karnofski index in 64% of cases. The median survival time was 13.8 months and the 3-, 6- and 12-month survival rates were 85%, 77% and 77%, respectively. When combined with biliary drainage and chemotherapy, PDT appears to be an effective treatment for unresectable CC, with low morbidity and mortality, a significant improvement in survival and better quality of life. On the basis of these results, the authors believe that PDT should become an integral part of the palliative treatment of CC, in combination with biliary drainage and effective chemotherapy.

A prospective clinical cohort study evaluated the efficacy of radical curative surgery (10 patients), stenting combined with chemotherapy (17 patients) and stenting combined with Photofrin PDT (23 patients) in 50 consecutive patients treated for hilar CC over a 5-year period (Quyn et al., 2009). Actual 1-year survival was 80%, 12% and 75%, respectively. Mean survival after resection was 1278 days. Mean survival was 173 days after stenting and chemotherapy and 512 days after stenting and PDT. Patient survival was significantly longer in the first and the last group of patients. This prospective clinical cohort study has demonstrated that radical surgery and palliative Photofrin PDT are associated with an increased survival in patients with hilar CC. Similarly, a study by Cheon et al. (2012) aimed to determine long-term outcomes and factors associated with increased survival after PDT compared with endoscopic biliary drainage alone in patients presenting with advanced hilar CC. A retrospective analysis of the institutional database was conducted. Of the 232 patients identified, 72 (31%) were treated with PDT and 71 (31%) were treated with endoscopic biliary drainage alone. PDT with stenting resulted in longer median survival than stenting alone (9.8 months vs. 7.3 months). Early PDT after diagnosis and multiple PDT treatments were shown to have survival benefits. In addition, metal stent patency was longer in patients receiving PDT. Tomizawa and Tian (2012), who conducted an electronic search for available scientific literature published between 1991 and 2010 for PDT in treatment of unresectable CC, concluded that although accumulated data and local expertise are limited, PDT can be regarded as a standard palliative therapy for unresectable CC. Overall, PDT improves survival, jaundice and quality of life, is well tolerated and can be repeated without losing its efficacy (Ortner, 2011).

### 3.2.4 Bladder cancer

Bladder cancers, which are often superficial and multifocal, can be assessed and debulked endoscopically. In addition, the geometry of the bladder should allow for improved and
homogeneous delivery of light. These factors would make superficial bladder cancer an attractive target for PDT (Agostinis et al., 2011). In general, early response rates to PDT have been observed in approximately 50% to 80% of patients, with longer term (1-2 years) durable responses noted in 20% to 60% of patients (Agostinis et al., 2011).

Studies combining intravesical immunotherapies such as Bacillus Calmette-Guérin (BCG) or chemotherapies such as mitomycin C with PDT showed that these therapies may significantly enhance the PDT responsiveness of bladder tumors (Skyrme et al., 2005; Pinthus et al., 2006). A randomized controlled study compared a single Photofrin-mediated PDT with multiple BCG treatments (induction plus maintenance) and found that these therapies are equivalent in durable treatment response. Jocham et al. (2009) designed a multicenter phase 3 study to compare the efficacy of BCG instillations and PDT in the treatment of patients with intermediate and high-risk non-muscle invasive bladder cancer (NMIBC). All patients were centrally randomized after transurethral resection (TUR) to receive BCG induction and maintenance therapy or a single PDT with Photofrin. 124 patients (63 PDT group, 61 BCG group) were enrolled at 7 institutions. Each patient had a follow-up for 2 years. No statistically significant differences were demonstrated between the two therapy arms with respect to recurrence-free survival after randomization. After intention-to-treat analysis and after as-treated analysis, the estimated median recurrence-free survival periods were 24.9 (BCG) versus 16.6 months (PDT) and 25.8 (BCG) versus 14.7 (PDT) months, respectively. A single PDT with Photofrin in intermediate and high-risk NMIBC patients could not be shown to be superior to BCG maintenance therapy.

Lee et al. (2010) evaluated PDT using chlorin e6-polyvinylpyrrolidone (Ce6-PVP) as a bladder sparing therapy for high-risk NMIBC refractory to intravesical BCG therapy. Patients with recurrent NMIBC after induction intravesical BCG therapy were treated with PDT. Five patients underwent PDT; one patient received intravenous Ce6-PVP, while the rest received intravesical Ce6-PVP. There were three patients with primary CIS of the bladder and two with T1 high grade TCC and CIS of the bladder. At a median follow-up of 29 months, two patients were disease free, two patients developed recurrence and one patient progressed to muscle invasive disease. There were no immediate adverse effects. Despite being a small pilot study, intravesical Ce6-PVP mediated PDT is a feasible bladder sparing treatment option for recurrent high risk NMIBC in selected individuals.

Despite these promising results, PDT for bladder cancer remains largely investigational with limited use. PDT for bladder cancer is approved in Canada and in some EU nations but has not been approved by the US FDA.

3.2.5 Brain cancer

PDT has been used very little in the treatment of malignant brain tumors. It has been used in addition to radiotherapy and/or chemotherapy, and is normally preceded by photodynamic diagnosis (PD; see also 2.2.3.2) to identify tumor tissue. Photodynamic techniques such as PD, fluorescence-guided tumor resection (FGR) and PDT are currently undergoing clinical investigations as adjuvant treatment for malignant brain tumors (Kostron, 2010). Besides many clinical phase 1/2 trials for PDT for malignant brain tumors, there are only few controlled clinical trials following tumor resection. The initial trials provided encouraging
results, and the authors concluded that PDT can be used as an adjuvant therapy in patients with brain tumors (Agostinis et al., 2011). Currently, photosensitizers (PSs) are being evaluated both as intraoperative diagnostic tools by means of PD and FGR as well as during PDT as an adjunctive therapeutic modality. All 3 approaches take advantage of the higher uptake of PS by the malignant cells and are used intraoperatively. Recently published trials that employed PD, FGR, and PDT provided encouraging results, but the initial delay in tumor progression did not translate to extended overall survival. Styli et al. (2005) reported the results of a total of 375 patients treated with HpD mediated PDT following surgical resection. Among the 375 patients, the majority consisted of those with newly diagnosed (138 patients) and recurrent (140 patients) glioblastoma multiforme (GBM). Additional histological types included newly diagnosed (41 patients) and recurrent (46 patients) anaplastic astrocytoma (AA). In the follow-up, the mean survival for both types of GBM was between 14.3 and 14.9 months, and approximately 28% to 41% of patients survived more than 2 years. For AA, the mean survival was between 66.6 and 76.5 months and 57% to 73% of patients survived more than 3 years. Eljamel et al. (2008) performed a prospective randomized controlled trial to evaluate ALA and Photofrin FGR and repetitive PDT in GBM. They recruited 27 patients; 13 were in the study group and 14 were in the control group. The mean survival of the study group was 52.8 weeks compared to 24.6 weeks in the control group. There were no differences in complications or hospital stay between the two groups. The mean time to tumor progression was 8.6 months in the study group compared to 4.8 months in the control group. Apparently, ALA and Photofrin fluorescence-guided resection and repetitive PDT offered a worthwhile survival advantage without added risk to patients with GBM. Lyons et al. (2012) reviewed the impact of PDT in conjunction with intraoperative radiotherapy. Patients received standard therapy (ST), ST + PDT or ST + PDT + IORT (intraoperative radiotherapy). Thirty of 73 patients received PDT and the remaining did not. The mean survival of PDT patients was significantly longer than those had ST alone (62.9 weeks vs. 20.6 weeks). IORT on its own did not make a significant difference to survival. However the average survival for patients who received PDT + IORT was substantially higher than those who received PDT alone (79 weeks vs. 39.7 weeks). PDT in high grade glioma was statistically significant, therapeutic modality and its effects were further improved by IORT.

In summary, there is limited evidence available on PDT for brain cancer and no definitive statements can currently be made. Fluorescence-guided resection with repeated ALA PDT may possibly have some effectiveness, but whether PDT has any role in treating brain cancer, using current technologies, is a subject needing further debate (Fayter et al., 2010). It remains to be seen whether PDT for brain tumors remains a palliative or, at most, an alternative treatment modality.

3.2.6 Cancer of the lower genital tract

PDT is evaluated in different fields in gynecology. Recently, PDT was proposed as a promising and highly selective therapeutic method for the treatment of cervical intraepithelial neoplasia (CIN). CIN is associated with genital human papillomavirus (HPV) infection and represents the precursor of cervical cancer. Soergel et al. (2008) suggested that PDT using a topical precursor of photoactive porphyrins may be a non-invasive alternative with minimal side effects for treating CIN. They assessed the feasibility and response rate of PDT with

This document provided by Reliable Cancer Therapies (RCT) does not replace a medical consultation. Material in this document may not be reproduced in any form without explicit permission. For permission, please contact RCT at info@reliablecancertherapies.com
hexaminolevulinate (HAL) in CIN and HPV infection. Twenty four patients with a CIN 2 or 3 or a persistent CIN 1 and a positive high-risk HPV-DNA test were included. HAL-thermogel was topically applied to the cervix, followed by illumination of both ecto- and endocervical canal using a PDT laser and a special light catheter. Fifteen out of the 24 patients (63%) had a complete response and a HPV remission 6 months after treatments. The remission rates were 71%, 50%, and 71% for CIN 1, 2 and 3. HAL PDT seems to be a non-invasive, repeatable procedure for CIN and cervical HPV infection with minimal side effects which can be performed on an outpatient basis. A study by Soergel et al. (2010) aims at evaluating the effect of HAL and methylaminolevulinate (MAL) PDT on cervical tissue. Twenty-five patients underwent 1-2 PDT cycles for CIN 1-3 applying topical HAL and MAL. No macroscopic changes of the cervix were encountered and histological evaluation revealed no signs of apoptosis, necrosis, irritation, vascular changes and fibroses 6 months after PDT. HAL and MAL PDT do not leave any sustained damage in normal cervical tissue. This is important because cervical insufficiency or stenosis may have implications on pregnancy and cervical cancer screening. Istomin et al. (2010) tested in clinics a previously developed novel organ-saving approach for the treatment of CIN using PDT with the photosensitizer Photolon applied in women of a childbearing age with CIN 2 and 3. All 112 patients had been observed at least during 1-year follow-up period after PDT. A complete response was revealed in 104 (92.8%) of treated women. In 3 months after treatment a complete eradication of the HPV infection was shown in 47 (53.4%) from 88 patients who have been infected with HPV of a highly oncogenic strain before PDT. PDT with Photolon is suggested as an alternative approach for the treatment of CIN which can be recommended for women of childbearing age. The simplicity of the procedure as well as its therapeutic efficacy defines the reasonability of its introduction into the clinical practice as a new organ-saving method for the treatment of patients with CIN (Istomin et al., 2010).

Limited data reviewed in the original guidelines suggested that topical ALA PDT could be effective in the treatment of vulval intraepithelial neoplasia (VIN). Topical PDT offers therapeutic benefit in VIN (Morton et al., 2008). Zawislak et al. (2009) appraised in a study PDT as a treatment method for VIN using a novel bioadhesive patch to deliver ALA. Twenty-three patients with VIN lesions underwent PDT. Most patients (52%) reported a symptomatic response, with normal pathology restored in 38% of lesions.

PDT has recently also been added to the list of treatment modalities used for patients with penile intraepithelial neoplasia. In a study by Paoli et al. (2006) lesions initially responded to PDT in 7 out of 10 patients. Four of these patients presented no recurrences during a mean follow-up of 35 months, and were completely cleared after 2-8 treatments. Three patients presented recurrences after treatment but no patient developed invasive penile cancer (mean follow-up 46.5 months).

### 3.2.7 Esophageal cancer

PDT was first introduced as a palliative treatment for esophageal cancer but it is now also used as a first-line treatment for patients with early esophageal cancer (Gray and Fullarton, 2007). The treatment objective in early-stage esophageal cancer is cure, whereas in advanced cancer it continues to be a palliative option. PDT can be used alone or in combination with a range of other therapies for curative and palliative purposes.
NICE reported in 2006 that the evidence on safety of PDT for early-stage esophageal cancer appears to be adequate. They further state that PDT appears to be efficacious in reducing tumor bulk in carefully selected patients with small early-stage tumors. However, the current evidence is of poor quality and relates only to short-term outcomes; it is therefore not adequate to support the use of this procedure without special arrangements for consent, audit and clinical governance (NICE, 2006). Also, current evidence on the safety and efficacy of palliative PDT for advanced esophageal cancer is of poor quality but appears adequate to support the use of this procedure to relieve symptoms in patients with a poor prognosis (NICE, 2007). To illustrate some of the findings in early stage esophageal cancer, a study by Craig et al. (2007) described the use of Photofrin PDT as an alternative to surgery in 28 patients medically unfit for esophagectomy. 18 of 28 patients had an initial complete response 8 weeks post procedure. Nine patients were non-responders. 7/18 complete responders remained disease free for a mean follow-up period of 1166 days. 11/18 developed recurrent local disease treated with further PDT with a median survival of 770 days. Fourteen patients had EUS staging which accurately predicted response: all T1N0 patients (9/14) had initial complete response to treatment although 5/9 have required further PDT. All remain disease free at a mean follow up of 1103 days. No patients with T2/3N0 disease had complete response to treatment. The major complication of PDT encountered was stricture formation which occurred in 50% of cases and required a median of five dilations. Filonenko et al. (2008) performed PDT in 48 esophageal cancer patients using photosensitizers (Photogem, Photosens, Radachlorin, Alasens) and equipment developed in Russia. Complete regression was observed in 77% of esophageal cancer lesions, partial regression was in 23%. The median of survival of esophageal cancer patient was 4.6 years. Leclerc et al. (2008) compared retrospectively the results and the complications rate of PDT between consecutive patients treated in primary intent for a superficial esophageal cancer versus patients treated by Photofrin PDT for a local recurrence after chemoradiotherapy (CRT). 40 consecutive patients were treated by PDT for a superficial esophageal cancer, 25 (group 1) in primary intent and 15 (group 2) for a local recurrence after CRT. In group 1, 19 out of 25 patients (76%) were successfully treated versus 8 out of 15 patients (53%) in group 2. Severe complications were significantly more frequent in patients treated after a prior CRT. PDT as a salvage therapy in patients with a local recurrence after CRT for esophageal cancer tended to be less efficient than in first-line treatment. Of interest is a retrospective single center study evaluating the effect of an individualized multimodal palliative treatment in 250 patients (Lindenmann et al., 2012). The treatment included PDT in 171 cases (in 118 as first measure), stenting in 124 (38), endoscopic dilatation in 83 (24), endoluminal brachytherapy in 92 (20), feeding enterostomy in 40 (14), external radiation in 67 (23), chemotherapy in 57 (29), and palliative resection in 3 patients. Distant metastases and nodal positivity were connected with a significantly reduced survival. If PDT was used in the first place, median survival was 50.9 months compared to 17.3 months if other options were used as initial modality. PDT, if used as initial endoluminal treatment in patients without gross tumor infiltration into the mediastinum, the great vessels or the tracheo-bronchial tree, enables a considerable beneficial effect in the palliative setting.
3.2.8 Eye cancer

Successful PDT applications to conjunctival squamous cell carcinoma (SCC) have been reported in a few patients (Barbazetto et al., 2004; Sears et al., 2008, Cekić et al., 2011). Barbazetto et al. (2004) described the use of PDT with verteporfin to conjunctival SCC in 3 patients. Sears et al. (2008) reported the case of a patient with conjunctival in situ SCC who received ocular PDT. Although the patient was unable to complete the course of laser treatment and subsequently underwent excision of the lesion, regression of the neoplasm was observed. PDT seems to be advantageous with regard to treatment morbidity compared with excision, cryotherapy, or radiation and may be useful in some cases of extensive ocular surface squamous neoplasia that is less than invasive (Cekić et al., 2011).

3.2.9 Head and neck cancer

Conventional treatments (surgery, radiotherapy) in head and neck cancer patients have proven to achieve at times significant and permanent disfigurement and disability. It would seem then that a minimally invasive local therapy such as PDT would be an ideal substitute for select patients (Allison et al., 2009b). PDT in the treatment of head and neck cancer, which is used with either curative or palliative intent, is normally a stand-alone treatment, but can be used in combination with other treatments. It is particularly well suited to the treatment of lesions of the head, neck, and oral cavity because it has little effect on underlying functional structures and has an excellent cosmetic outcome (Hopper, 2000). Hence, the management of head and neck cancer has been the focus of significant study in the past years seeking to improve local-regional disease control rates while striving to preserve function in these anatomical locations. Multiple institutions have published small series of results demonstrating the efficacy of PDT. The technique has been successfully employed to treat early carcinomas of the oral cavity, pharynx, and larynx, preserving normal tissue and vital functions of speech and swallowing (Jerjes et al., 2010). For select patients without nodal metastases or those at very low risk for nodal metastases, including patients with in situ disease, early lip, superficial T1N0M0 cancers and early vocal cord lesions, PDT as currently practiced, can be highly successful (Allison et al., 2009b). Very select patients who have symptomatic local failure are another distinct cohort who may also potentially be palliated, so long as the light source can be appropriately placed (Allison et al., 2009b) or with advanced cancer of the head and neck, who have exhausted other treatment options, can also achieve improvement in quality of life with PDT (Nyst et al., 2009). However, to date there is not a single prospective phase 3 curative intent randomized trial comparing PDT versus conventional treatments in head and neck cancer patients.

Copper et al. (2007) assessed meta-tetrahydroxy-phenyl chlorine (mTHPC)-mediated PDT in the management of second or multiple primary tumors in the head and neck. A total of 27 patients with 42 second or multiple primary head and neck tumors were treated by PDT. Twenty-eight of 42 tumors were cured (67%). Cure rates for stage I or in situ disease were 85% vs. 38% for stage 2/3. Cure rates for PDT of the multiple primary head and neck tumors were lower than previously described for first primaries. In another study, Photofrin-mediated PDT was assessed for the treatment of 30 patients with diffuse field cancerization and Tis-T2N0M0 SCC of the oral cavity and oropharynx in patients not amenable to or that
have failed conventional head and neck cancer treatment (Schweitzer and Somers, 2010). Twenty-four of 30 patients (80%) have demonstrated complete remission in a follow-up of 3-144 months. Eleven of 24 patients were cancer disease free at 2 years. The authors came to conclude that PDT provides a surgical oncologic modality for potentially curative treatment of early stage oral cavity and oropharyngeal malignancies either as a primary modality or for treatment in patients that have previously failed surgery and/or radiation therapy. In addition, Karakullukcu et al. (2011) analyzed the institutional experience of early stage oral cavity and oropharynx neoplasms (Tis-T2) to identify the success rates for each subgroup according to T stage, primary or non-primary treatment and subsites. In total, 170 patients with 226 lesions were treated with PDT. From these lesions, 95 are primary neoplasms, 131 were non-primaries (recurrences and multiple primaries). The overall response rate was 90.7% with a complete response rate of 70.8%. Subgroup analysis identified oral tongue, floor of mouth sites with more favorable outcome. PDT thus seems to have more favorable results with certain subsites and with previously untreated lesions.

Jerjes et al. (2011a) conducted a prospective clinical study to evaluate the outcome following ultrasound guided interstitial PDT (US-iPDT) of tumors in the head and neck. One hundred and ten patients underwent US-iPDT using mTHPC (Foscan) as the photosensitizing agent. Following treatment, patients were followed-up for a mean of 26 months. Four out of five patients who presented with visual problems reported improvement after treatment. Also, 27/32 reported improvement of breathing. Improvement of swallowing was reported by 30/37 patients; while speech improvement was evident in 22/29 patients and 43/52 reported reduction in the disfigurement caused by their pathology. Clinical assessment showed that nearly half of the patients had good response to the treatment and 5 became disease free. Moderate clinical response was reported by 39 patients. This study provided further evidence that PDT is a useful modality in the management of these pathologies that are otherwise resistant to conventional treatments, and with minimal side effects. A study by the same group on T1/T2 oral cancer showed that 3 rounds of PDT are as successful as surgery in terms of mortality with minimal morbidity (Jerjes et al., 2011b). This study assessed the oncological outcomes following surface illumination mTHPC PDT of oral squamous cell carcinoma in 38 patients. Pathological analysis revealed that 12 patients had well differentiated SCC, 16 moderately differentiated and 10 had poorly differentiated cancer. At last clinic review post-PDT, 26/38 patients showed complete normal clinical appearance of their oral mucosa in the primary tumor site. Recent surgical biopsies from the study cohort showed that 17 had normal mucosa, five with hyperkeratinization, 10 with dysplastic changes and six showed recurrent SCC. The overall recurrence was 15.8% and the 5 year survival was 84.2%. Death from loco-regional and distant disease spread was identified in three patients. The authors concluded that mTHPC PDT is a comparable modality to other traditional interventions in the management of low-risk tumors of the oral cavity. Morbidity following PDT is far less when compared to the three conventional modalities: surgery, radiotherapy, and chemotherapy. Yet another study by the same group evaluated the outcome following US-iPDT of stage IV tongue base carcinoma patients (Jerjes et al., 2011c). Twenty-one patients were treated for advanced and/or recurrent tongue base cancer using mTHPC. Two-thirds of the patients had not been offered further conventional therapeutic options apart from palliative treatment. Following treatment, patients were followed-up for a mean of 36 months. Nine of the 11 patients who presented with breathing problems reported improvement after treatment. Also, 19 of the 21 patients reported
improvement of swallowing; improvement of speech was reported by 11 of 13 patients. Clinical assessment showed that more than half of the patients had good response to the treatment and about a third reported moderate response. Radiological assessment comparing imaging 6-week post-PDT to the baseline showed stable pathology with no change in size in four patients, minimal response in seven patients, moderate response in six patients, and significant response in two patients. Eight patients died; four of which due to loco-regional disease; and two from distant tumor spread. This study concludes that PDT is a successful palliative modality in the treatment of advanced and/or recurrent tongue base carcinoma.

3.2.10 Lung cancer

PDT is increasingly being utilized to treat thoracic malignancies. It is a treatment option for patients with localized endobronchial cancer that is unsuitable for surgical resection and for patients with inoperable non-small cell lung cancer (NSCLC), which have a poor prognosis. PDT is intended to reduce the bulk of the tumor, therefore reducing symptoms caused, for example, by bronchial obstruction. PDT may also be employed to downstage disease as part of surgery or to treat surgical margins post resection (Agostinis et al., 2011). It can be repeated if necessary, and can be used alongside other lung cancer treatments. NICE reported in 2004 and 2005 that evidence on the safety and efficacy of PDT for localized inoperable endobronchial cancer and for advanced bronchial carcinoma appears adequate to support the use of this procedure. The use of PDT for both early-stage or advanced NSCLC has several advantages over other therapies. The technique has a relatively favorable side effect profile when compared to other treatment modalities like surgery, external beam radiation therapy, or endobronchial brachytherapy. PDT for lung cancer is particularly useful for patients with advanced disease in whom PDT is used as a palliation strategy and for patients with early central lung cancer when patients are unable to undergo surgery. PDT is considered to be more specific and lesion-oriented compared with other available modalities and produces less collateral damage, and therefore fewer complications (Agostinis et al., 2011). Multiple peer reviewed publications have shown the efficacy of PDT for endobronchial obstructing lesions, early stage and minimally invasive endobronchial tumors and in particular in situ and dysplastic lesions.

3.2.10.1 PDT in early stage lung cancer

For early-stage disease, PDT is primarily employed as an endobronchial therapy to treat endobronchial or roentgenographically occult tumors (Simone et al., 2012). PDT can be considered as well for the curative treatment of early central lung cancer, especially for tumors 1 cm or less in diameter and provided there is no imaging evidence of extra-bronchial involvement (Du Rand et al., 2011). Kato et al. (2006) reporting on 264 early lesions treated with Photofrin found a 81% complete response rate and a 95% 5 year disease specific survival rate. Usuda et al. (2007) employed NP6 for both PDT and PD and noted a 92% complete response (CR) for 38 lesions. In a study by Corti et al. (2007) 40 patients with early (T1N0M0) medically inoperable lesions (n=12) or recurrent carcinoma in situ following previous treatment for invasive lung cancer (n=28) were treated with PDT and achieved a 72% overall complete response rate, with similar complete response rates for Tis lesions and
T1 lesions (73% vs. 69%). The median overall survival for the cohort was 91 months, patients with Tis lesions demonstrating a longer median survival (120 vs. 36 months). Moghissi and Dixon (2008) investigated the practice and results of PDT in early central lung cancer based on the review of the literature and personal experience. Fifteen articles (626 patients/715 lesions) were selected. PDT was typically employed for patient ineligibility for operation, and porfimer sodium photosensitizer followed by bronchoscopic laser illumination after an interval of 48-72 hours was the most common treatment course. PDT-related death occurred in 1 patient (0.15%), whereas adverse events included photosensitivity skin reactions in 5-28%, respiratory complications in 0-18%, and non-fatal hemoptysis in 0-8%. A complete response was achieved in 30-100% of patients for 2-120 months. The overall 5-year survival rate was estimated to be 61% which is only slightly inferior to that achieved by surgical resection in a similar stage of disease according to the authors. More recently, Endo et al. (2009) treated 48 medically operable patients with roentgenographically occult bronchogenic squamous cell carcinomas with bronchoscopic longitudinal tumor lengths of ≤1 cm with PDT. A complete response was achieved in 94% of patients, and the 5-year and 10-year overall survival rates for the cohort were 81% and 71%, respectively. Ali et al. (2011) treated 16 centrally located early lung carcinomas with PDT and achieved a complete response in 88% of lesions, but 29% of lesions that completely responded were subsequently found to recur within 12 months of PDT administration. Usuda et al. (2010a) employed NPe6 to treat 91 endobronchial lesions. Lesions less than 1 cm (n=70) achieved CR in 94% of cases. Lesions greater than 1 cm achieved CR in 90% of cases, though the majority of these cases had undergone debulking just prior to PDT. The authors felt that NPe6 PDT may be more versatile than Photofrin as the longer wavelength of treatment (664 nm) may allow for improved outcomes to larger lesions. NPe6 which would have a stronger antitumor effect than Photofrin, however, showed similar treatment outcome even for large tumors >1.0 cm in diameter (Ikeda et al., 2011).

3.2.10.2 PDT in advanced lung cancer

A range of options are available to help alleviate symptoms for patients with advanced lung cancer. These include brachytherapy, electrocautery, laser therapy, PDT (Cardona et al., 2008) as well as cryotherapy. For patients with advanced-stage NSCLC, PDT can be used to palliate obstructing endobronchial lesions, as a component of definitive multi-modality therapy, or to increase operability or reduce the extent of operation required (Simone et al., 2012). Ross et al. (2006) treated 41 patients with locally advanced NSCLC, including 78% with stage III disease, received induction PDT and chemotherapy and/or radiation therapy. PDT-based induction allowed 57% of patients initially deemed unresectable to undergo definitive surgical resection and 27% initially deemed in need of pneumonectomy to undergo lobectomy, pathological downstaging in 64%, and a pathologic complete response in 18% undergoing surgery. Overall, 46% of patients were alive at 3 years following therapy, and the mean survival was greatest in patients undergoing lobectomy (35.9 months) and shortest in those unable to undergo surgery after multi-modality therapy (14.7 months). Moghissi et al. (2007) reviewed Photofrin PDT in early central lung cancer in subjects not eligible for surgery. Indications for bronchoscopic PDT were recurrence or metachronous endobronchial lesions following previous treatment with curative intent in 10 patients (11 lesions), ineligibility for surgery because of poor cardiorespiratory function in 8 patients (9 lesions)
and declined consent to operation in 3 patients. 29 treatments were performed in 21 patients (23 lesions). All patients expressed satisfaction with the treatment and had a complete response of variable duration. Six patients died at 3-103 months (mean 39.3), three of which were not as a result of cancer. Fifteen patients were alive at 12-82 months. The authors concluded that bronchoscopic PDT in early central lung cancer can achieve long disease-free survival and should be considered as a treatment option in those ineligible for resection. More recently, Weinberg et al. (2010) reviewed the outcome of combined PDT and high dose rate brachytherapy (HDR) for patients with symptomatic obstruction from endobronchial NSCLC in nine patients. Combined HDR/PDT treatment for endobronchial tumors was well tolerated and can achieve prolonged local control with acceptable morbidity when PDT follows HDR and when the spacing between treatments is 1 month or less.

3.2.10.3 PDT in other lung cancer indications

Patients with pleural dissemination of NSCLC may also be treated with intraoperative PDT following macroscopically complete surgical resection (Simone et al., 2012). A phase 2 trial of porfimer sodium-mediated PDT was performed to investigate the efficacy of combined surgery and PDT for patients with either recurrent or primary NSCLC with pleural spread, the majority of whom had N2 lymph node involvement and bulky pleural disease (Friedberg, 2009). In this study, local control of pleural disease at 6 months was achieved in 11 of 15 patients (73%) and the median overall survival for all 22 patients was 21.7 months. These results are highly encouraging in this population of patients and suggest that additional investigation in this area is warranted (Agostinis et al., 2011).

Employing auto fluorescence bronchoscopy, Usuda et al. (2010b) identified 22 patients with multiple early lesions. These individuals were treated either by PDT alone or PDT in some lesions and surgical resections in others. All patients achieved complete response. The authors contend that PDT alone is a potentially curative option. Similarly Jung et al. (2011) analyzed a cohort of 32 patients treated by pneumonectomy, lobectomy, more limited surgery or PDT. PDT was able to ablate most lesions. These authors felt that PDT may be the optimal option. Sokolos et al. (2010) evaluated the outcome of 104 patients with multiple early tumors. PDT alone was able to ablate all lesions less than 1 cm in size. These reports confirm that PDT alone for this cohort of patients may provide acceptable local control and disease free survival. Minnich et al. (2010) conducted a retrospective cohort study of a prospective database. 133 symptomatic patients were treated with PDT for endobronchial lung lesions of varying histologies. Indications for intervention were NSCLC in 89 patients, metastatic airway lesions in 31 patients, small cell disease in 4 patients, benign disease in 7 patients, other or unknown in 2 patients. PDT was best used for bloody tumors that block the tracheobronchial tree, even in severely debilitated patients with profound shortness of breath from advanced malignancy who fail conventional core-out or laser treatments. It allowed for significant improvements in dyspnea in 74% of patients.

Malignant pleural mesothelioma (MPM) is a cancer of the pleura that, similar to NSCLC with pleural spread, has no currently available curative options. A recent study of macroscopically complete, lung-sparing surgical debulking followed by intraoperative porfimer sodium-mediated PDT for patients with locally advanced MPM found a median survival that had not been reached with a 2.1-year median follow-up in patients after radical pleurectomy with
PDT (Friedberg and Cengel, 2010). Friedberg et al. (2011) reviewed the results of patients who underwent a macroscopic complete resection, by two different surgical techniques, and intraoperative PDT as a treatment for MPM. 28 patients with MPM underwent macroscopic complete resection, 14 by modified extrapleural pneumonectomy (MEPP) and 14 by radical pleurectomy (RP) and intraoperative PDT. Stage III/IV disease was present in 12 of 14 patients, with 50% or more with +N2 disease. The median overall survival for the MEPP group was 8.4 months, but has not yet been reached for the RP group at a median follow-up of 2.1 years. In addition to the inherent advantages of sparing the lung, RP plus PDT yielded a superior overall survival than MEPP plus PDT in this series. The overall survival for the RP plus PDT group was, for unclear reasons, superior to results reported in many surgical series, especially for a cohort with such advanced disease. Given these results, the authors believe RP plus PDT is a reasonable option for appropriate patients pursuing a surgical treatment for MPM.

In summary, PDT is effective in the curative treatment of early stage lung cancer, in tumor debulking and palliation of symptoms in tracheobronchial obstruction from NSCLC. It is effective in the palliation of advanced tracheobronchial lung cancer, although adverse events including hemoptysis can occur (Durand et al., 2011).

3.2.11 Prostate cancer

Currently, PDT is being explored as a treatment option for localized prostate cancer. In a report of temeporfin-mediated PDT as a first-line therapy, 6 patients with organ-confined, Gleason score 6 prostate cancer were treated with 4 to 8 interstitial fibers with implants designed to cover only the areas of the prostate with biopsy proven disease (Moore et al., 2006). Four of these patients had a second PDT session due to biopsy confirmed persistent disease at 3 months of follow-up. Although the treatment was relatively well tolerated, and all patients showed evidence of necrosis on post-procedure imaging or biopsy, all 6 patients had biopsy confirmed residual disease after PDT. Another group has studied motexafin lutetium (MLu) as a photosensitizer for PDT of the prostate (Du et al., 2006; Patel et al., 2008). Also, vascular targeted PDT using padoporfin-mediated PDT has been studied in recurrent prostate cancer (Weersink et al., 2005; Trachtenberg et al., 2007). In a phase 1 trial, 24 patients after definitive radiotherapy for prostate adenocarcinoma were treated with padoporfin-mediated PDT using 2 interstitial fibers (Trachtenberg et al., 2007). This study demonstrated that vascular-targeted PDT could be safely performed in this patient population. In the follow-up phase 2 study, 28 patients were treated with increasing light doses (Trachtenberg et al., 2008). After 6 months of follow-up, less residual cancer was noted on biopsy as the light dose increased, however, toxicities were significant.

3.2.12 Skin cancer

Extensive experience has been gained with PDT for pre-malignant and malignant disorders of the skin. Most experience has been in the treatment of actinic keratosis and cutaneous basal cell carcinoma but there are also preliminary results in Bowen’s disease and squamous cell carcinoma. Topically active agents are preferred in the treatment of dermatological cancers and pre-cancerous conditions, as most systemic photosensitizers produce prolonged...
generalized photosensitivity. In addition to high clinical response rates, the cosmetic outcome is excellent, and in controlled studies patients preferred PDT compared to other therapy options (Braathen et al., 2007; Morton et al., 2008; Babillas et al., 2010; Christensen et al., 2010; Kleiopenning et al., 2010; Sidoroff and Thaler, 2010). NICE and NCCN indeed reported that there is adequate evidence of efficacy of PDT for the treatment of actinic keratosis (AK), Bowen’s disease (BD) and basal cell carcinoma (BCC) to support its use for these conditions. According to the British Association of Dermatologists (BAD) Guidelines (update 2008), multicenter randomized controlled studies now demonstrate high efficacy of topical PDT for AK, BD, superficial BCC and efficacy in thin nodular BCC, while confirming the superiority of cosmetic outcome over standard therapies (e.g. cryotherapy, surgical excision). Long term follow-up studies are also now available, indicating that PDT has recurrence rates equivalent to other standard therapies in BD and superficial BCC, but with lower sustained efficacy than surgery in nodular BCC. PDT can reduce the number of new lesions developing in patients at high risk of skin cancer and may have a role as a preventive therapy (Morton et al., 2008). However, the results of PDT for squamous cell carcinoma (SCC) of the skin using topical PSs have been disappointing, with recurrence rates of greater than 50% (NICE, NCCN). According to a recent Cochrane review, there is a clear need for well-designed randomized studies in order to improve the evidence base for the management of this condition (Lansbury et al., 2010).

PDT is being utilized at NCCN institutions for premalignant or superficial low-risk lesions on any location on the body. In patients with low-risk shallow cancers, such as SCC in situ (Bowen’s disease) or low risk superficial BCC, a topical therapy such as PDT may be considered (NCCN). Guidelines for practical use of MAL PDT in non-melanoma skin cancer have been published by the Norwegian PDT group (Christensen et al., 2010). It should be clear that the skill set of the operator very often will make a tremendous difference in the chance of achieving outstanding outcome with regard to treatment of cutaneous disease (Allison and Sibata, 2010b). In the definitive setting, PDT is currently approved in the United States, Canada, and the European Union (EU) for the treatment of AK and approved in the EU and Canada for the treatment of BCC. The role of PDT in primary and metastatic melanoma is so far quite limited. As melanoma has a propensity for regional and systemic spread any local therapy is of limited value to the majority of patients (Allison and Sibata, 2010b). Recent findings of PDT for the treatment of AK, BD and BCC will be highlighted.

3.2.12.1 Actinic keratosis

Current national and international guidelines recommend the treatment of actinic keratoses (AKs) in order to prevent their potential progression into SCC (Stockfleth and Kerl, 2006; Braathen et al., 2007; de Berker et al., 2007). Of interest is however that AKs are classified by others as in situ SCC anyway (Röwert-Huber et al., 2007). Several therapeutetic options are available, although PDT and imiquimod are the treatments of choice for patients with multiple AK and field cancerization, as both are effective in treating wide areas of skin with excellent cosmetic results (Serra-Guillén et al., 2012).

According to the guidelines devised by international experts from the International Society for Photodynamic Therapy in Dermatology in 2005, PDT was highly suited for AK treatment, leading to high cure rates (complete response of around 90% after 2 sessions) as well as good-to-excellent esthetic results (>84%) (Braathen et al., 2007). The French Dermatology
Recommendations Association (aRED) also recognizes PDT as an effective treatment option for multiple AK or AK in areas of skin with poor healing (Bonerandi et al., 2011). In the open, multicenter, clinical trial by Morton et al. (2006a) 1,501 AK cases of the face and scalp in 119 patients were treated, and intra-individual MAL PDT was compared with cryotherapy. The percentage rate of complete AK regression at 12 weeks in the per protocol (PP) population was better for PDT (86.9%) than for cryotherapy (76.2%), with similar results observed at 24 weeks (89.1% vs. 86.1%). Cosmetic results for PDT in the PP population were also better according to patients and assessors alike (Morton et al., 2006a; 2008). Similarly, PDT versus cryotherapy which used ALA as the photosensitizer utilized a standardized cryotherapy protocol and reported complete clinical clearance rates at 12 weeks to be significantly better for patients treated with ALA PDT than with cryotherapy (89% vs. 77%) (Hauschild et al., 2009). Also Szeimies et al. (2010) evaluated the efficacy and safety of PDT of AK with a new stable nano-emulsion-based ALA i.e. BF-200 ALA. The study was performed as a randomized, multicenter, double-blind, placebo-controlled, inter-individual, two-armed trial with BF-200 ALA and placebo. A total of 122 patients with four to eight mild to moderate AK lesions on the face and/or the bald scalp were included. PDT with BF-200 ALA was superior to placebo PDT. Also Dirschka et al. (2011) demonstrated in a randomized trial of 600 patients that BF-200 ALA is superior to the registered MAL medication. Serra-Guillén et al. (2012) sought to determine whether PDT or imiquimod provides a better clinical and histologic response in patients with AK and whether sequential use of both was more efficacious than each separately. 105 patients were randomly assigned into three treatment groups: PDT only; imiquimod only; or sequential use of PDT and imiquimod. This study concluded that sequential application of PDT and imiquimod provides a significantly better clinical and histologic response in the treatment of AK than PDT or imiquimod monotherapy for patients with multiple AK or field cancerization on the face or scalp.

3.2.12.2 Bowen’s disease

Bowen’s disease (BD) is also known as squamous cell carcinoma in situ (SCC in situ). Topical PDT is an effective therapy for BD, with equivalence to cryotherapy and equivalence or superiority to topical 5-FU. Cosmetic outcome is superior to standard therapy. Topical PDT offers particular advantages for large/multiple patch disease and for lesions at poor healing sites (Morton et al., 2008). Topical PDT should achieve clearance rates of 86-93%, with up to 18% recurrence at 3-5 year follow-up (Ibbotson, 2010).

In a large randomized controlled trial (n=225) comparing topical MAL PDT with either cryotherapy or 5-FU, estimated lesion sustained response at 12 months following treatment was 80% for PDT, 67% for cryotherapy and 69% for 5-FU and superior cosmetic outcome with PDT (Morton et al., 2006b). Cosmetic outcome at 3 months was good or excellent in 94% of patients treated with MAL-PDT vs. 66% with cryotherapy and 76% with fluorouracil, and was maintained at 12 months. Thus topical PDT proved to be at least as effective as cryotherapy and 5-FU and with superior cosmetic outcome. Calzavara-Pinton et al. (2008) assessed MAL PDT for the treatment of BD and SCC. In total, 112 lesions of BD and SCC in 55 subjects were treated in an outpatient setting. The overall complete response rates were 73.2% at 3 months and 53.6% at 2 years. The maximal diameter of the lesion was a predictor of relapse at 24 months of treatment outcome. MAL PDT may represent a valuable, effective and well tolerated treatment option with good cosmetic outcome for superficial, well-
differentiated BD and microinvasive SCC. In contrast, its use for superficial SCCs with a microinvasive histological pattern and for nodular, invasive lesions, particularly if poorly differentiated keratinocytes are present should be avoided. In the study by López et al. (2011), the overall response rate of BD was 90% at 3 months after MAL PDT and decreased to 87% at the 12-month follow-up. Recent guidelines suggest that PDT is an effective treatment for BD (Christensen et al., 2010).

### 3.2.12.3 Basal cell carcinoma

Other indications for PDT include superficial and nodular BCC. Evidence-based guidelines support the use of topical PDT in the treatment of BCC, particularly low risk, superficial lesions (Braathen et al., 2007; Morton et al., 2008). PDT may be considered where cosmetic outcomes are of a high priority and/or the lesion is too large for surgery (NICE, 2006). It appears to be useful in the short-term, especially for people who wish to avoid scarring. However, long-term follow-up is needed according to a Cochrane review (Bath-Hextall et al., 2006).

Szeimies et al. (2008) compared the efficacy and cosmetic outcome of topical MAL PDT with excision surgery for superficial BCC over a 1-year period. In this multicenter, randomized, controlled, open study, 196 patients were treated with either MAL PDT (n=100) or surgery (n=96). Similar high efficacy rates were seen at 12 months for the two treatment arms with 9.3% recurrence for PDT and no recurrences in the surgery group. However, superior cosmetic outcome was reported with PDT. Basset-Seguin et al. (2008) performed a multicenter, randomized study comparing PDT using topical MAL PDT with cryotherapy for treatment of superficial BCC. A total of 118 randomized patients were treated; 60 patients with MAL PDT and 58 patients with cryotherapy. Complete response rates at 3 months were 97% and 95%, respectively. There was no difference in 5-year recurrence rates with either treatment (20% with cryotherapy vs. 22% with MAL PDT). However, more patients had an excellent cosmetic outcome with MAL PDT (60% vs. 16% with cryotherapy). PDT resulted in statistically better cosmetic appearance when compared with cryotherapy at both 3-month and 5-year follow-up points. These results provide evidence to support the use of MAL PDT as an effective, non-invasive, selective treatment for superficial BCC with favorable cosmesis. However, topical PDT has limitations in the treatment of thick skin tumors. Christensen et al. (2009) evaluated the effect of pre-PDT deep curettage on tumor thickness in thick (>2mm) BCC. At 3-month follow-up, complete tumor response was found in 93% and the cosmetic outcome was rated excellent or good in 100% of cases. Deep curettage significantly reduces BCC thickness and may with topical PDT provide a favorable clinical and cosmetic short-term outcome.

Topical MAL PDT is also effective in nodular BCC (nBCC), although with a lower efficacy than excision surgery, and may be considered in situations where surgery may be suboptimal (Morton et al., 2008). Other studies have shown that the cosmetic outcome with MAL PDT is superior to surgery in nodular BCC (Szeimies et al. (2008). A multicenter controlled study showed estimated sustained response rates of 76% and 96% when comparing MAL PDT and surgery respectively for nodular BCC, with recurrence rates of 14% and 4% respectively at 5 years (Rhodes et al., 2007). Furthermore, in a smaller study topical PDT was shown to be
inferior to surgery for nBCC (Berroeta et al., 2007). Mosterd et al. (2008) have shown that, despite curettage and cautery 3 weeks before fractionated ALA PDT, 30% recurrence rates were seen when treating nodular BCCs compared with only 2% following surgery. In another randomized, double blinded study of nBCC the complete response rates were higher with MAL PDT than with placebo (73% vs. 27%) (Foley et al., 2009).

In summary, PDT can be an appropriate and effective treatment alternative to cryosurgery or surgical excision for selected patients with BCC (Agostinis et al., 2011). However, when topical PDT is compared with surgery for BCC, topical PDT with ALA or MAL consistently shows an increase in the recurrence rate compared with surgery for both superficial and nodular BCC. In the treatment of primary nBCC, excision surgery is preferred over PDT following this treatment regimen.

4. Is it safe?

4.1 Does photodynamic therapy have any complications or side effects?

In essence PDT is ablating a lesion and creating a wound that needs to heal. For small superficial therapies this process may occur in a fairly mild form with minimal pain, wound healing or other cosmetic and functional issues. However, for larger tumor volumes or located deeper within the body specific complications may occur depending on tumor location. Pain is currently the main limiting factor for cutaneous PDT (Apalla et al., 2010; Attili et al., 2011). However, the number of patients reporting significant pain and having to stop treatment because of this varies considerably. Maximal pain usually occurs in the early part of irradiation during PDT and then gradually reduces. Pain is restricted to the illuminated area and may reflect nerve stimulation and/or tissue damage. A range of techniques has been used in an attempt to reduce PDT-related pain, including local anesthesia and cooling the skin with fans or sprayed water (Morton et al., 2008). Arits et al. (2010) reported a slightly higher pain score in patients treated for skin cancer during the follow-up PDT session. Lindeburg et al. (2007) also found that the follow-up PDT session was experienced more painful by the patients compared to the first PDT session.

Other side effects of PDT include long-lasting skin photosensitivity and occasional systemic and metabolic disturbances (Castano et al., 2004). The photosensitizers are said to be essentially inert, therefore, application should be well tolerated unless the patient is allergic to the drug. However, once applied with PS the patient is photosensitive almost immediately so photosensitivity precautions are critical to prevent improper and unwanted PDT. For topically applied PS this means a local bandage to prevent local light exposure. For systemic PS this translates to avoiding direct sunlight for various lengths of time depending on the PS employed. For instance, the use of systemic photosensitizers such as Photofrin or Foscan is associated with generalized photosensitivity to visible light which can be prolonged over weeks to months (Ibbotson, 2010). Thus, patients are advised to avoid direct sunlight and bright indoor light for at least 6 weeks. While this side effect pales in comparison to those experienced by patients receiving extensive surgical procedures, radiation therapy, chemotherapy and combinations thereof and though it is generally manageable it remains a concern and can cause significant problems particularly in non-compliant patients (Mang, 2008). Nevertheless, current evidence suggests that there are no major safety concerns

This document provided by Reliable Cancer Therapies (RCT) does not replace a medical consultation. Material in this document may not be reproduced in any form without explicit permission. For permission, please contact RCT at info@reliablecancertherapies.com
associated with PDT for non-melanoma skin tumors (including premalignant and primary non-metastatic skin lesions) (NICE, 2006). Although the used photosensitizer porfimer sodium is selectively retained in tumor tissue compared to normal tissue at a ratio of at least 2:1, the drug does accumulate to significant levels in the skin and in the reticuloendothelial system, especially of the liver and spleen (Lindenmann et al., 2012). Importantly, PDT has not been reported to produce second malignant neoplasms, and PDT typically does not compromise future treatment options for patients in need of additional definitive therapy. Because PDT is a cold photochemical process (Hopper, 2000), there is no tissue heating, and connective tissues such as collagen and elastin are largely unaffected. There is therefore much less risk to the integrity of underlying structures than with thermal ablation techniques and surgery. Other complications specifically occurring per tumor type are addressed in 3.2 and in the scientific literature.

4.2 Contraindications for using photodynamic therapy

No clear evidence was found implying that PDT should definitely not be used for certain clinical conditions except a few. Contraindications to PDT include a history of porphyria and allergy to active ingredients of the applied photosensitizer (Hohwy et al., 2007). In some cases patients whose pulmonary capacity is limited may not be candidates for PDT as well. Other contraindications of PDT include tumors known to be eroding into a major blood vessel in or adjacent to the illumination site; a planned surgical procedure within the next 30 days; coexisting ophthalmic disease likely to require slit-lamp examination within the next 30 days and existing therapy with a photosensitizing agent (see ref. in Jerjes et al., 2011b). Cutaneous illumination gives a very vigorous response in the entire illumination field often with tissue slough. While this may heal in previously untreated patients, those whose illumination fields overlap as well as, operated upon or irradiated regions, have significant chronic tissue healing issues. Again, PDT will not be offered to these individuals due to this morbidity risk (Allison and Sibata, 2010b). In studies published about the use of topical PDT in dermatology to date there has been no evidence of increased phototoxicity or adverse effects in immunosuppressed patients (Ibbotson, 2010).

5. Conclusions

Photodynamic therapy (PDT) relies on the presence of a photosensitizing agent (PS) which, once activated by light of the appropriate wavelength, generates cytotoxicity. This is an inherently complex process that depends on multiple variables including the chemical and photochemical properties of the PS, the PS dosage and delivery vehicle, the drug-light time interval, the wavelength, energy dose, power density and pulse structure of the light, and the oxygenation state of the tissue. However, the technique in itself is simple, can commonly be carried out in outpatient clinics, and is highly acceptable to patients. PDT is currently most accepted in the treatment of malignant and pre-malignant non-melanoma skin lesions. In this review we found evidence of effectiveness for the treatment of actinic keratosis and basal cell carcinoma. It is also useful in the treatment of Barrett’s esophagus and unresectable cholangiocarcinoma. Its acceptance into mainstream clinical practice is exemplified by approval for its use in several conditions for instance by NICE. Although the clinical results mentioned in 3.2 attest PDT an important role in the treatment of selected
cancer patients, it is remarkable that this therapeutic modality is not being generally offered to patients with these diseases. The small number of randomized clinical trials in patients and insufficient reporting on study methods and treatment outcomes do not enable us to draw conclusions regarding PDT efficacy and safety in the remaining cancers described ad hoc. However, we did not find any clear evidence implying that PDT should definitely not be used for certain clinical conditions; rather there are a number of uncertainties that require further investigation.

Compared with standard approaches PDT can achieve equivalent or greater efficacy in the treatment of certain cancers, particularly in the head and neck and basal-cell carcinoma, with greatly reduced morbidity and disfigurement. The advantages of PDT compared with surgery, chemotherapy, or radiotherapy are reduced long-term morbidity and the fact that PDT does not compromise future treatment options for patients with residual or recurrent disease. The excellent cosmetic outcome makes it valuable for skin lesions and lesions of the head, neck, and oral cavity. With endoscopic delivery of light to hollow structures, PDT has been successful in the treatment of early gastrointestinal cancers, such as esophageal cancer, and lung cancer. However, PDT is not yet a front-line therapy for most indications, presumably owing to the lack of large randomized clinical trials. It remains in many cases an alternative or palliative treatment or is used within the context of a clinical trial. We do not yet fully know the effectiveness of PDT in relation to other treatments and optimal parameters for PDT do not appear to be firmly established. There are no randomized phase 3 trials comparing PDT with other treatment modalities. Thus for most treatments, it is premature to state whether PDT is superior, equivalent, or inferior to other ablative treatments. Researchers continue to study ways to improve the effectiveness of PDT and expand it to other cancers. In the future, it is likely that PDT will continue to be used as a stand-alone modality or in combination with chemotherapy, surgery or other new strategies. Other ways to improve PDT include the development of new photosensitizers, as well as the optimization of PDT protocols such as fractionation of light or drugs. Well-designed clinical trials that involve selectively localized photosensitizers and convenient light sources may improve the prospects for the use of PDT in cancer. As PDT treatment is not available in all centers at the moment, patients should be referred to a specialized center that conducts PDT.

6. References

6.1 Scientific publications


This document provided by Reliable Cancer Therapies (RCT) does not replace a medical consultation. Material in this document may not be reproduced in any form without explicit permission. For permission, please contact RCT at info@reliablecancertherapies.com


This document provided by Reliable Cancer Therapies (RCT) does not replace a medical consultation. Material in this document may not be reproduced in any form without explicit permission. For permission, please contact RCT at info@reliablecancertherapies.com


Huang JD, Lo PC, Chen YM, Lai JC, Fong WP, Ng DKP. Preparation and in vitro photodynamic activity of novel silicon (IV) phthalocyanines conjugated to serum albumins. J. In org. Biochem. 2006;100:946-51.


Raab O. On the effect of fluorescent substances on infusoria (German). Z Biol 1900;39:524.


This document provided by Reliable Cancer Therapies (RCT) does not replace a medical consultation. Material in this document may not be reproduced in any form without explicit permission. For permission, please contact RCT at info@reliablecancertherapies.com


6.2 Books

Photodynamic Therapy with ALA: A Clinical Handbook (Comprehensive Series in Photochemical & Photobiological Sciences). Roy Pottier (Editor), Barbara Krammer (Editor), Herbert Stepp (Editor), Reinhold Baumgartner (Editor). Royal Society of Chemistry, 2006 edition


This document provided by Reliable Cancer Therapies (RCT) does not replace a medical consultation. Material in this document may not be reproduced in any form without explicit permission. For permission, please contact RCT at info@reliablecancertherapies.com
Advances in Photodynamic Therapy: Basic, Translational and Clinical (Engineering in Medicine & Biology) Michael R. Hamblin (Editor), Pawel Mroz (Editor) Artech House Publishers; 2008 edition

Photodynamic Therapy: Methods and Protocols (Methods in Molecular Biology) Charles J. Gomer (Editor) Humana Press; 2010 edition

6.3 Professional Societies/Organizations

European Society for Photodynamic Therapy in Dermatology (www.euro-pdt.com)
European Platform for Photodynamic Medicine (http://www.eppm-photomedicine.org)
International Photodynamic Association (http://sites.pcmd.ac.uk/ipa)