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RESEARCH ARTICLE

PROSPECTS OF APPLICATION OF PHOTODYNAMIC THERAPY IN THE TREATMENT OF ORAL CANCER

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ABSTRACT

Surgery, chemotherapy and radiotherapy are the prime treatment options when it comes to treatment of malignant lesions. Photodynamic therapy (PDT) is a new treatment modality against cancer with special emphasis on the physical and biochemical principles. PDT is also known as photoradiation therapy, phototherapy or photochemotherapy. It is been more than 25 yrs since PDT was proposed as a useful tool in oncology. But now it is clinically approved and more widely used. PDT was developed as a therapy for several diseases such as tumor, periodontitis, other oral lesions and pre-malignant diseases. It is a minimally invasive treatment with great promise in malignant diseases. It is not only well tolerated but also simple and quick to execute. It has proved to show less morbidity and better function; it also shows excellent cosmetic outcome. Soon PDT has the potential to become integrated into the mainstream of cancer treatment.

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INTRODUCTION

Every year there are about 300 to 400 new cases of oral cancers and about 145,300 cancer related deaths (Saini *et al.,* 2016; Ferlay *et al.,* 2015) The worldwide incidence of head and neck cancer is, approximately, 640,000 new cases per year (Bicalho *et al.,* 2010; Brasil, 2010). The greatest incidence is in India where, in 1990, there were more than 80,000 cases with 50,000 deaths (Hopper, 2004; Ferlay, 1998) The main predisposing factors being tobacco and alcohol abuse, which seem to have a drastic effect. Oral cancer acts as a global health burden with poor survival rate; especially when diagnosed at the later stage of the disease. Despite notable advances in current treatment modalities, there has been minimal improvement in survival rates over the last few decades. The poor outcome of the disease is the result of local recurrence, regional failure & formation of second primary tumors. Oral cancer accounts for an average 5 yr survival rate below 60%. The quality of life is compromised after conventional oral cancer treatment. It causes psychosocial impact & functional disabilities such as post treatment tissue morbidity, xerostomia, mucositis & fibrosis being prevalent. Photodynamic therapy is one such upcoming technique in treatment of oral cancer. Although still emerging, it is a successful & clinically approved therapeutic modality used for management of neoplastic & non-malignant lesion.

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It is a minimally invasive technique & thus has a pivotal role in improving the quality of life drastically. Photodynamic therapy involves the administration of light sensitive drug; called as Photosensitizer. This therapy is used due to its sensitivity and specificity for tumor cells. It is used as a stand-alone therapy or an adjuvant therapy in the treatment of oral cancer (Saini, 2016; Dougherty, 1998)

HISTORY

The emergence of photodynamic therapy is the work of 'Dougherty *et al*' in 1970s at the Roswell park cancer institute (Mimikos, 2016). The term photodynamic was coined by Joddlbaner and Von Tappeiner in 1904 (Andreadis, 2016). In 1903, VON TAPPEINER & JESIONEK were probably the first to use PDT in oncology. They treated skin carcinomas by topical administration of eosin and irradiation with high doses of light. In 1913, MEYER-BETZ injected himself with hematoporphyrin and was the first author to describe the resulting skin photosensitivity with severe skin edema and erythema. Following the experiments of HAUSMAN in 1911 with hematoporphyrin, there has been an increased interest in the use of porphyrin- based photosensitizers. In 1955, SCHWARTZ *et al.* described the photosensitizer hematoporphyrin derivative (HpD). In the early sixties LIPSON *et al.* demonstrated that experimental rat tumors could be detected by fluorescence, following systemic administration of HpD and UV light illumination. A renewed and more widespread interest in the therapeutical application

of PDT started in the seventies with the experiments of DOUGHERTY *et al.*

DISCUSSION

Photodynamic therapy (PDT), defined as ''the light-induced inactivation of cells, microorganisms, or molecules,'' which combines the use of a photosensitive agent or photosensitizer (PS) activated by irradiation with a light source to produce reactive oxygen species and highly reactive singlet oxygen.[9] The concept and methodology concerning photodynamic therapy are discussed in brief as follows.

Principles of PDT: Photodynamic therapy uses a light sensitive drug, oxygen and visible light to achieve the therapeutic response. To activate the photosensitizer, a laser light source is used to illuminate the treatment area. The wavelength of the laser light source varies depending on the photosensitizer. Most clinically approved photosensitizers are activated with the help of red light. The high absorption peak of the photosensitizer is between 600-800 nm. Absorption of photons with wavelength longer than 800nm does not provide enough energy to excite oxygen to its singlet state. The higher the wavelength, deeper the penetration of light into the tissues. Therefore chlorins, bacteriochlorins & phthalocyanines offer extensive improved effects in tumor control. The anti tumor effect of PDT is directly due to tumor cell death, or indirectly due to damage to tumor vasculature and specific immune responses against the tumor cells. The photosensitizer should show minimum phototoxic side effects. The interval between the administration of drug and irradiation is long as it shown to give time to the photosensitizer to diffuse well into the tissues. But some reports says that, short drug-light interval produces better results. This is because the drug is still present in the blood vessels, it results in marked vascular damage. The light mediated destruction caused by the photosensitizer is termed as Photobleaching.[13,14]Healing with minimal scarring, safety in repetition of the procedure and the fact that it majorly does not produce the need for further surgery or radiation are some of the advantages of photodynamic therapy whereas pain, cost of FDA approved drug and the extended period of photosensitivity (upto 6 weeks) counts as the disadvantages.

Photosensitizers: The photosensitizers are based on tetrapyrrole structure. The ideal photosensitizing agent consists of single pure compound to allow quality control analysis with low manufacturing cost and good stability in storage. Various types of PS are (1) dyes, (2) chlorines, (3) porphyrins, (4) xanthenes, and (5) monoterpene (Andreadis, 2016) Photosensitizers approved by the FDA are used in the photodynamic therapy. A few of them are:

- Porforin sodium (photofrin); a haematophyrin derivative
- 5- aminolevulinic acid (5-ALA, Levulan); used for dermatological conditions
- Temoporfin (m THPC, Foscan); which is approved for use in Europe

The first clinically employed photosensitizer was a water soluble mixture of porphyrins called hematoporphyrin derivative (HPD). HPD showed disadvantages which included long lasting skin sensitivity and relatively low absorption of light at 630 nm. Verteporfin which is a benzoporphyrin derivative has been developed as a treatment option for macular degeneration.

1st generation photosensitizers: -PORFIMER SODIUM was the first photosensitizer to receive approval. It is moderately active in the tissues. It requires a wavelength of 630 nm for activation. The penetration at this level is slightly low. Also the absorption is weak. Therefore the depth effect is SS limited to 0.5 cm. -ALA is a naturally occurring precursor in heme biosynthetic pathway. It has received approval for non-malignant disorders. It can be delivered topically, orally or by IV formulation. It has a non specific light source, that is; it can be triggered by any light source. The depth effect shown by it is <0.2 cm.

2nd generation photosensitizers: 2nd generation PS are more potent than 1st generation PS. They show short periods of photosensitivity. They have longer activation wavelength and therefore higher depth effect, higher yield of singlet oxygen and better tumor selectivity. Chlorins, hexaphyrine, purpurines & phthalocyanines are 2nd gen photosensitizers to name a few.

Synthetic Chlorine Temoporfin is very potent photosensitizer among them. It is activated at 650 nm. It shows residual photosensitivity only for 2 weeks. Several other drugs are still under invention (Hopper, 2000)

Light source: Even if the PS is kept unchanged, there can't be a single light source that could be stated as ideal for photodynamic therapy. The choice of light source depends on the absorption of photosensitizer. Blue light shows less efficient penetration whereas red and infrared radiations shows deeper penetration. The wavelength between 600-1200 nm is termed as the optical window of tissues. The choice of light source varies depending on many factors. It depends on the disease, location and size of the lesion, accessibility and tissue characteristics. Also the cost and size of the light source plays an important role in selection of the source. Lasers and incandescent light sources shows similar efficacies in treatment of the lesion. The effect is more local than systemic with the use of lasers. Alternative light sources include LEDs i.e light emitting diodes. The choice of optimal combination of photosensitizer, light source and treatment parameters is crucial for successful PDT (Agostinis, 2011; Brancaleon, 2002)

MECHANISM OF ACTION

The photodynamic therapy uses 3 mechanisms of action (Mimikos, 2016)

- Creation of singlet oxygen and free radicals
- Inciting an immune response
- Vascular response

The photosensitizer is activated by a light source, it follows with an interaction with molecular oxygen to produce an excited state; termed as; reactive singlet oxygen. It is a highly cytotoxic state. It has a short lifetime (<0.04 microseconds) and short radius of action (<0.02 micrometers).[3] The photosensitizer may also bounce back to its ground state after the emission of fluorescence or it may also transit to a higher energy triplet state. The cytotoxic activity and the microvascular damage that occurs leads to the destruction of tumor cells. This reaction is manifested by a swelling and formation of necrotic tissue. The necrotic tissue sloughs off gradually over a period of time, and there is normal healing and re-epithelialization of the treated site.

Table 1. Clinically used photosensitizer drugs

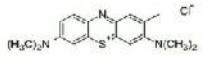
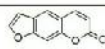
Platform	Example
Dyes	
- tricyclic dyes with different *meso*-atoms	Acridine Orange Methylene Blue Rose Bengal
	Toluidine Blue O
- phthalocyanines	
	sulphonated metallo-phthalocyanines (Photosense®)
Porphyrins	
	porphyrin derivative (HPD) (Photofrin®) 5-aminolevulinic acid (ALA) as prodrug benzoporphyrin derivative (BPD) lutetium texaphyrin
Chlorins	
	mono-L-aspartyl chlorin e_6 (NPe6) temoporfin (Foscan®) tinethyletiopurpurin (SnET2) talaporfin sodium (LS11)
Furocoumarins	 psoralen

Table 2. Types of photosensitizing drugs:[15,16]

Class	Approved drug for photodynamic therapy	Typical maximum absorption (nm)	Typical absorption coefficient
Porphyrins	Porfirmer sodium	630	10000
	Protoporphyrin IX	633	10000
Chlorins	Verteporfin	690	35000
Bacteriochlorins	Temoporfin	652	30000
Phthalocyanines	None yet approved	740	32000
Phenothiazinium compounds	Sulphonated aluminium phthalocyanine mixture	680	110000
Texafrins	None yet approved	670	60000
	None yet approved	734	42000

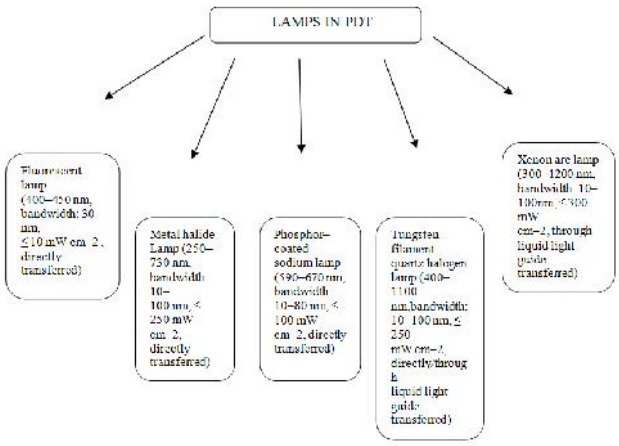


Table 3. Lamps used as light sources in PDT

PDT evokes three main cell death pathways; apoptotic, necrotic and autophagy associated cell death; wherein the major cell death occurs due to apoptosis (Hopper, 2000; Henderson, 1992; Sharman, 1999).

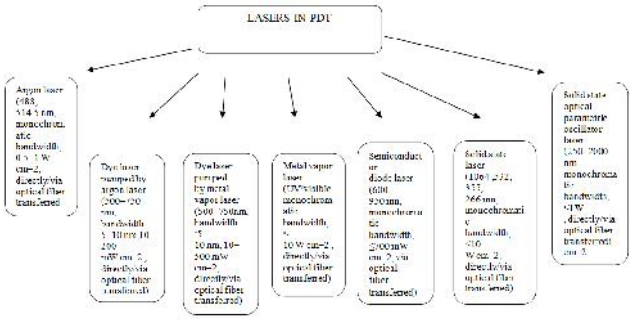


Table 4. Lasers used as light sources in PDT

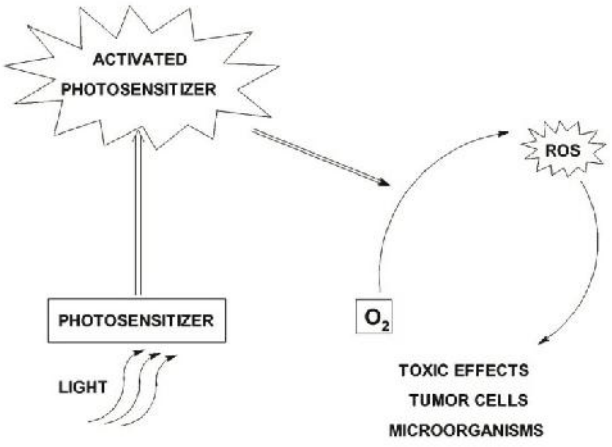


Figure 1. Schematic representation of photodynamic reaction and photodynamic therapy. Light (photon) of an appropriate energy (e.g., with wavelength at the absorption maximum) is absorbed by a photosensitizer, which undergoes a transition from a low-energy ground state to the excited-singlet state. The activated photosensitizer interacts with oxygen to produce singlet oxygen and other radical species that cause a toxic effect in tumor cells or micro-organisms; ROS, reactive oxygen species

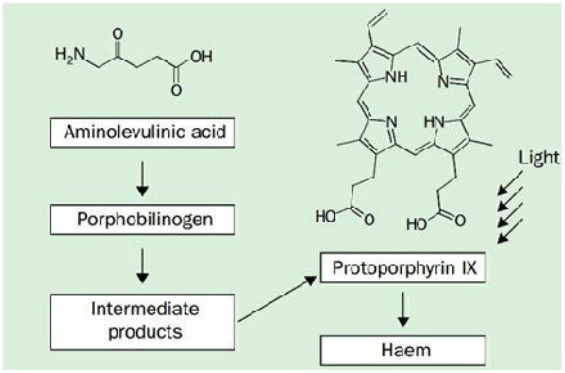


Figure 2. A simplified scheme of the haem biosynthetic pathway. After the accumulation of porphyrin, light of an appropriate wavelength (633 nm) can be administered to obtain a therapeutic response

Mechanisms by which photodynamic therapy harnesses the energy of light to damage or destroy target tissue (Brown, 2004)

Sensitizer + light _ Activated sensitizer

Activated sensitizer + oxygen _ Sensitizer + activated (singlet) oxygen

Activated oxygen + target _ Oxidized (damaged) target

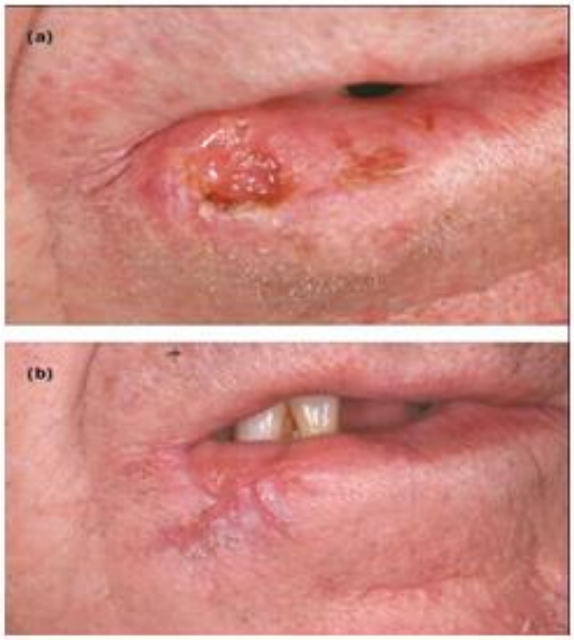


Figure 3. A 68-year-old patient with an infiltrative squamous-cell carcinoma on the right oral commissure, (a) before and (b) 3 months after PDT treatment with temoporfin

PHOTOCHEMISTRY

Most PSs in their ground (i.e. singlet) state have two electrons with opposite spins located in an energetically most favorable molecular orbital. Absorption of light leads to a transfer of one electron to a higher-energy orbital. This excited PS is very unstable and emits this excess energy as fluorescence and/or heat. Alternatively, an excited PS may undergo an intersystem crossing to form a more stable triplet state with inverted spin of one electron. The photosensitizer in triplet state can either decay radiationlessly to the ground state or transfer its energy to molecular oxygen (O2), which is unique in being a triplet in its ground state.[3] This step leads to the formation of singlet oxygen (1O2), and the reaction is referred to as a Type II process. 23 A Type I process can also occur whereby the PS reacts directly with an organic molecule in a cellular microenvironment, acquiring a hydrogen atom or electron to form a radical. Subsequent autoxidation of the reduced PS produces a superoxide anion radical (O2•-). Dismutation or one-electron reduction of O2•- gives hydrogen peroxide (H2O2), which in turn can undergoone-electron reduction to a powerful and virtually indiscriminate oxidant - hydroxyl radical(HO•). ROS generation via Type II chemistry is mechanistically much simpler than via TypeI, and most PSs are believed to operate via Type II rather than Type I mechanism (Agostinis *et al.,* 2011; Plaetzer 2019; Nauta, 1996)

Potential Advantages of Photodynamic Therapy over Conventional Anti-cancer therapies (Konopka, 2007; Cerrati, 2015)

- It is non-invasive procedure and very convenient for the patients
- Can be performed in outpatient or day-case (inpatient) settings
- Can be targeted accurately and selectively in early or localized diseases
- It can improve quality of life drastically and lengthen survival rate
- Repeated doses are often given without the necessity for total-dose limitations
- Has moderate side-effects
- Can have excellent cosmetic results, and the healing process results in little or no scarring
- Can offer organ-sparing treatment worldwide, with little or no investment in infrastructure

PDT: SIDE EFFECTS & PREVENTION

The major side effect of PDT is photosensitivity. When the photosensitizer is administered systemically, there occurs a period of residual photosensitivity. This is due to the accumulation of the photosensitizer into the skin. Photosensitizer can be activated by day light, this can cause first or second degree burns. To prevent this one must avoid exposure to bright light or direct sunlight. This helps prevent sunburn, redness and swelling. Sunlight must be avoided for a period of several hours to several weeks till the PS is eliminated from the body. To minimize the side effects it is important to prevent damage to the normal mucosa during PDT. The photosensitivity occurs in matter of minutes, thus it is necessary to shield the eyes and skin from exposure to intense lights.

Unplanned light delivery to adjacent healthy mucosa can cause mucositis and ulcerations. To prevent the undesirable toxic effects of PDT first of all it is important to improve the specificity of PS to target tissues; Use of physical barriers to prevent the exposure of normal adjacent mucosa, use of specialized devices which can focus the delivery of light to targeted tissues and prevention of unwanted injury to adjacent healthy mucosa are some few measures to reduce the side effects caused due to PDT. To prevent the non diseased mucosa from the cytotoxic effects of PDT, it is necessary to shield the area. It can be shielded with a black, thermal resistant material such as wax or saline soaked surgical packing which can be molded to cover the adjacent mucosal surface. Topically applied ALA does not cause photosensitivity, but it causes burning sensation during illumination. PDT is not a painful procedure in itself but after a few hours of exposure patients may experience severe pain. PDT can also cause pain, scarring, burns and swelling in the nearby areas. In the treated areas it may cause coughing, difficulty in swallowing, stomach ache, painful breathing and shortness of breath. Other side effects includes allergic reaction to the patient.[1,11,24]

CLINICAL ADVANCES IN PDT

PDT has emerged as an extremely successful treatment due to it's assuring results and simplicity in the clinical procedure. It is highly appealing to the patients as well as the clinicians due to it's cytotoxic and vasculotoxic reaction towards tumor cells and it's ability of sparing normal healthy tissues. The current application of PDT is majorly in the field of oncology but, in future, it is believed to extend it's application in other fields too. According to various studies, PDT is used in the treatment of various histologically different tumors; and yet no malignancy has seemed to be resistant to PDT. Also the recurrence rate of the PDT treated malignancies is fairly low. PDT requires less infrastructure and less investment, which makes it a cost effective treatment.

The light sources are also portable and dependent. Thus, PDT has proved itself effective and sufficient in primitive conditions as well. PDT is widely used in tumors pertaining to breasts, brain, skin, prostate, cervix, pancreas, peritoneal cavity, lymphatic nodes. Light sciences corporation, Issquah, WA, USA developed a new device based on LED technology that allows for the production of light in the target tissues. This new technology helps prevent cytotoxicity to healthy tissues.

FDA has also approved the use of PDT in the treatment of early- and late- stage lung tumor. Gynaecological tumors can also be treated with PDT, these tumors can be accessed easily. PDT that uses Photofrin based photosensitizer was approved in 1995 or the treatment of advanced and obstructive esophageal tumors. It is an effective therapy in the treatment of tumors of vagina, vulva and cervix. Canadian government in 1993, approved PDT for the treatment of papillary bladder cancer. The risk of bladder fibrosis is reduced due to ALA based treatment. Photofrin based PDT is the choice of treatment for almost all skin related cancers (Allison *et al.*, 2004c, 2006). For example; Kaposi's sarcoma, squamous cell carcinoma, basal cell carcinoma, melanoma, lymphoma. PDT has been showing promising results in the treatment of acne, hair removal, warts & psoriasis, but is yet to acquire a FDA approval for the same. Visudyne TM (Verteroporfin; QLT Phototherapeutics, Inc., Vancouver, BC, Canada) obtained FDA and worldwide approval in 1999 for the treatment of the wet form of age-related macular degeneration (Houle and Strong, 2002; Kozak *et al.*, 2006).

LIMITATIONS OF PDT: PDT is a procedure with absolute clinical simplicity, this has led to it's expansion in the field of oncology. It only consists of a photosensitizer drug, a light source and an oxygen based reaction which acts together to put forth the results. A sensitizer is delivered into a patient; the affected region with malignancy is exposed to a appropriate light source, resulting in apoptosis and tumor necrosis with vascular cessation. Even the best photosensitizer accumulates in the skin and causes photosensitivity. Not every photosensitizer possesses the quality of an ideal photosensitizer. The characteristics of an ideal photosensitizer are: it can be administered easily and safely, it must target the tumor cells appropriately, it should be activated atan clinically useful wavelength, it should be pain free and should be easily obtained. The photosensitizers though efficient lack some of these qualities. PDT was initially considered as a local treatment, but it has shown to initiate regional and systemic response. To overcome the limitations, it is necessary to address the problems caused by PDT such as toxicity, mutagenicity, elimination of drug from the body of the patient, activation by appropriate wavelength, effects of exposure to sunlight, simple procedure, pain free treatment and cost effectiveness. Due to low activation wavelength, penetration is limited to approximately 1.5 cm, hence to increase the depth of the penetration. The future of PDT will depend upon the interactions between clinical applications and technological innovations (Konopka, 2007; Dolmans, 2003; Biel, 2010).

PDT AS AN ADJUVANT OR COMBINED MODALITY: Combination of various therapeutic treatment modalities are commonly used treatment strategies to improve the treatment quality in modern oncology. Care should be taken to make sure that the combined treatment plan do not have any overlapping toxicities. The combination of PDT with conventional treatment warrants further investigations. PDT was used along with other chemo preventive agents in a recent in vitro in vivo study. It can be safely combined with other antitumor treatments without the risk of including cross resistance. PDT can be used in combination along with surgery as a neoadjuvant, adjuvant or repetitive adjuvant treatment therapy. It has also been successfully combined with chemotherapy and radiotherapy. These combined therapy has shown enhanced anticancer effects.

This could be due to the fact that cancer is a multifactorial disease, there are many pathological conditions associated with it. Thus if different treatment modalities are combined, it will act on various diseased tissues and cause cell death by different mechanisms. In comparison to stand alone therapy, combination of different modalities leads to finer tumor selectivity and thus efficacy of the treatment (Saini, 2016; De Rosa, 2000; Gursoy, 2013). PDT is a cold photochemical process, as a result there is no tissue heating; connective tissue like collagen and elastin remain largely unaffected, therefore there is much less risk to the integrity of the underlying structures (Hopper, 2000; Agostinis *et al.*, 2011)

CONCLUSION

PDT is considered to be a promising step in the future of oncology. The new aspects of PDT are yet to be discovered and is in the process. PDT has proved it's efficiency as an adjuvant as well as a stand alone therapy. PDT as a treatment option is compared to surgery, radiotherapy and chemotherapy and by far has proved superior when it comes to future recurrence or any other treatment options applicable to the patient. Despite of a few drawbacks, PDT has never compromised on it's antitumor efficacy. PDT can be used for the treatment of a early lesion to late stage malignancy, without any second thought about compromise concerning the health of the patient. PDT can be repeated without any side effects, which is not possible when it comes to chemotherapy or radiotherapy. Also, other treatment plans have a high risk of compromising the immune system of the patient, which is not the case with PDT. This process provides clinical simplicity; and minimal scarring which makes it appealing to the patients. The uniqueness of PDT has inspired scholars of many fields. In the coming years there will be a definite expansion in the application of PDT and it will make a mark in the field of medicine as one of the mainstream curative treatment for the malignant as well as non-malignant lesions.[1,13,29,30]

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