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Management of Oral Premalignant Lesions Using Topical Photodynamic Therapy: An Overview

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Abstract
Photodynamic Therapy (PDT), a widely investigated therapeutic tool in the local management of premalignant lesions, is based on the topical administration of a photosensitive drug which preferentially accumulates in tumor tissues. This target site when irradiated with an appropriate wavelength of light triggers a photochemical reaction resulting in the production of singlet oxygen having cytotoxic effects. Agents used in the past include haematoporphyrins, photofrin, dyes and non-thermal lasers. Before formulating PDT as the first line of treatment, protocols such as illumination scheme, light source, lesion size, thickness of surface keratin and degree of epithelial dysplasia must essentially be considered. This paper provides an overview on the newer Topical Aminolevulinic acid (ALA) based PDT, which, owing to its high efficacy, low side effects, high patient compliance, low toxicity and minimal tissue invasion is believed to have potential to play a significant role in the management of low-grade dysplasia.

Keywords: cytotoxic effects, dysplasia, photodynamic therapy, tissue invasion.

Introduction

The use of light to treat diseases can be traced back to ancient civilizations of Greece, China, Egypt and India1. This use of light energy to treat various pathologies is referred to as *Phototherapy.* Von Tappeiner and Jodlbauer defined Photodynamic Therapy as the *dynamic interaction* among light, a photosensitizing agent and oxygen resulting in tissue destruction2. The earliest use of photodynamic therapy or the use of an exogenous photosensitiser to absorb light and render a therapeutic effect dates back to 1400 B.C2. Since then many potential applications of using light for therapeutic purposes came into the lime light. It involves the use of a photoactive dye (photosensitizer) which is activated by exposure to light of specific wavelength in the presence of molecular oxygen and results in formation of toxic oxygen species, causing localised photodamage and cell death3. Clinical studies have revealed that PDT can be curative, particularly in early stage tumors, prolong survival in patients with inoperable cancers and significantly improve quality of life. [1]

History-A Brief Review

The first documented case of photodynamic therapy as an effective therapeutic modality dates back to the year 1900 when Oscar Raab discovered that a *combination of light* on *acridine* improved its cytotoxic potency on malarial parasites [1]. Neils Finsen, a Danish physician was awarded the Nobel Prize in 1903 for his success at treating skin lesions using an artificial irradiation source [1]. The first use of PDT in clinical settings was reported in 1903 by Tappeiner and Jesionek who treated skin cancers using topical application of eosin prior to light exposure [3]. The current era of PDT was revived when studies conducted by R.L Lipson and Schwartz demonstrated tumour-localising properties of Haematoporphyrin derivatives (HpDs) in the early 1960s [2].In 1975, Thomas Dougherty carried out the first large scale experiment on humans. In 1987, Aminolevulinic Acid-Based PDT was used for the first time to treat human diseases [1]. It is now gaining recognition as an imperative treatment modality for various precancers and superficial cancers.

Photosensitiser

A substance *capable of absorbing light* is known as a *photosensitiser[1]*. This photosensitiser, in the presence of an appropriate light source, undergoes a photochemical reaction which results in the conversion of the absorbed light photons to chemical energy which culminates in the generation of highly lethal oxygen species.

The first clinical PDT of the modern era was performed in patients with bladder or skin cancer using Haematoporphyrin-Derivatives (HpD) [4]. Examples include Porfimer Sodium/Photofrin. They were established as *First generation* photosensitisers. However they were soon outdone by *Second Generation* photosensitisers which were associated with better light absorption properties and significantly reduced post-treatment photosensitivity [1].

Other relative advantages of the second generation photosensitisers are their chemical purity, higher yields of singlet oxygen, greater tumour specificity and increased penetration depths into tissues (Gomer, 1991). Lately, *Third generation photosensitisers* have been introduced which

include drugs that are modified by targeting with monoclonal antibodies or with non-antibody-based protein carriers and protein/ receptor systems, and conjugation with a radioactive tag. However, they are not commercially available.

Aminolevulinic Acid-Based Pdt

The second generation 5-Aminolevulinic Acid received approval for treatment of cancerous lesions in 1999 [3]. It is an endogenous amino acid, synthesized in the mitochondria from glycine and Succinyl CoA. It is a *biological precursor* of Protoporphyrin IX and participates in the heme pathway[1] which ends with the conversion of Protoporphyrin IX into heme by enzyme *ferrochelatase*. Application of exogenous ALA bypasses internal feedback mechanisms that are governed by concentration of free heme and leads to intracellular accumulation of free heme. Cells in rapid division tend to accumulate more ALA-derived porphyrins owing to their low *ferrochelatase activity* which favours the build-up of Protoporphyrin IX in the cytoplasm [Peng *et al*, 1997a]. This explains the mechanism of tumour-localising properties of ALA.

ALA can be activated under a light source at 635-nm wavelength. For topical application, a preparation of 10-20% of ALA is commonly used to apply on the target lesion. Two topical ALA-based drugs, Levulan and Metvix have received approval from the FDA and EMA for the treatment of basal cell carcinoma. So far 5-aminolevulinic acid (5-ALA) is the *only photosensitiser* that can be *applied topically*; all others have to be given intravenously[7]. The advantage of topically applied ALA is the complete lack of systemic photosensitivity and therefore, ALA-treated patients do not have to avoid exposure to light following treatment. The major disadvantage of a topically applied photosensitiser is the shallow treatment depth of only 1–2 mm that can be obtained[7]. Therefore only very superficial lesions of less than 1 mm can be treated successfully with topical application.

Light Source

Light of wavelength in the range *600-800 nm* is considered as the '*therapeutic window'* optimal for PDT as most energetic photons with wavelengths shorter than 600 nm do not penetrate the desired depth and wavelengths above 800 nm have insufficient energy to generate singlet oxygen and initiate a photodynamic reaction [Juzeniene *et al*,2006].

Human tissue transmits red light efficiently, and the longer activation wavelength of the photosensitizer results in deeper light penetration. Consequently, most photosensitizers are activated by *red light* between *630 and 700 nm*, corresponding to a light penetration depth from 0. 5 cm (at 630 nm) to 1.5 cm (at ~ 700 nm).

The earliest light sources to be employed were Non-coherent light sources, such as conventional lamps used in combination with filters to obtain light of desired wavelength [Huang, 2005]. Conventional lamps were soon replaced by lasers which produced monochromatic wavelength which facilitated easy calculation of light dosimetry. Non-laser light sources include light emitting diodes (LED). They are economical, small, lightweight and highly flexible. The selection of light sources relies on the tumour characteristics (location, depth, size and accessibility); type of photosensitiser used (absorption spectra and mode of administration) [1.]

Oxygen

The cytotoxic effects of PDT are dependent on tissue oxygen [Lee See *et al*, 1984]. Activation of the photosensitizer upon absorption of the light results in excitation of the drug from its ground state (1PS.) into singlet state (1PS.).However, to obtain a therapeutic photodynamic effect the photosensitizer usually undergo electron spin conversion to its triplet state (3PS.)[3]

Type 1 reaction

In the presence of oxygen, the excited molecule can react directly with a substrate, by proton or electron transfer, to form radicals or radical ions, which can interact with oxygen to produce highly reactive oxygen species (superoxide, hydroxyl radicals, and hydrogen peroxide)[3].

Type 2 reaction

Alternatively, the energy of the excited photo sensitizer can be directly transferred to oxygen to form singlet oxygen, which is the most damaging species generated during PDT. As a result of its high reactive nature and short half-life, the radius of action of *Singlet Oxygen* is restricted to < 0.02μm (Moan and Berg, 1991).

Mechanism of Tumour Destruction

All three major pathways of cell death have been found to play a significant role in PDT-associated cytotoxicity: Apoptosis, Necrosis and autophagy.

The discovery that PDT can lead to an apoptotic response in malignant cells has provided a rationale for the widespread efficacy observed. *Agarwal et al.* reported an apoptotic response to PDT in 1991. Reports that PDT could rapidly induce apoptosis, both *in vitro* and *in vivo,* have provided an insight into the nature of photokilling. Apoptosis is a mechanism whereby organisms initiate cellular death *via* a process that is normally part of the genetic apparatus. The end result is fragmentation of nuclear DNA and dissociation of the cell into membrane-bound particles that are engulfed by adjoining cells, minimizing release of inflammatory products, e.g., lysosomal enzymes.

80% of the cell population shows response within 1-3 days of PDT. Recent studies have reported of mitochondrial photodamage as a major contributory factor responsible for initiation of cell death.

PDT damage to the plasma membrane can be observed within minutes after light exposure. This type of damage is manifested as swelling, bleb formation, shedding of vesicles containing plasma membrane marker enzymes, cytosolic and lysosomal enzymes, reduction of active transport, and depolarization of the plasma membrane.

Furthermore, major photodamage to the endoplasmic reticulum (ER) and consequent Ca^{+2} depletion were observed post PDT. PDT has also shown to cause photoinactivation of caspase initiators in cytosol which results in the propagation of a necrotic cell death pathway.[1]

PDT induces the host's innate immune response by accumulation of inflammatory cells, including neutrophils and macrophages, at the treatment site as well as causing activation of the complement system. These macrophages accumulate PS which renders the cell highly susceptible to lytic changes. It also causes release of various inflammatory mediators including cytokines IL-1β, TNF-α, IL-6, IL-10, and histamine and coagulation factors. Another [1] popular theory of PDT induced

damage includes damage to the tumour microvasculature, vascular stasis leading to tumour hypoxia.

Review of Current Literature Using Topical PDT for the Management of Oral Pmds.

PDT has been an emerging area of research as an efficient therapeutic modality in the treatment of oral dysplasia and superficial tumours.

Topical ALA, 10% and 20% preparations, in the form of emulsion has been the most commonly used PDT for treating dysplastic lesions in literature.

The only study using Topical PDT for more than 50 dysplasias and longer than 5 year follow-ups is from UK by Jerjes *et al.* 2011.

DYSPLASIA	COMPLETE RESOLUTION RATE
MILD	100%
MODERATE	82%
SEVERE	81%
CARCINOMA IN SITU	69%

In a recent prospective study, 147 patients with homogeneous and non-homogenous leukoplakias, and erythroplakias were treated with ALA-PDT/mTHPC-PDT depending on their clinical and histological appearance.[1]

After more than 5 years of follow up,

Complete Resolution Rate	Malignant Transformation Rate
119 out of 147 patients	11 out of 147 patients
81%	7.5%

The study by Hopper *et al.* of patients with early oral cancer, in whom the tumors measured up to 2.5 cm in diameter, reported a complete response rate of 85% (97 of 114 patients) at 12 weeks and a disease-free survival rate of 75% at 2 years.[5]

Grant *et al.* [15] reported the use of PDT to treat 11 patients with "field cancerization" occurring in the oral cavity. Six patients had multiple primary cancers and five had single primary tumours. Six to eight weeks later, treated areas in 10 of the 11 patients showed a complete response to PDT. One patient had areas of residual leukoplakia; while 2 patients developed further areas of leukoplakia or erythroplakia within 12 months. However, no patient has had evidence of recurrent invasive carcinoma in the treated areas. Fan *et al.* [7]. treated 12 patients with oral dysplastic lesions using orally administered ALA. All 12 patients showed regression of the lesions to normal or less dysplastic. Chen *et al.* [3] treated eight patients with OVH and 24 patients with OL using the topical ALA-PDT (20% gel). A complete regression of OVH lesions was obtained after fewer than 6 treatments once a week, while all OL lesions had at least a partial response after 8 treatments twice a week.[3]

Advantages of PDT

1. is non-invasive and convenient for the patient
2. Can be performed in outpatient or day-care (inpatient) settings
3. Can be targeted accurately and selectively in early or localized diseases
4. Although it cannot cure advanced disseminated disease, because illumination of the whole body is not possible, it can improve quality of life & lengthen survival.
5. Repeated doses can be given without the need for total-dose limitations.
6. Economical
7. Shows faster post-operative healing with no long term side effects
8. Can have excellent cosmetic results, and the healing process results in little or no scarring.
9. The absence of genotoxic and mutagenic effects of PDT is an important factor for long term safety during treatment.

Limitations of PDT

1. Light needed to activate photo sensitizer cannot penetrate more than 1.5cm of tissue depth using standard laser and low powered LED technology and hence is less effective in treatment of large tumors and metastasis.
2. It may leave many people very sensitive to light post therapy (photosensitivity)
3. Cannot be used in people allergic to porphyries.
4. It involves some specialized equipment and training.
5. There is a large capital outlay.
6. The lack of accurate dosimetry and suitable illumination devices has diminished the success of PDT.

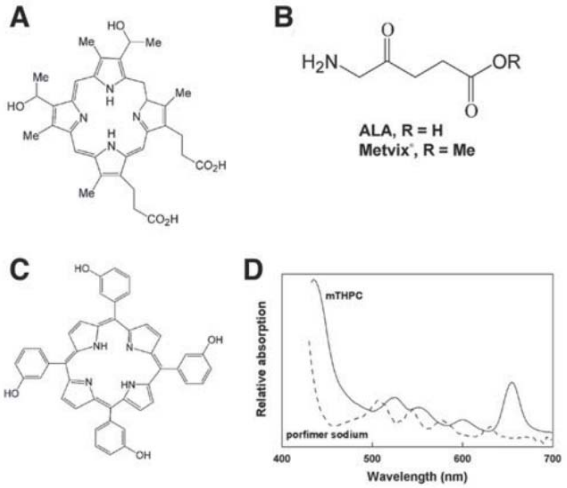

Fig I: Chemical structures of porfimer sodium **(A)**, 5-Aminolevulinic acid (ALA) and Metvix® **(B)** and *meso*-tetrahydroxyphenyl-Chlorin (mTHPC) **(C),** and absorption spectra of porfimer sodium and mTHPC **(D)**. The relative absorption Spectrum of ALA is comparable with that of porfimer sodium[3]

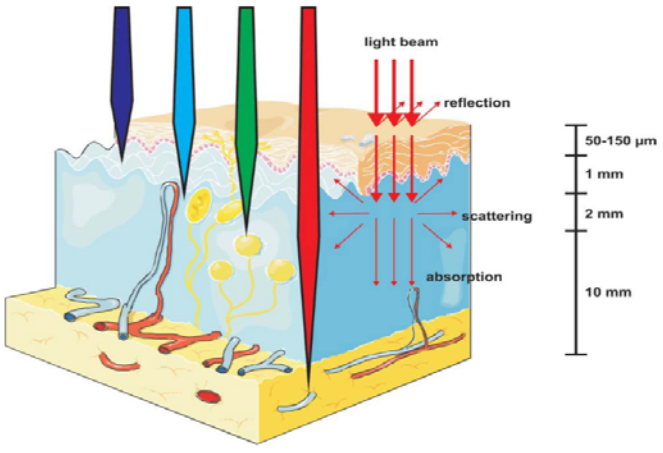

Fig II: Absorption spectrum in the human tissues where red light shows maximum absorption.

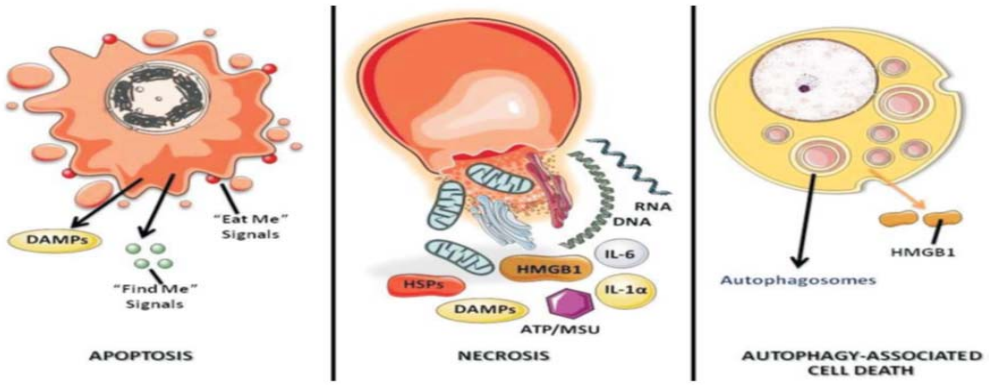

Fig III: The three major cell death pathways initiated by PDT.

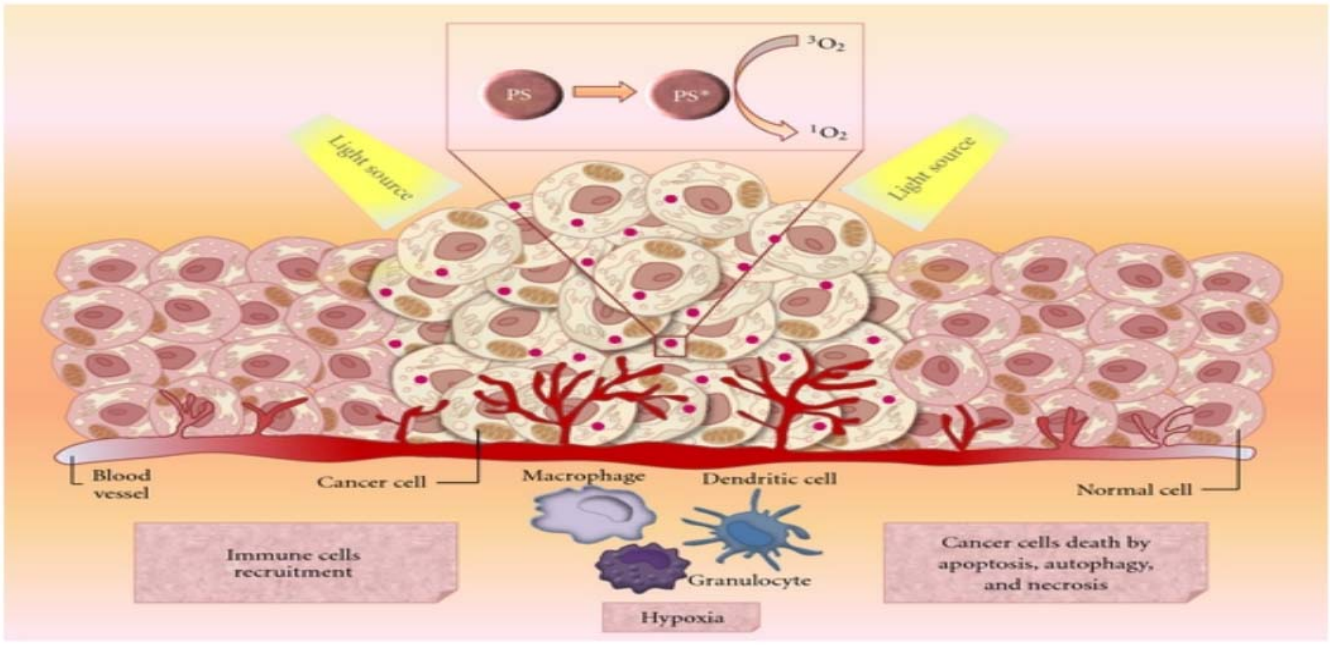

Fig IV: Graphic representation of the mechanism of action of PDT.

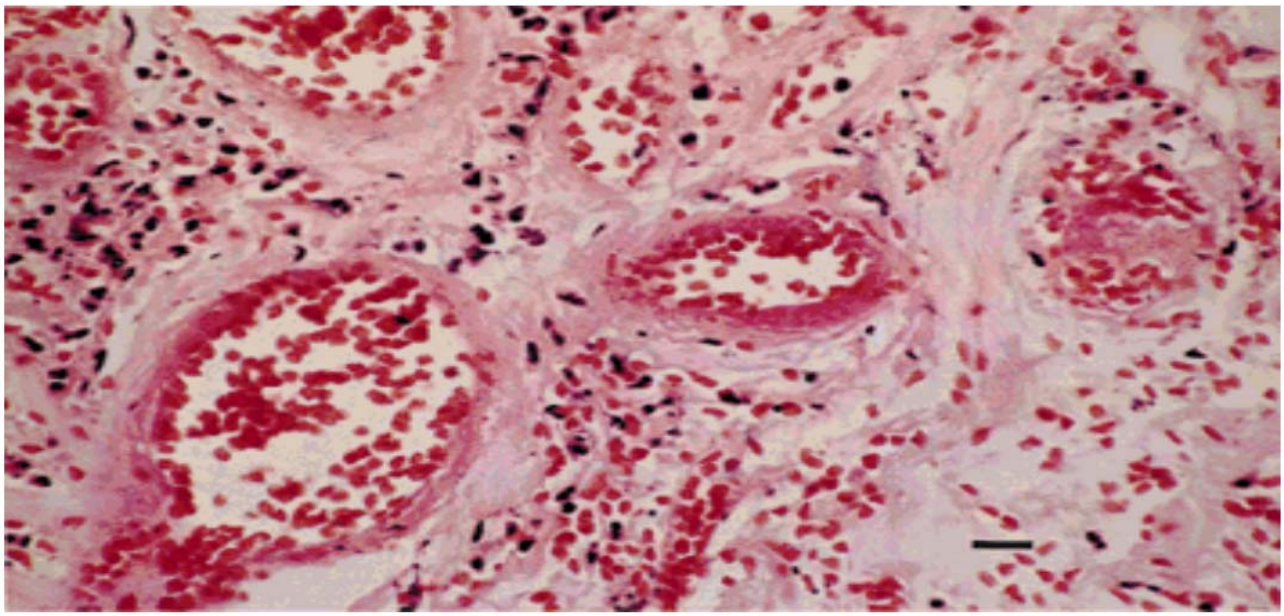

Fig V: Characteristic changes in blood vessels 3 days after PDT. There is extensive vascular damage with loss of endothelial cells, resulting edema, extravasations of red blood cells and inflammation. Thrombus formation is prominent. H&E; bar: 20 µm.

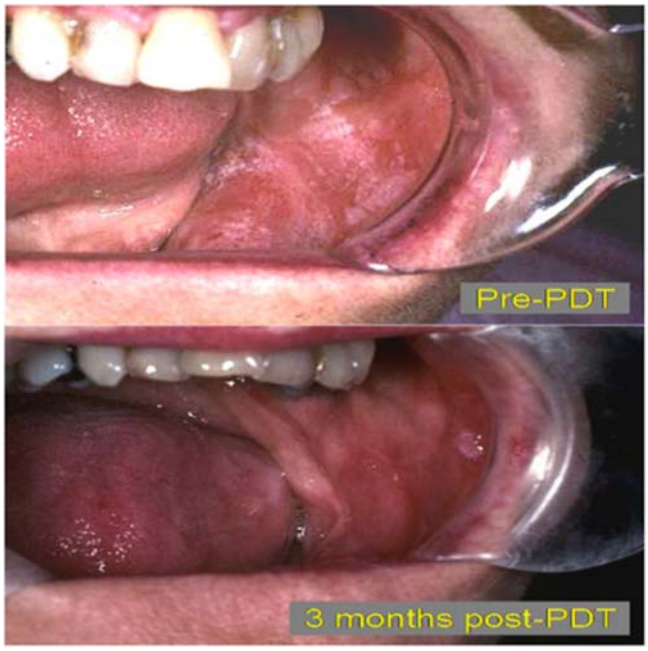

FIG VI: Clinical images showing response of moderate oral dysplasia to photodynamic therapy.[7]

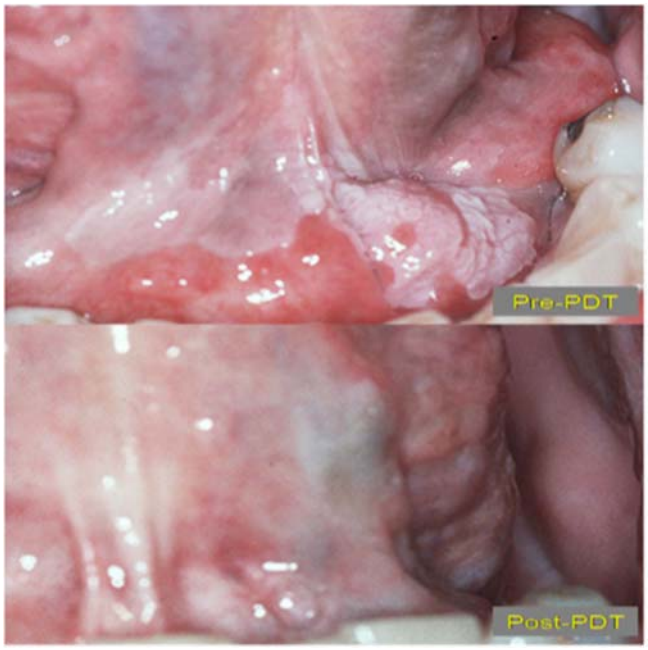

FIG VII: Clinical image of SCC of the oral cavity and ventral tongue responded favourably to photodynamic therapy.[7]

Conclusion

PDT is still considered to be a new and promising antitumor strategy.

With its tremendous potential to treat and cure recurrent lesions it has shown to be the treatment of choice for managing premalignant lesions.

Studies with standardized treatment protocols, randomized clinical trials with interim and long-term follow up goals are needed urgently before advocating its use. The development of new, more tumour-specific photo-sensitizers and light delivery systems still more improve its efficacy and thus the future of PDT depends on interactions between clinical applications and technological innovations.

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