ROSWELL PARK
COMPREHENSIVE CANCER CENTER

Photodynamic Therapy

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Photodynamic Therapy (PDT)

- Food and Drug Administration (FDA) approved treatment for a variety of oncologic and non-oncologic conditions originally developed at Roswell Park (*Dougherty, 1974*).

- Involves photoactivation of a tissue-localized drug by light of a specific wavelength.

T.J. Dougherty (1974)@Roswell
Photo-destruction of cells *in vitro* by fluorescein

> While using a technique called "vital staining" to test the toxicity of an ionizing sensitizer he had made, Dougherty accidentally discovered that when cancer cells that contained the vital stain (fluorescein diacetate) were exposed to room light, they died.

Buffalo Physician, Autumn 2004

History of PDT

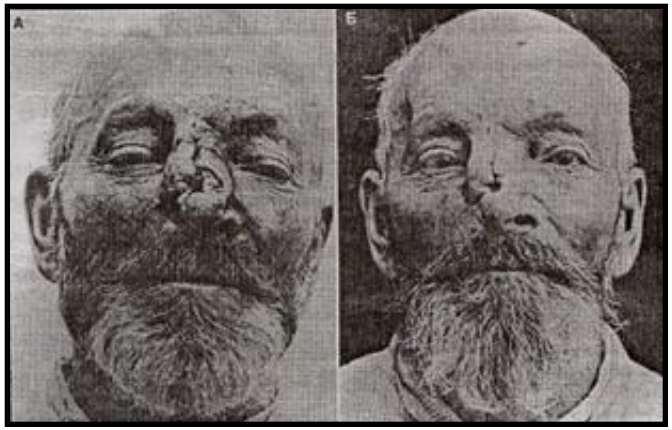
- Oscar Raab (1900) – medical student in Munich

Certain wavelengths of light were lethal to paramecia that were exposed to acridine orange.

- Professor Hermann Von Tappeiner

'photodynamic action'

Used eosin for treatment of skin lesions



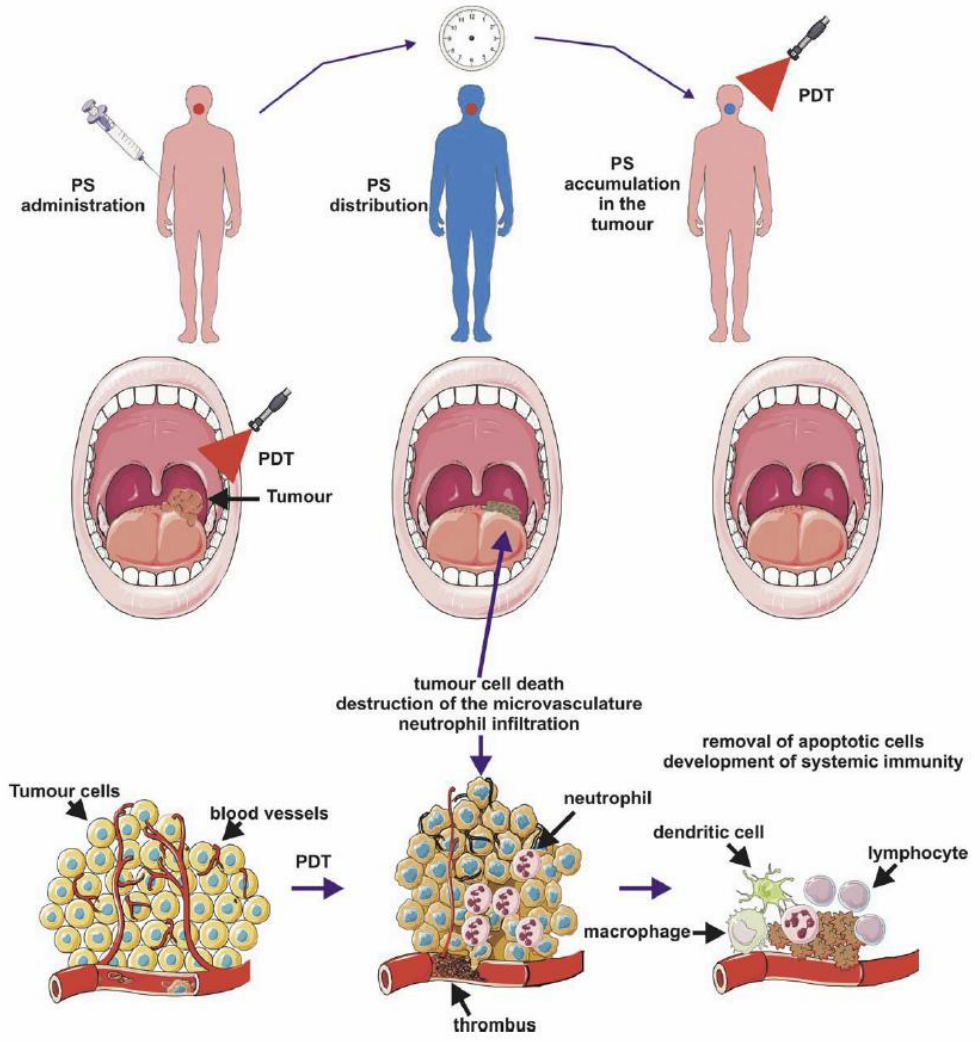
Before **After**

Tappeiner and Jesionek, 1903

http://www.magicray.ru/ENG/lecture/L2/2.html

http://www.photobiology.info/HistPhotosens.html

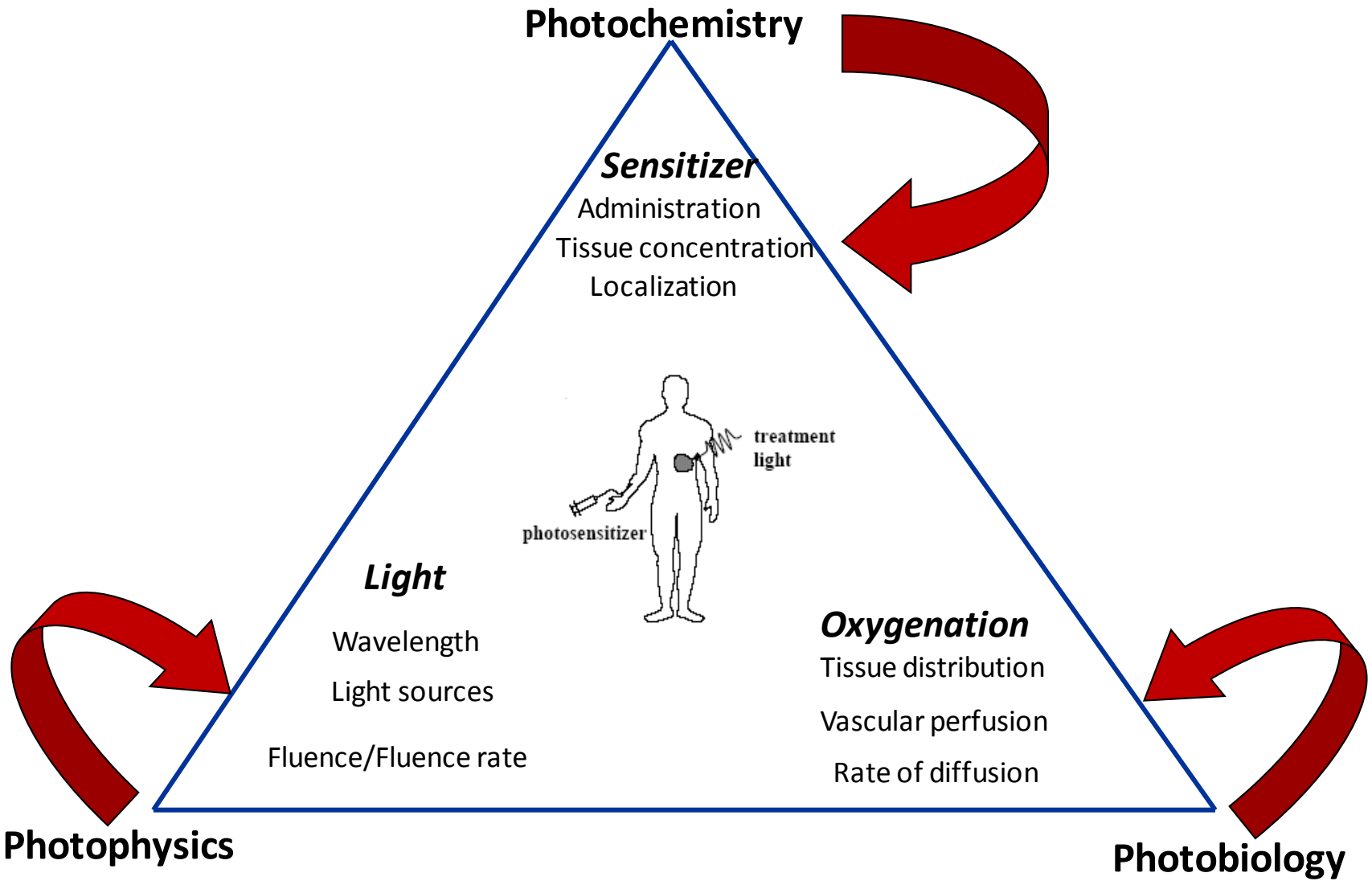
Basic principles of PDT



- **Administration** of a drug - photosensitizer (PS)
- **Localized activation** (excitation) of the sensitizer in tissue by light of a specific wavelength
- **Generation** of highly reactive free radicals
- **Oxidization** of biological substrates causing cytotoxic effects within the illuminated tissue.

Agostinis et al., CA Cancer J Clin 2011

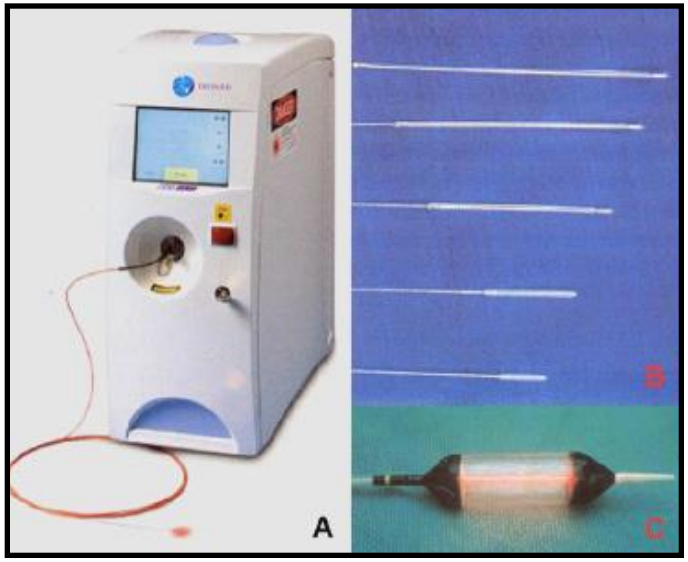
Photodynamic Triad



Photophysics

- Laser source is used to deliver monochromatic light through optical fibers

- Wavelength of activation generally corresponds to the absorbance maxima of the sensitizer used.



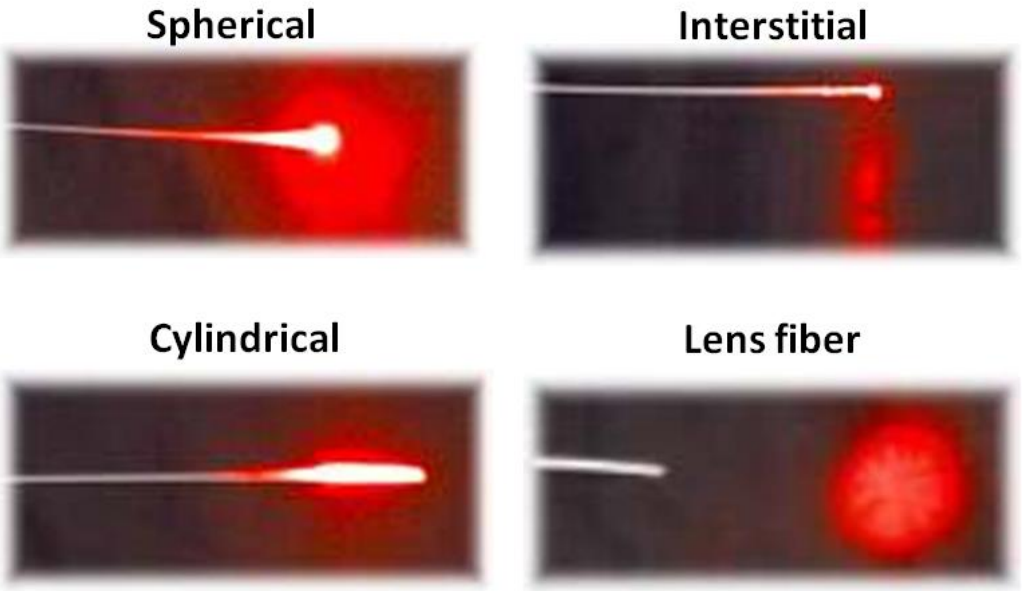
Longer wavelength sensitizers (~800 nm) are preferred

- **Light sources – pumped dye lasers (bulky, inefficient), diode lasers (compact, portable, cost-effective)**

Agostinis et al., CA Cancer J Clin 2011

Tang *et al*, 2004

Light delivery



No single light source is ideal for all PDT applications even with the same PS

Choice of light source/delivery fiber depends on the disease site (location, size of lesions, access, tissue characteristics)

Photophysics

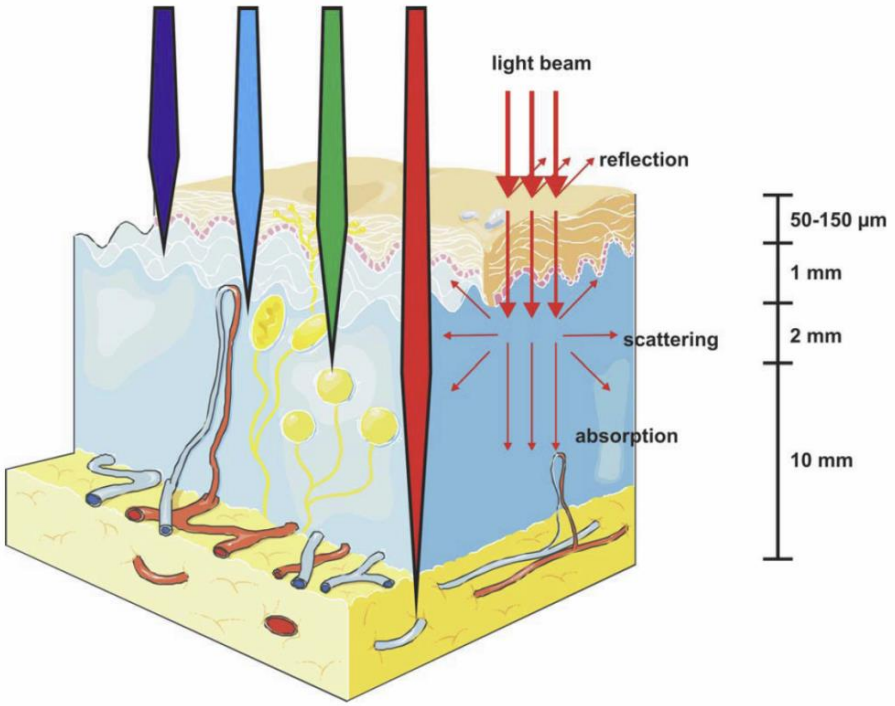


FIGURE 2. Light Propagation Through the Tissues.

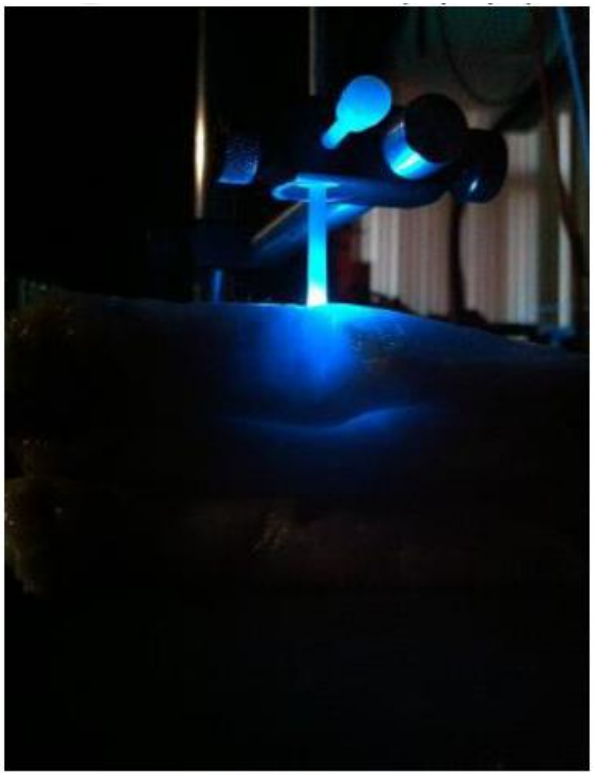
Blue light penetrates least efficiently through tissue,
whereas red and infrared radiations penetrate more deeply.

600-1200 nm (tissue optical window)

Beyond 800 nm, there is insufficient energy for initiation of photodynamic reaction

Agostinis et al., CA Cancer J Clin 2011

Photophysics



514nm

720nm

Light Dosimetry

- Defined by the fluence and fluence rate

- **Fluence**: Total amount of light dose delivered (J/cm^2).
- **Fluence rate**: Rate at which the light dose is delivered (mW/cm^2).

- The photochemical process associated with singlet oxygen generation is also oxygen-consuming.

- Biological response to PDT is critically dependent on the regimen employed

Biophysical Basis of PDT

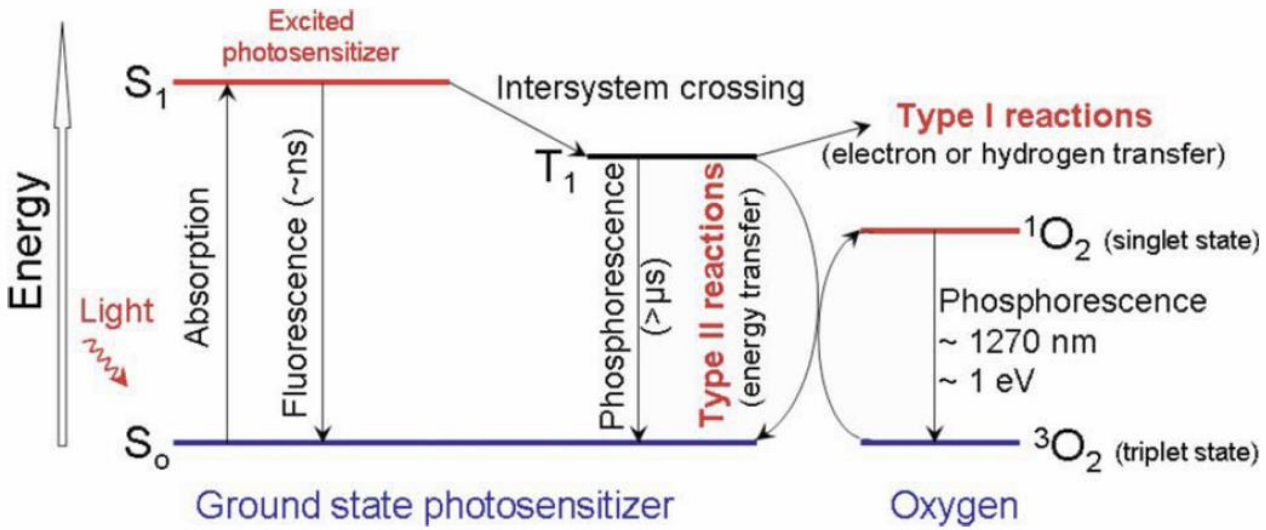


FIGURE 3. Photosensitization Processes Illustrated by a Modified Jablonski Diagram. Light exposure takes a photosensitizer molecule from the ground singlet state (S_0) to an excited singlet state (S_1). The molecule in S_1 may undergo intersystem crossing to an excited triplet state (T_1) and then either form radicals via a Type I reaction or, more likely, transfer its energy to molecular oxygen ($^3O_2$) and form singlet oxygen ($^1O_2$), which is the major cytotoxic agent involved in photodynamic therapy. ns indicates nanoseconds; µs, microseconds; nm, nanometers; eV, electron volts.

The biological effects of PDT are a consequence of a dynamic interaction between the PS, light and tissue/molecular oxygen

Agostinis et al., CA Cancer J Clin 2011

Photosensitizers

Guidelines for 'ideal' photosensitizers

- Toxicity
- Activation
- High singlet oxygen yield
- Ease of administration
- Elimination
- Cost-effective

Table 2 Photosensitizer families.

Porphyrin platform
HpD (hematoporphyrin derivative)
HpD-based
BPD (benzoporphyrin derivative)
ALA (5-aminolevulinic acid)
Texaphyrins
Chlorophyll platform
Chlorins
Purpurins
Bacteriochlorins
Dyes
Phtalocyanine
Napthalocyanine

Increased interest in developing targeted photosensitizers

Allison et al., 2004

Photochemistry

PHOTOSENSITIZER	STRUCTURE	WAVELENGTH, nm	APPROVED	TRIALS	CANCER TYPES
Porfimer sodium (Photofrin) (HPD)	Porphyrin	630	Worldwide		Lung, esophagus, bile duct, bladder, brain, ovarian
ALA	Porphyrin precursor	635	Worldwide		Skin, bladder, brain, esophagus
ALA esters	Porphyrin precursor	635	Europe		Skin, bladder
Temoporfin (Foscan) (mTHPC)	Chlorine	652	Europe	United States	Head and neck, lung, brain, skin, bile duct
Verteporfin	Chlorine	690	Worldwide (AMD)	United Kingdom	Ophthalmic, pancreatic, skin
HPPH	Chlorin	665		United States	Head and neck, esophagus, lung
SnEt2 (Purlytin)	Chlorin	660		United States	Skin, breast
Talaporfin (LS11, MACE, NPe6)	Chlorin	660		United States	Liver, colon, brain
Ce6-PVP (Fotolon), Ce6 derivatives (Radachlorin, Photodithazine)	Chlorin	660		Belarus, Russia	Nasopharyngeal, sarcoma, brain
Silicon phthalocyanine (Pc4)	Phthalocyanine	675		United States	Cutaneous T-cell lymphoma
Padoporfin (TOOKAD)	Bacteriochlorin	762		United States	Prostate
Motexafin lutetium (Lutex)	Texaphyrin	732		United States	Breast

Abbreviations: ALA, 5-aminolevulinic acid; AMD, age-related macular degeneration; Ce6-PVP, chlorin e6-polyvinypyrrolidone; HPD, hematoporphyrin derivative; HPPH, 2- (1-hexyloxyethyl)-2-devinyl pyropheophorbide-a; MACE, mono-(L)-aspartylchlorin-e6; mTHPC, m-tetrahydroxyphenylchlorin; nm indicates nanometers; SnEt2, tin ethyl etiopurpurin.

Agostinis et al., CA Cancer J Clin 2011

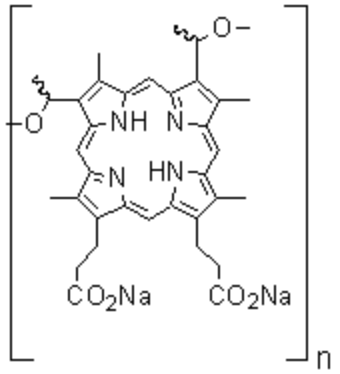
Photochemistry

- **Porphyrins**

  - Useful sensitizers, high singlet oxygen yield, absorption in the visible spectrum

Photofrin®

- combination of monomers, dimers & oligomers derived from chemical manipulation of Hp, 630 nm absorption

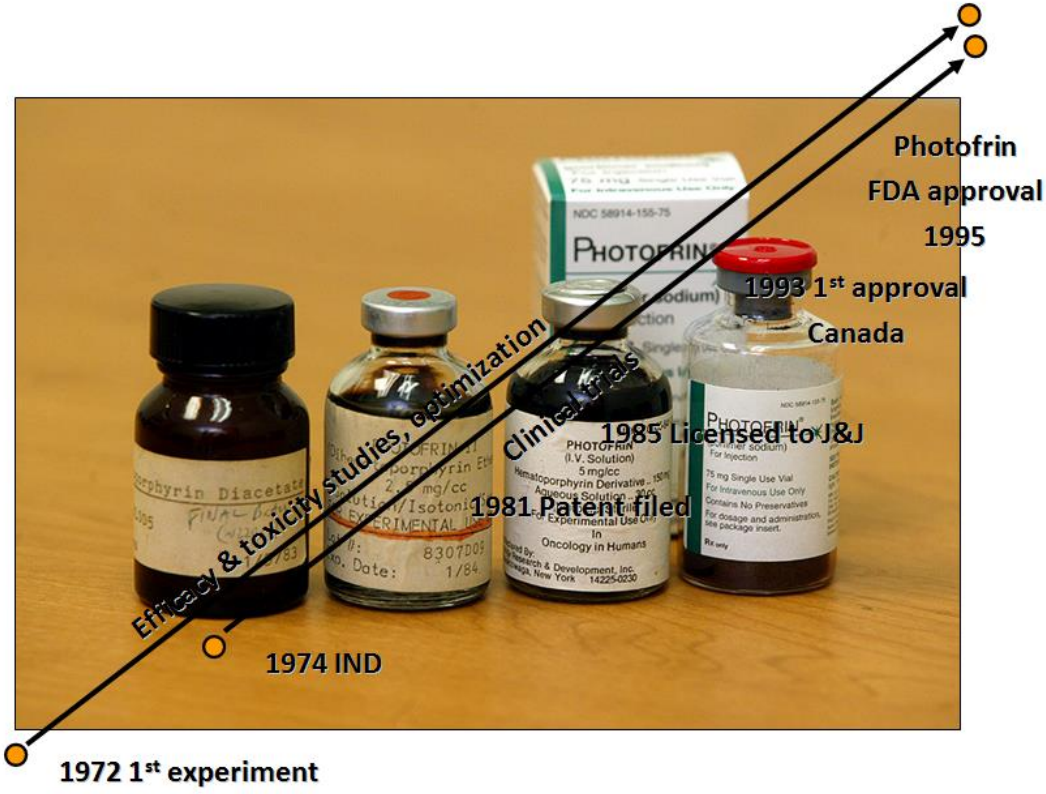


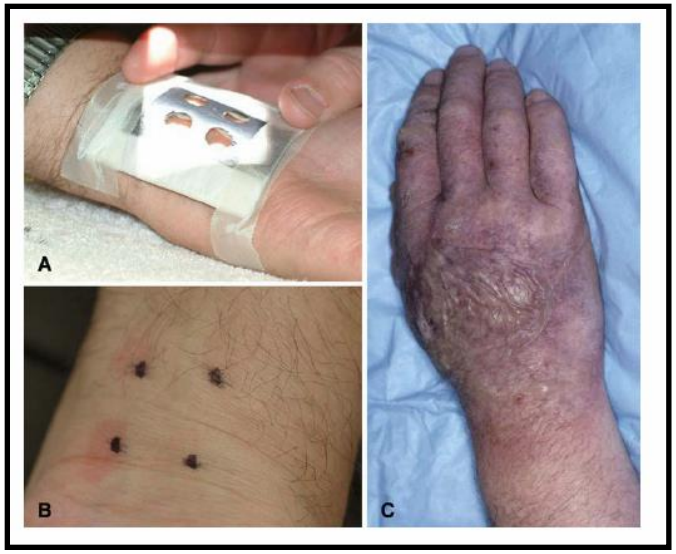
Photofrin (n = 1-9)

Allison *et al*, 2004

Photofrin

- 1st photosensitizer to be approved by the FDA
- Approved indications in endobronchial and lung cancers, Barrett's esophagus
- ***Limitation***: Prolonged cutaneous sensitivity





Adam Sumlin/Thomas Dougherty

Bellnier *et al.*, 2006

Photochlor

Photosensitizer: HPPH

2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a)
(665 nm)

- Chlorin-based sensitizer - Pandey et al., (1991)
- Significantly decreased photosensitivity than Photofrin in patients
- Currently undergoing clinical evaluation in head and neck and lung cancers

Photochlor

Study

45 patients

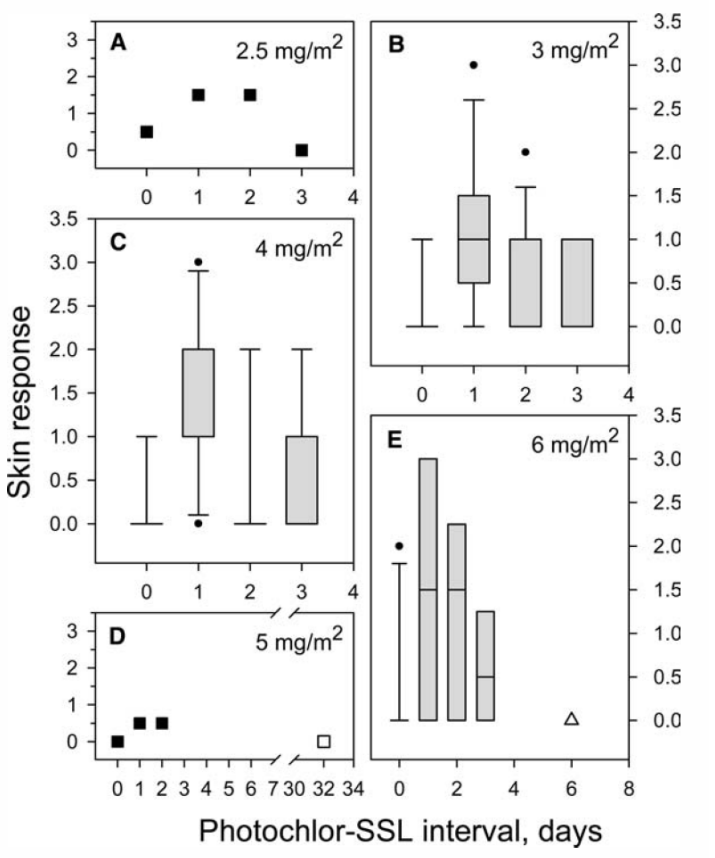
- 3,4,5 or 6 mg/m^2 HPPH
- Up to 133 J/cm^2 solar-spectrum light (SSL) on 3 consecutive days after HPPH

Results

18% had *no reaction* to SSL

- 16% had strongest reaction obtained in the study-
  erythema w/o edema
  or blistering
- Response appears to be related to HPPH-dose

Skin phototoxicity (HPPH)



Photochlor, at clinically effective antitumor doses, causes only mild skin photosensitivity that declines rapidly over a few days.

Bellnier *et al.*, 2006

Clinical PDT – Skin phototoxicity (HPPH)

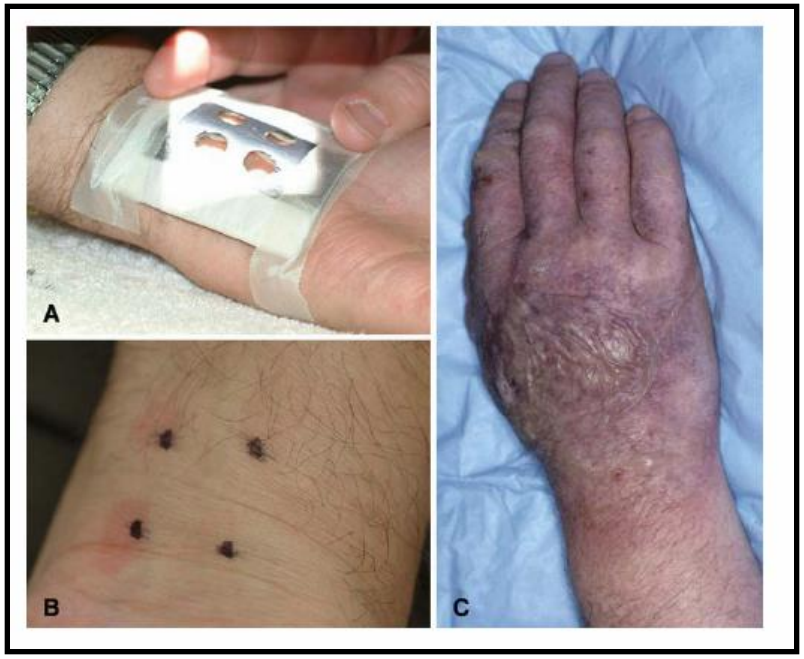
Conclusions

90% of the subjects exposed to SSL 3 days after Photochlor infusion had responses that were less severe than those obtained with either the 1- or 2-day sensitizer-SSL interval.

Photochlor, at clinically effective antitumor doses, causes only mild skin photosensitivity that declines rapidly over a few days.

Bellnier *et al.*, 2006

Cutaneous phototoxicity



0*No reaction*
1*Minimal perceptible erythema, blotchy areas of faint erythema confined to the illuminated site*
2*Minimal erythema with sharp borders*
3*More pronounced erythema without edema*
4*Marked erythema with edema*
5*Marked erythema with edema and vesiculation*

Bellnier *et al.*, 2006

Biological response to PDT

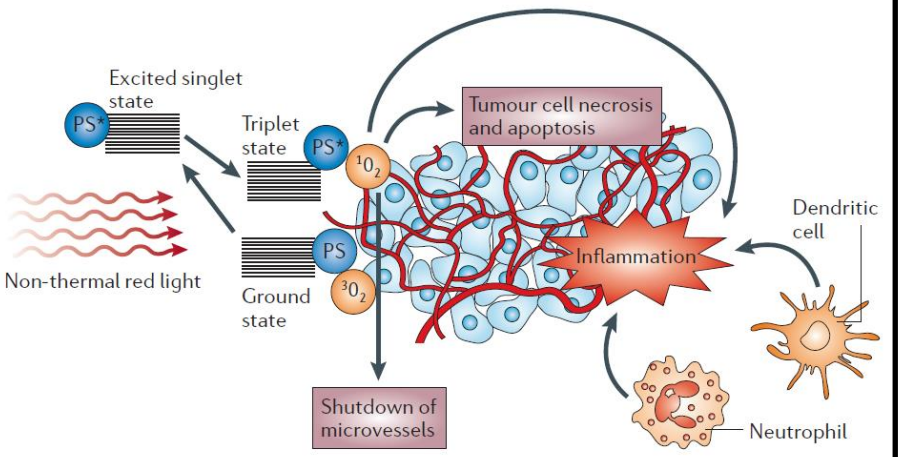


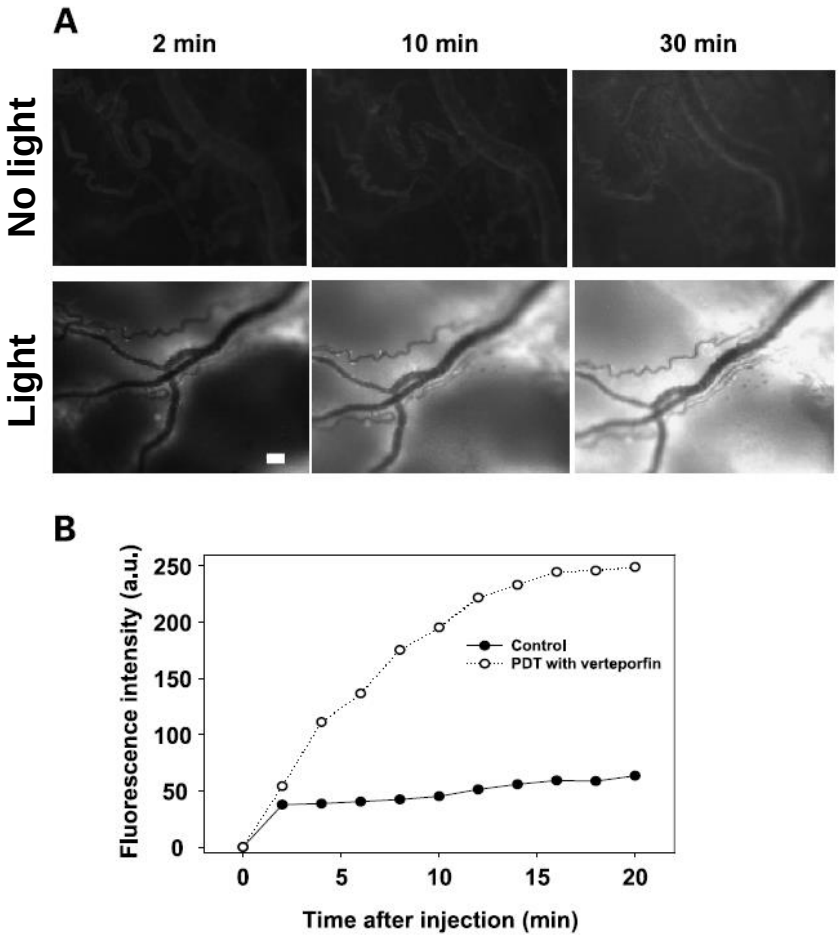
Figure 1 | **The mechanism of action on tumours in photodynamic therapy.** The photosensitizer (PS) absorbs light and an electron moves to the first short-lived excited singlet state. This is followed by intersystem crossing, in which the excited electron changes its spin and produces a longer-lived triplet state. The PS triplet transfers energy to ground-state triplet oxygen, which produces reactive singlet oxygen ($^1O_2$). $^1O_2$ can directly kill tumour cells by the induction of necrosis and/or apoptosis, can cause destruction of tumour vasculature and produces an acute inflammatory response that attracts leukocytes such as dendritic cells and neutrophils.

- Complex
- Combination of direct cytotoxicity, vascular damage and the induction of immune/inflammatory responses
- The efficacy of the photodynamic reaction depends on several parameters:
  - PS used
  - Light treatment conditions
  - Tissue oxygenation

Unlike tissue factors (vascularity/oxygenation), light treatment conditions are under the direct control of the clinician

Castano *et al*, Nature Reviews Cancer 2006

Vascular response to PDT

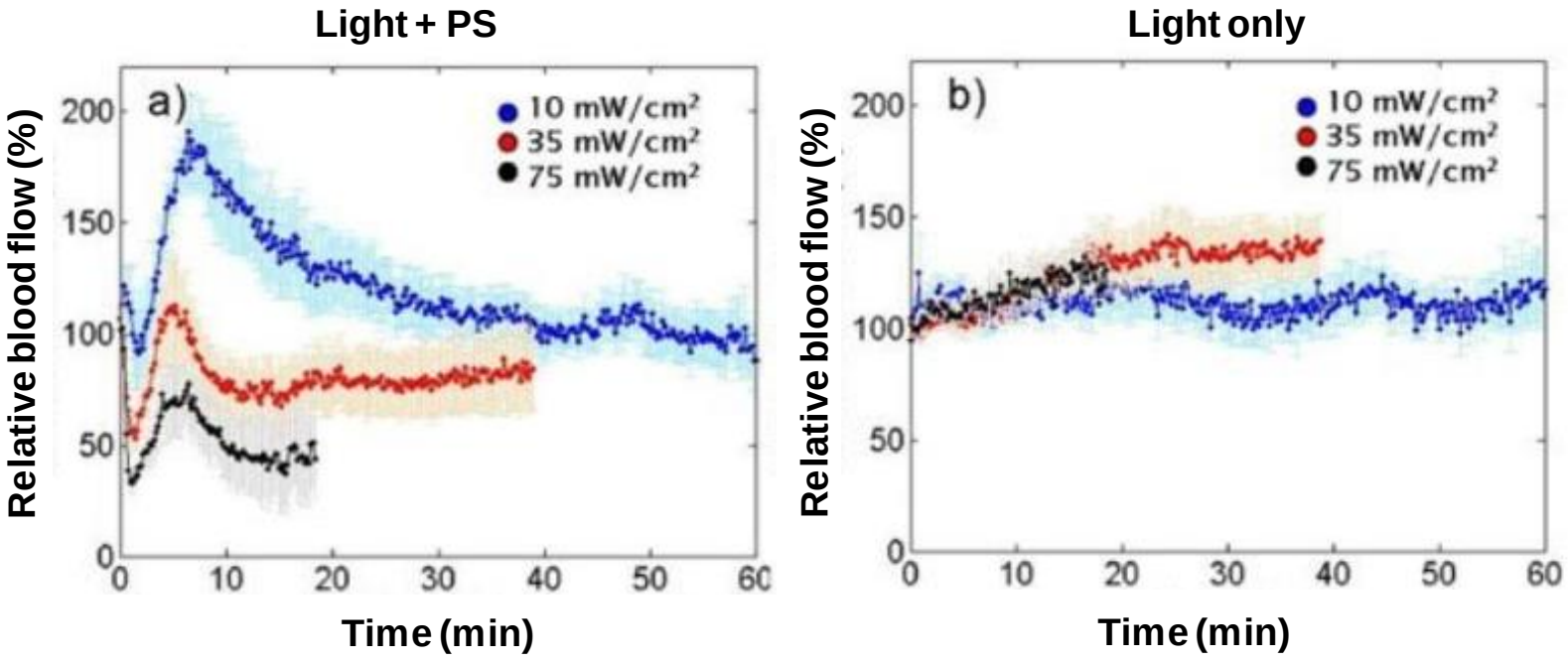


- Increased vascular permeability
- Hemorrhaging
- Loss of perfusion (shutdown)

Depending on sensitizer and treatment conditions

Chen *et al,* 2006

Vascular response to PDT



Changes in blood flow can occur during treatment, and are impacted by fluence rate

Adapted from Becker et al 2011 Biomed Opt Express

Immune/inflammatory response to PDT

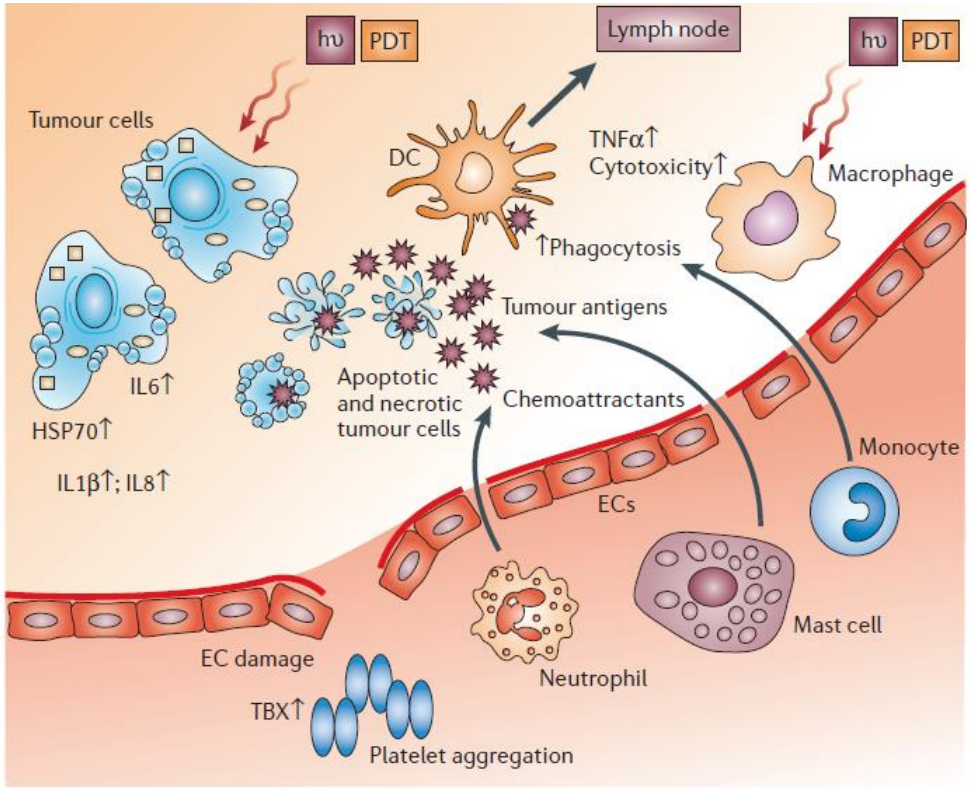


Figure 3 | **Consequences of photodynamic therapy-induced inflammation.** Damage to endothelial cells (ECs) activates a casade of events that lead to local inflammation, vessel dilatation and platelet aggregation. Much of this is caused by the release of thromboxane (TBX), cytokines such as interleukin 1β (IL1β), IL6 and IL8, the production of tumour-necrosis factor-α (TNFα), and infiltration of the treated tumour by cells of the immune system. Necrotic and apoptotic tumour cells express heat-shock proteins (HSPs) and provide antigens to dendritic cells (DCs) that migrate to lymph nodes. hν, light; PDT, photodynamic therapy.

- Prostaglandins
- Cytokines
- Chemokines
- Inflammatory cell infiltration (neutrophils and macrophages)

Castano *et al*, Nature Reviews Cancer 2006

Clinical PDT

✓ Emerging as a viable clinical treatment for nearly every histological type/site.

* Head and neck cancers (*Biel et al.,1998*)
* Skin cancers (Oseroff *et al.,2005*).
* Intra-abdominal sarcomas (*Hahn et al., 2006*).

Table 2. Approved photodynamic-therapy drugs for oncological indications

Chemical name	Generic name	Date and country of approval	Indications
Haematoporphyrin derivative, polyhaematoporphyrin	Porfimer sodium	First approved in 1995; now approved in more than 40 countries	Advanced and early lung cancer, superficial gastric cancer, oesophageal adenocarcinoma, cervical cancer, and bladder cancer
Methyl-tetrahydroxyphenyl chlorin	Temoporfin	Approved in 2001 in European Union, Norway, and Iceland	Palliative head and neck cancer
5-aminolevulinic acid	Aminolevulinic acid	Approved in 1999 in USA	Actinic keratosis
Methyl 5-aminolevulinate	Methyl aminolevulinate	Approved in 2001 in Europe	Actinic keratosis, superficial basal-cell carcinoma, and basal-cell carcinoma

Off-label use Brain, bladder, prostate, breast.

http://oncology.thelancet.com

Brown *et al*, 2004

Clinical PDT

Advantages

✓ Equivalent or greater efficacy compared to standard therapies

✓ Reduced morbidity/disfigurement

✓ Can be repeated for large bulky tumors – interstitial PDT

✓ Use of PDT is not precluded by prior/subsequent surgery or chemotherapy

✓ Excellent cosmetic outcome – skin lesions, HNC

✓ PDT as an adjunct could eliminate residual disease

Skin Conditions

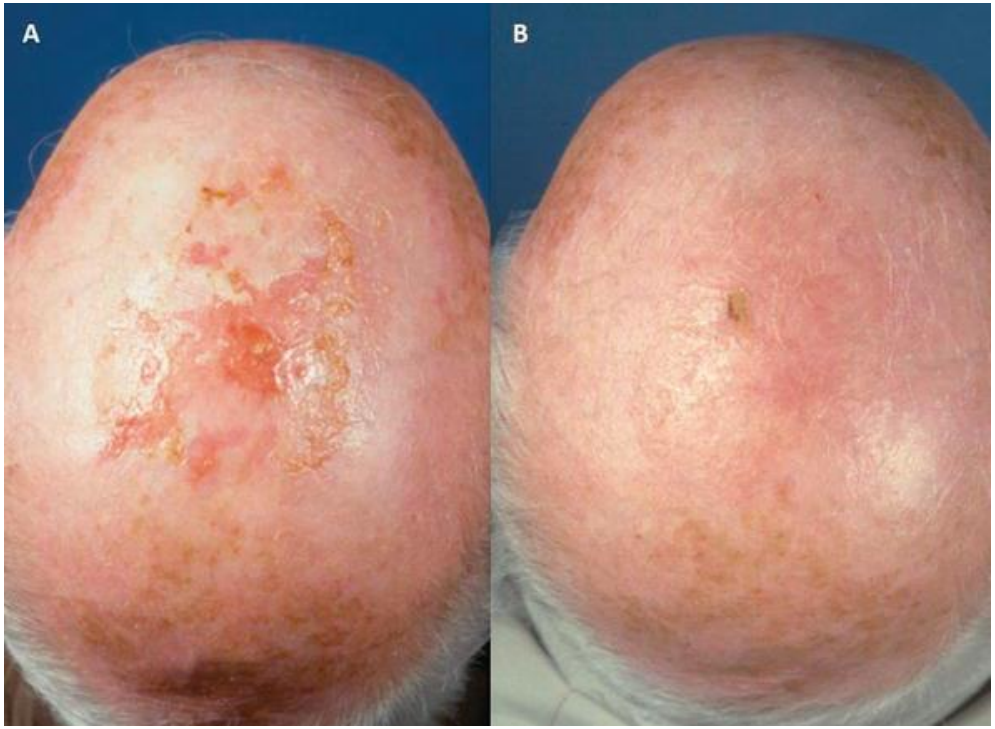


Table 1. ALA preparations.

Product name	Ingredients
Metvix®	16% methyl-5-amino-4-oxopentanoate as hydrochloride
Levulan Kerastick® (not approved for clinical use in Europe)	20% aminolevulinic acid hydrochloride
Magistral preparation	20% ALA gel/cream/emulsion
PD P 506 A (photonamic GmbH & Co KG, Wedel, Germany) (not yet approved for clinical use)	5-ALA released from bandage
BF-200 ALA (Biofrontera AG, Leverkusen, Germany) (not yet approved for clinical use)	5-ALA nanoemulsion

Papakonstantinou et al (2018) Dermatologic Surgery and Procedures

Lung cancer

Endobronchial Lung Cancer

- Advanced disease, palliative intent (airway obstruction)

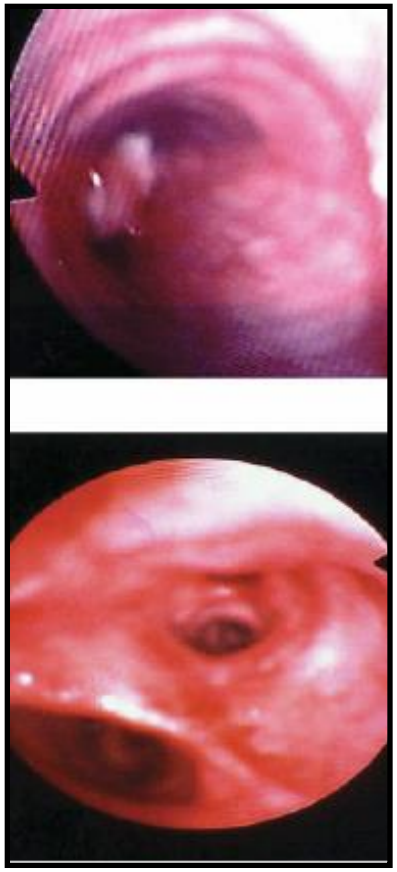
TABLE 1. PDT for Palliation of Endobronchial Obstruction: Selected Studies

Reference	Patients (n)	Drug	Palliation	Complications
Kato, 1998 [43]	111	HPD	74%	Sunburn 21.5%
Balchum, 1984 [44]	22	HPD	OR 21/22	Pneumothorax 9%, Pneumonia 13%
Lam, 1986 [45]	24	Photofrin	79%	None
Zwirewich, 1988 [22]	20	Photofrin	89% OR in patients with intraluminal tumor	None
LoCicero, 1990 [46]	10	HPD	100% palliation of symptoms	Sunburn 20%
Moghissi, 1993 [47]	15	Photofrin	RT plus PDT versus YAG	None
Moghissi, 1997 [27]	17	Photofrin	YAG plus PDT 100% palliation of symptoms	Sunburn 5.8%
Dougherty, 2002 [25]	106	Photofrin	PDT superior to YAG at 1 month	Sunburn 20%
Diaz-Jimenez, 1999 [26]	31	Photofrin	PDT improved survival over YAG	Sunburn 28%
Moghissi, 1999 [20]	100	Photofrin	100% palliation of symptoms[a]	Sunburn 5%
Jones, 2001 [30]	10	Photofrin	100%	None

OR, overall response rate (e.g., % relief of endobronchial obstruction).
[a], included small cell lung cancer cases.

Loewen et al, Lasers in Surgery and Medicine 2006

Clinical PDT – Endobronchial lung cancer



Endobronchial obstruction of the distal left main bronchus not suitable for ND: YAG.

Close-up view of distal left main bronchus post-PDT, with erythema.

Following debridement, the left lung re-expanded and the patient was weaned from the ventilator within 24 hours.

Loewen et al, Lasers in Surgery and Medicine 2006

Head and neck cancers

- Management often requires aggressive surgical intervention
- Morbidity issues – speech, appearance and function
- **<u>Alternative Rx</u>:**

PDT – could be of potential benefit

non-invasive

excellent cosmetic results

single/adjunct

Oral cancer

Cancer Therapy: Clinical

Clinical Cancer Research

Photodynamic Therapy with 3-(1′-Hexyloxyethyl) Pyropheophorbide *a* for Cancer of the Oral Cavity

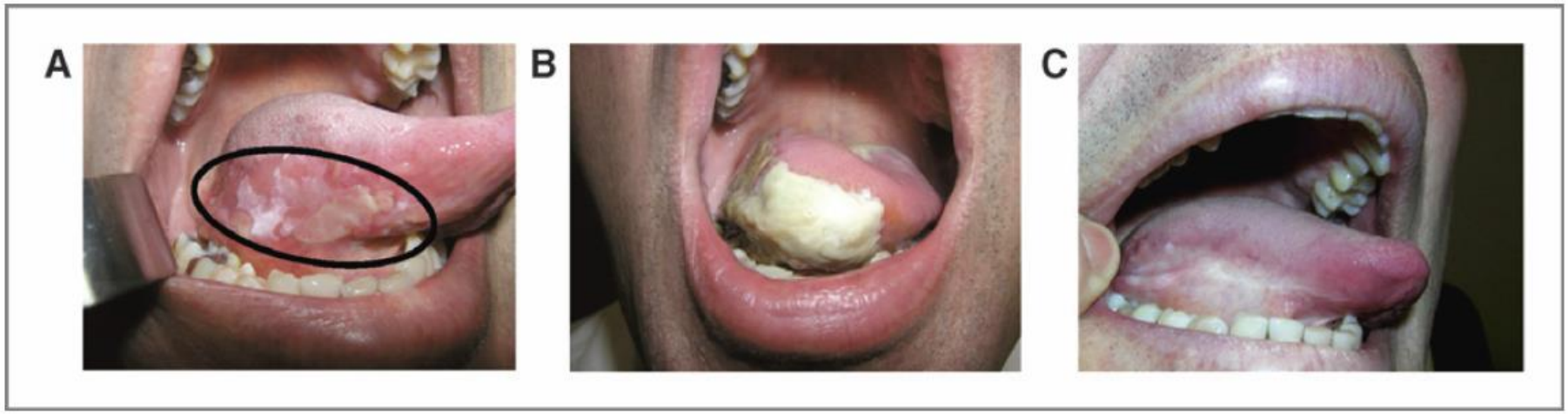


Figure 1. A, high grade dysplasia with microinvasion (within the ellipse) before therapy. B, response to PDT at 7 days posttreatment. C, complete clinical disappearance of the target lesion at 9 months after PDT.

Rigual et al., 2013

Combination strategies with PDT

TABLE 3. Combinations of PDT and Various Therapeutic Modalities in Cancer Treatment: A Comprehensive Summary

DRUG OR TREATMENT MODALITY	OUTCOME/RESULTS
CHEMOTHERAPEUTICS AND NOVEL ANTICANCER DRUGS	
Anthracyclines	Doxorubicin improves PDT-mediated tumor growth control in mice[103]
Platinum compounds	Cisplatin potentiates antitumor activity of PDT in mice[103]
Antimetabolites	Methotrexate enhances in vitro cytotoxicity of PDT with ALA by upregulation of protoporphyrin IX production[104]
Microtubule inhibitors	Vincristine administered prior to or immediately after PDT improves its antitumor activity in mice[105]
DNA methyltransferase inhibitors	5-azadeoxycytidine prolongs survival of PDT-treated animals and improves tumor growth control[106]
Proteasome inhibitors	Bortezomib enhances PDT-mediated ER stress in cancer cells in vitro and significantly delays post-PDT tumor regrowth in mice[48]
RADIOTHERAPY	
Two-way enhancement of antitumor effects: PDT sensitizes cancer cells to radiotherapy[107] and radiotherapy increases anticancer efficacy of PDT,[108] prolonged tumor growth control induced by combined treatment[109]	
DRUGS MODULATING ARACHIDONIC ACID CASCADE	
COX-2 inhibitors	COX-2 inhibitors (such as NS-398,[110] nimesulide,[111] or celecoxib[112]) potentiate antitumor effects of PDT, possibly through indirect antiangiogenic effects
LOX inhibitors	MK-886, which also serves as a FLAP inhibitor, sensitizes tumor cells to PDT-mediated killing[113]
AGENTS INCREASING PS ACCUMULATION IN TUMOR CELLS	
Vitamin D	Increases ALA-induced protoporphyrin IX accumulation and thus potentiates PDT cytotoxicity in vitro[114]
Imatinib	Increases intracellular accumulation of second-generation PSs and thus potentiates PDT cytotoxicity in vitro and in vivo[115]
Lipid-lowering drugs	Lovastatin, a HMG-CoA reductase inhibitor, improves in vitro LDL binding and porfimer sodium uptake by cancer cells[116]
Salicylate and related drugs	Enhancement of PDT efficacy in vitro via increased PS uptake by tumor cells[117]
APPROACHES INCREASING OXYGEN DELIVERY TO TUMOR CELLS	
EPO	EPO improves chemotherapy-induced anemia and restores antitumor efficacy of PDT in mice[118]; however, EPO might also inhibit direct PDT-mediated cytotoxicity toward certain cancer cells[119]

Agostinis et al., 2011

Limitations & Potential Solutions

X The FDA-approved sensitizer Photofrin® is associated with prolonged and sometimes severe cutaneous sensitivity in patients lasting for 1-2 months.

Develop newer sensitizers with decreased phototoxicity

X Improve therapeutic efficacy

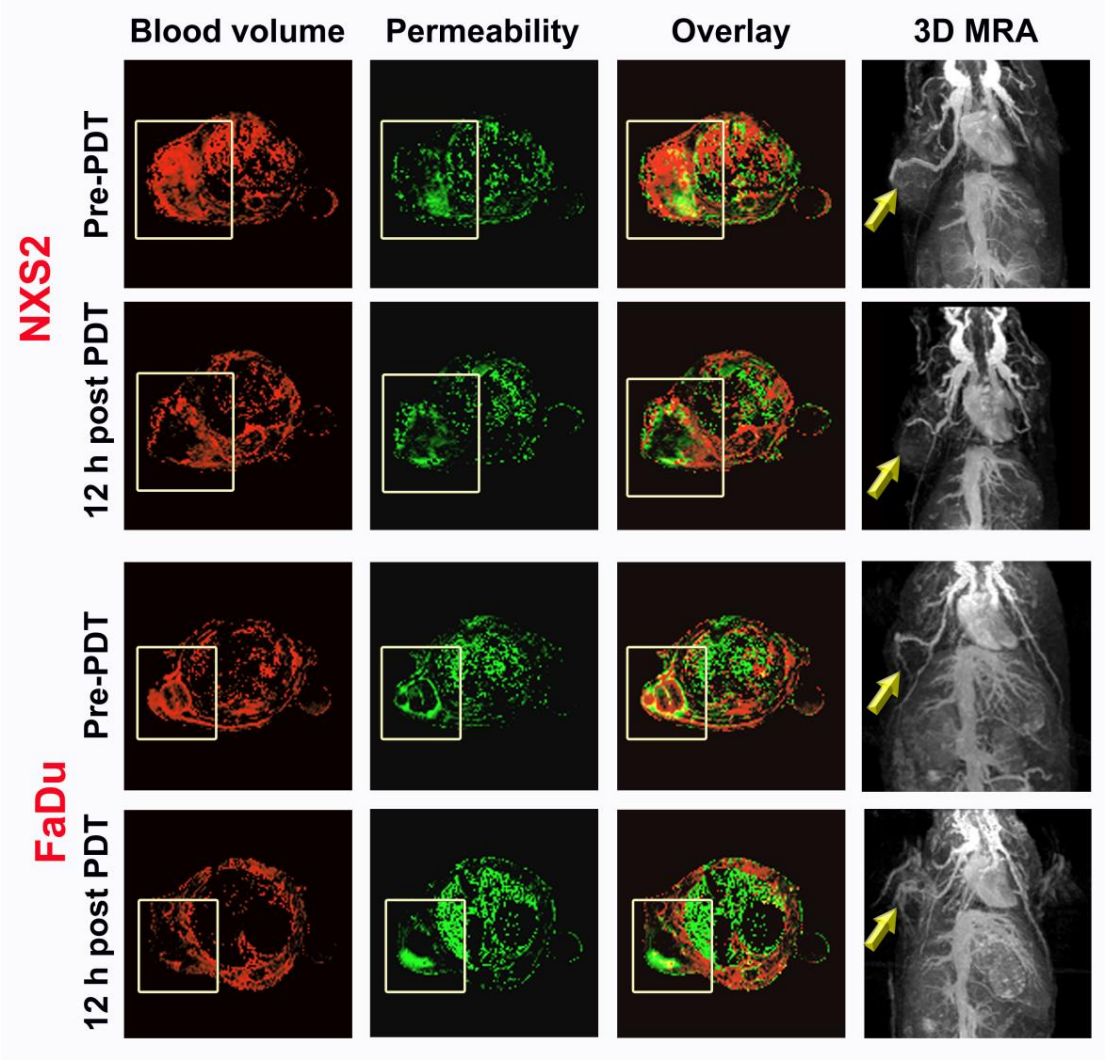
Combination strategies?

X Develop methods for detection/monitoring efficacy or activity

How can imaging help in treatment planning/monitoring?

Image-guided PDT

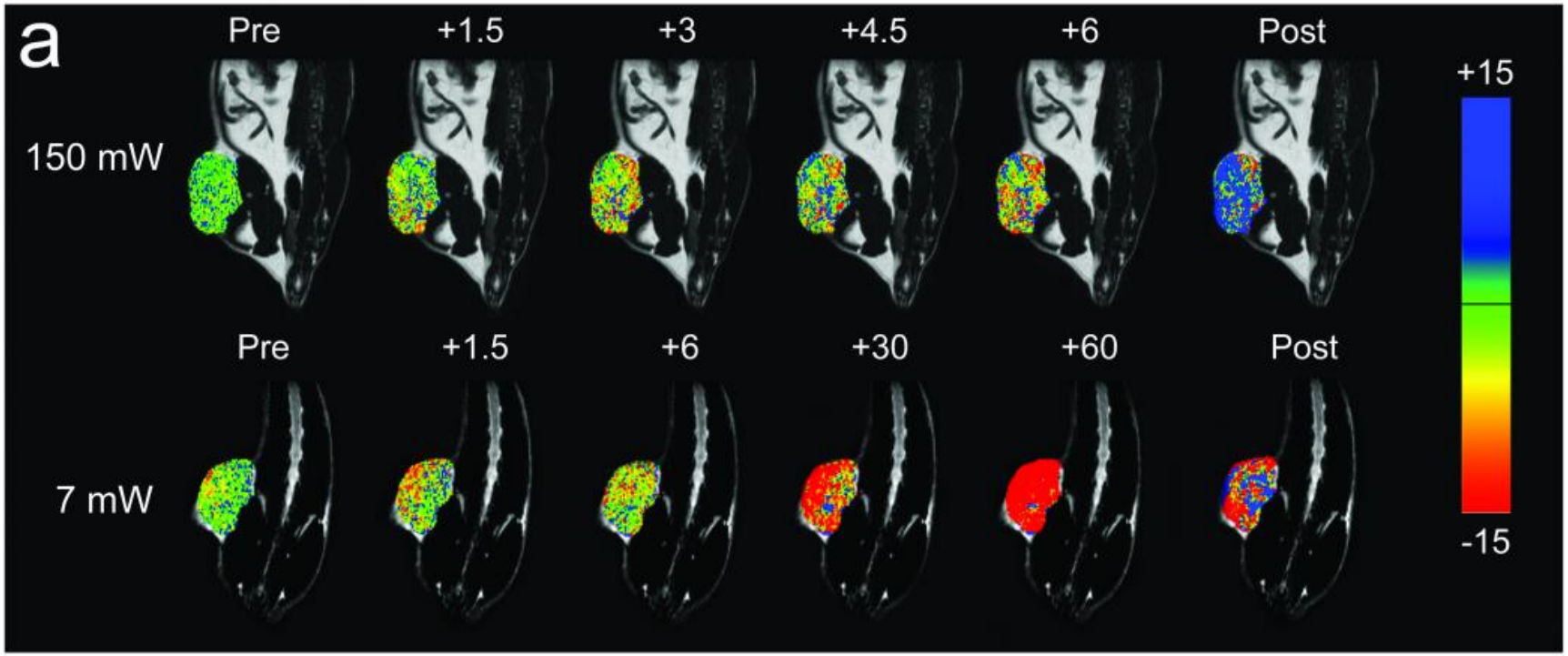
MRI of Vascular Response to PDT



Parametric maps and 3D MR angiography (MIP image)

Gil et al., Brit J Cancer 2010

MRI based real-time monitoring of PDT



Real-time monitoring of PDT efficacy using blood oxygenation level dependent MRI

Seshadri et al.,2008

MRI-guided Photodynamic Therapy

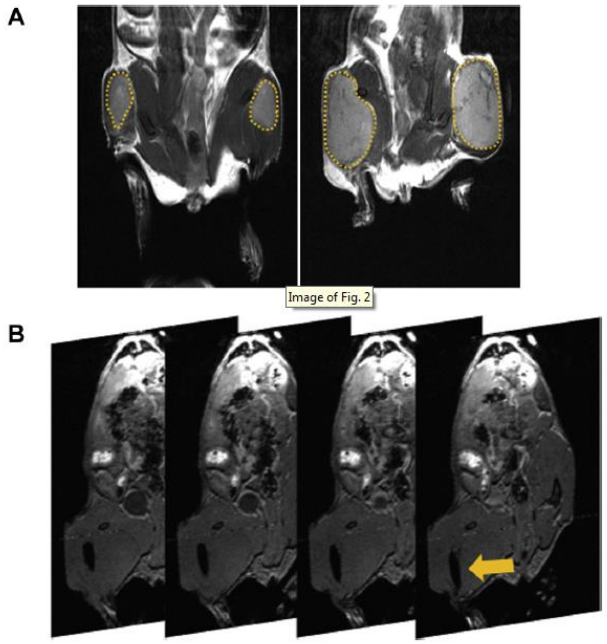
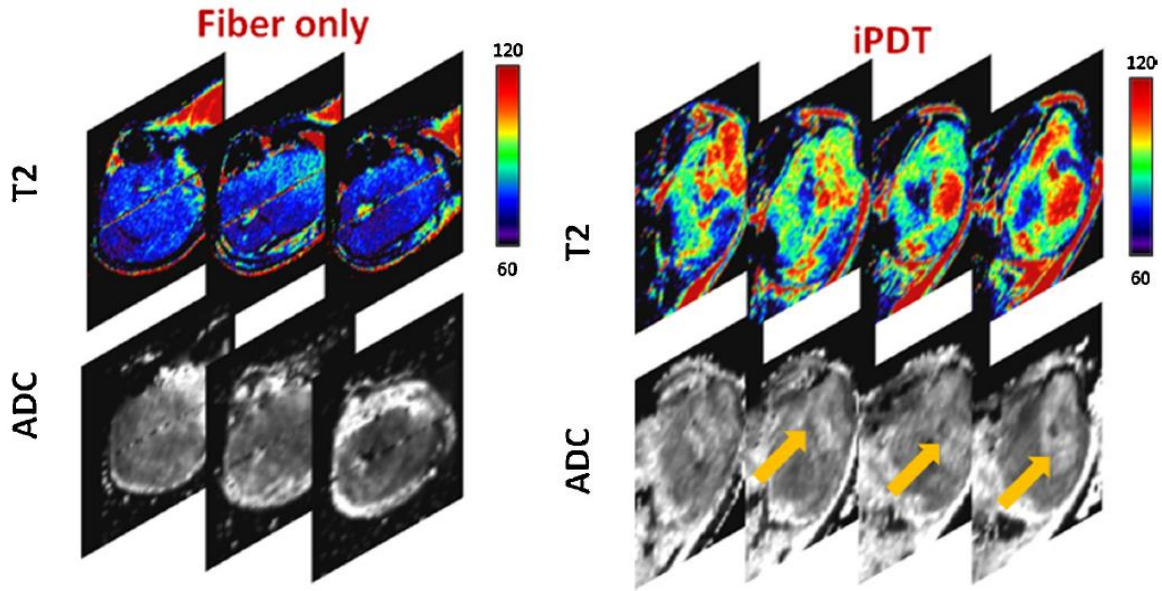


Fig. 2. Image-guided interstitial PDT of SCC tumors. (A) Coronal T2-weighted MRI was performed at different times (days 5–10) post implantation for serial monitoring of the growth of intramuscular SCCVII tumors (*dotted outline*). (B) Contiguous slices from a 3D spoiled-gradient echo scan of a mouse bearing intramuscular SCCVII tumor with the visible trace of the fiber placed in the tumor interstitium (*arrow*).

Original Research

Image-guided interstitial photodynamic therapy for squamous cell carcinomas: Preclinical investigation

Mirabelle Sajisevi[a], Nestor R. Rigual[a,b], David A. Bellnier[b], Mukund Seshadri[a,c,d,*]

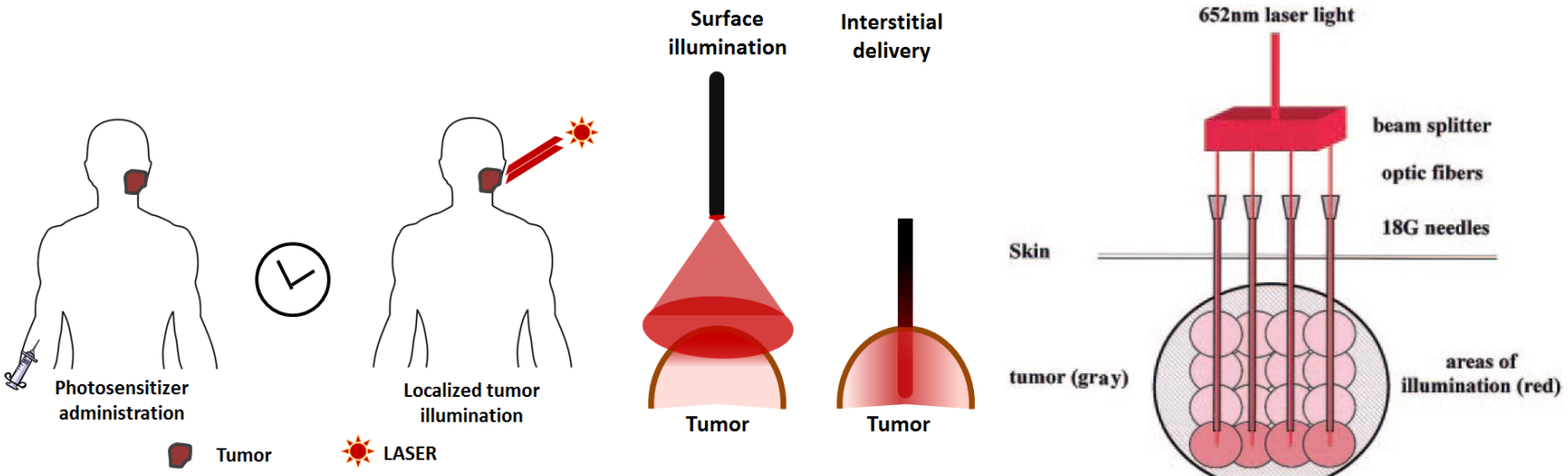


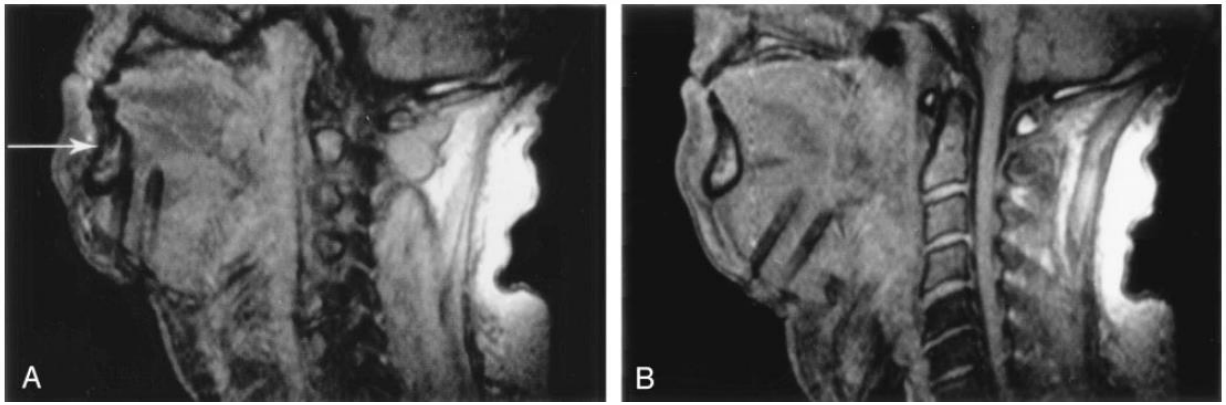
Utility of MRI as a non-invasive tool to guide fiber placement and map early tissue response to PDT.

Sajisevi et al., J Oral Max Surg Med Pathol 2015

MRI-guided Photodynamic Therapy

Image-guidance interstitial PDT

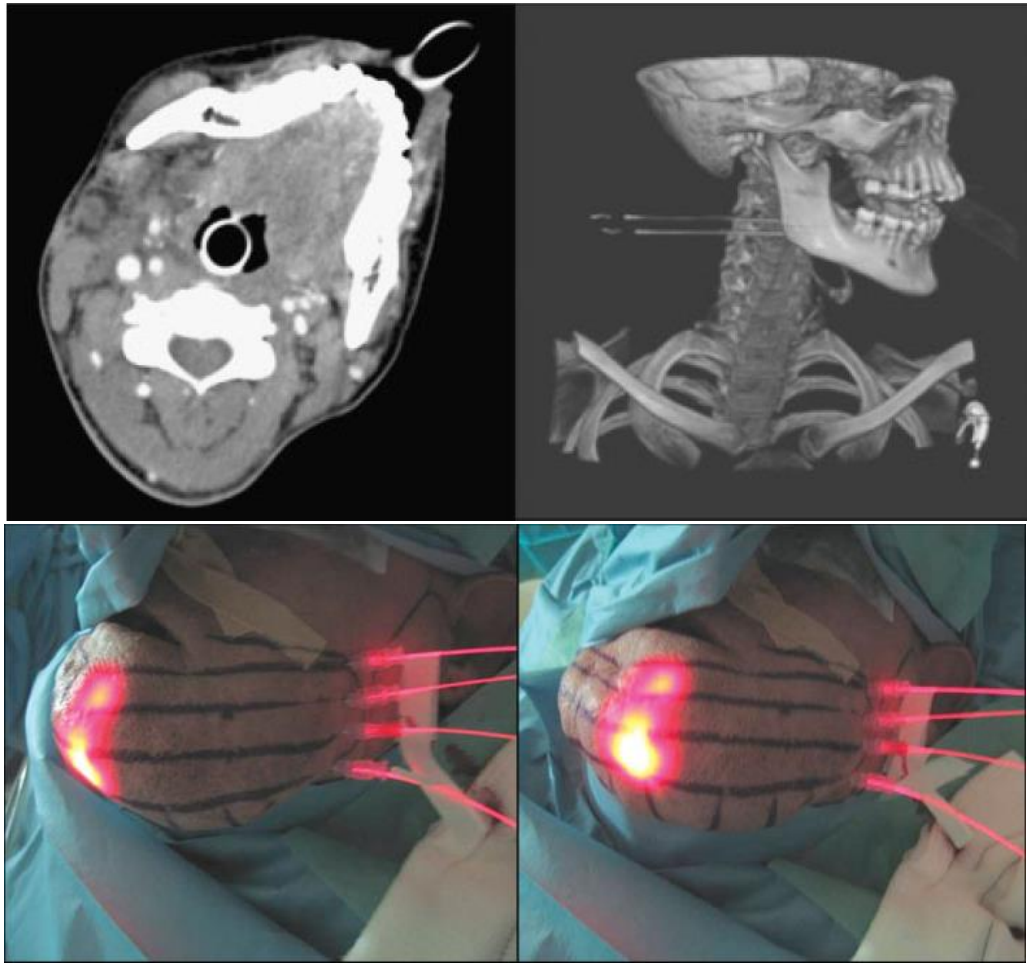




Sajisevi et al., 2015

Jerges et al.,2008

Imaging-guided interstitial PDT



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Imaging-guided interstitial PDT

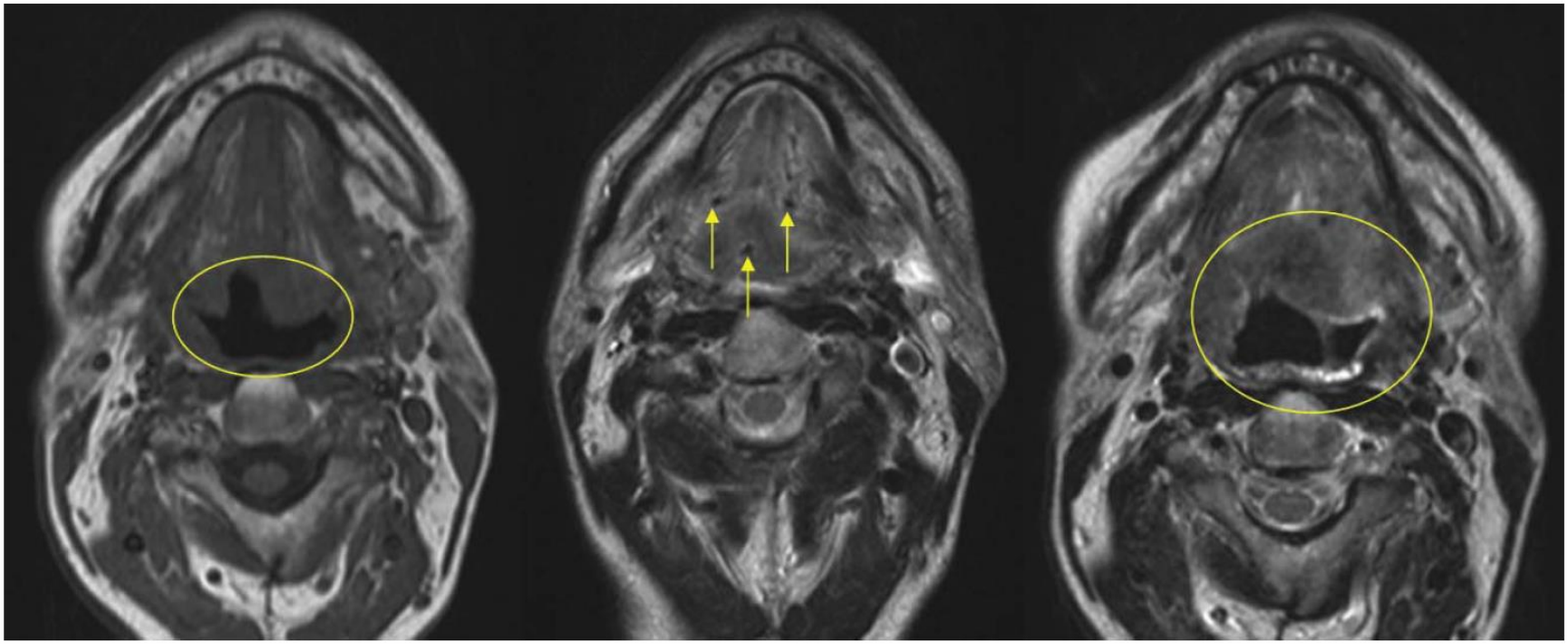


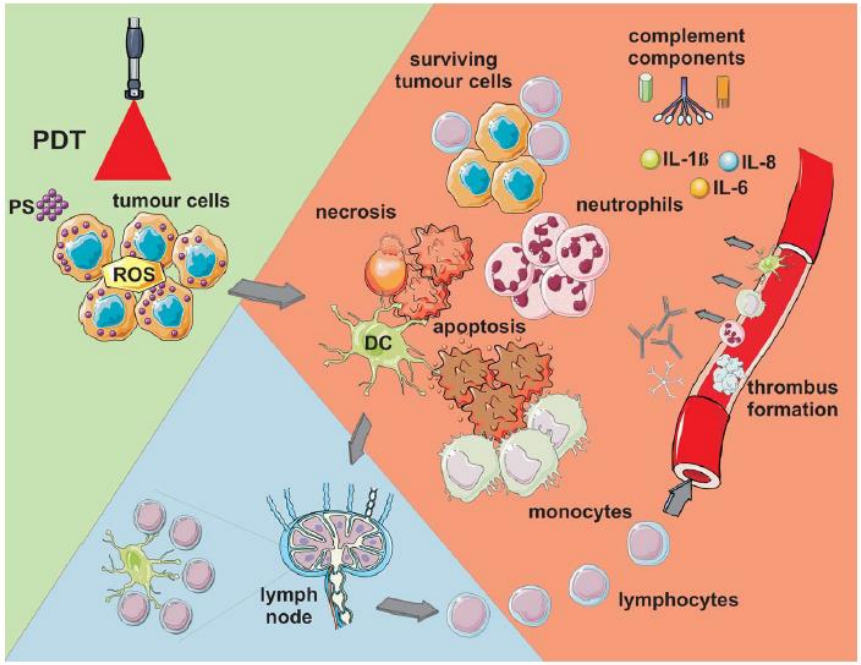
Figure 2: MRI Guided interstitial photodynamic therapy. Left image: preoperative MRI scan showing base of tongue tumour. Middle image: perioperative; arrows indicating needles placement for light delivery. Right image: postoperative scan revealing areas of necrosis and subsequent increase patency of airway.

Jerges et al.,2008

Next Generation Strategies for PDT

- Alternative light delivery methods
  - 2-photon PDT (short laser pulses using high peak power)
- Modified time intervals of treatment
  - Metronomic PDT (lower drug/light doses, longer periods)
- Modifications of PS agents to enhance drug internalization (photochemical internalization)
- Nanoformulations
  - Drug combinations, targeting, enhanced delivery, and imaging

Concluding remarks



Understand basic principles
Basic components:
Photo-physics/chemistry
Biological response
Clinical indications/applications

PDT is a multidisciplinary endeavor
(scientists, physicists, surgeons, radiologists, nurses)

Vogl et al, 2004