European Dermatology Forum

Guideline on Photodynamic Therapy

Developed by the Guideline Subcommittee of the
European Dermatology Forum

Subcommittee Members:
Prof. Dr. Nicole Basset-Seguin, Paris (France)
Prof. Dr. Lasse R. Braathen, Bern (Switzerland)
Prof. Dr. Piergiacomo Calzavara-Pinton,Brescia (Italy)
Prof. Dr. Yolanda Gilaberte, Huesca (Spain)
Prof. Dr. Gunter FL Hofbauer, Zurich (Switzerland)
Prof. Dr. Robert Hunger, Bern (Switzerland)
Prof. Dr. Sigrid Karrer, Regensburg (Germany)
Prof. Dr. Percy Lehmann, Wuppertal (Germany)
Dr. Colin A. Morton, Stirling (United Kingdom)
Prof. Dr. Stefano Piaserico, Padova (Italy)
Prof. Dr. Alexis Sidoroff, Innsbruck (Austria)
Prof. Dr. Rolf-Markus Szeimies, Recklinghausen (Germany)
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Prof. Dr. Torsten Zuberbier, Berlin (Germany)

Chairman of EDF Guideline Committee:
Dr. Alexander Nast, Berlin (Germany)
Assistant Professor

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EDF Guidelines Secretariat to Dr. Alexander Nast:
Bettina Schulze, Klinik für Dermatologie, Venerologie und Allergologie, Campus Charité Mitte,
Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
phone: ++49 30 450 518 062, fax: ++49 30 450 518 911, e-mail: bettina.schulze@charité.de

European Dermatology Forum

Guideline on Topical Photodynamic Therapy (PDT)

On behalf of the European Dermatology Forum

PDT Subgroup of the EDF guidelines committee:

Prof. Nicole Basset-Seguin, Paris (France)
Prof. Lasse R. Braathen, Bern (Switzerland)
Prof. Piergiacomo Calzavara-Pinton, Brescia (Italy)
Prof. Yolanda Gilaberte, Huesca (Spain)
Prof. Gunther FL Hofbauer, Zurich (Switzerland)
Prof. Robert Hunger, Bern (Switzerland)
Prof. Sigrid Karrer, Regensburg (Germany)
Prof. Percy Lehmann, Wuppertal (Germany)
Dr. Colin. A. Morton, Stirling (UK)
Prof. Stefano Piaserico, Padova (Italy)
Prof. Alexis Sidoroff, Innsbruck (Austria)
Prof. Rolf-Markus Szeimies, Recklinghausen (Germany)
Dr. Claas Ulrich, Berlin (Germany)
Prof. Ann-Marie Wennberg, Gothenburg (Sweden)

Conflicts of interest

		C A Morton	R-M Szeimies	A. Sidoroff	A-M Wennberg
1	Grant	no	E.C. grant	no	no
2	Consulting fee or honorarium	Galderma, Spirit Healthcare Leo Pharma, Abbvie, Almirall	Almirall, Biofrontera, Galderma, Leo Pharma, Roche	no	no
3	Support for travel to meetings for the study or other purposes	Leo Pharma	no	no	no
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3	Employment	no	no	no	no
4	Expert testimony	no	no	no	no
5	Grants/grants pending	no	no	no	no
6	Payment for lecture including service on speakers bureaus	no	Almirall	no	no
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		N Basset-Seguin	***P Calzavara-Pinton***	***Y Gilaberte***	***G Hofl***
1	Grant	no	no	no	none
2	Consulting fee or honorarium	Galderma	no	Galderma	Galder
3	Support for travel to meetings for the study or other purposes	Galderma	no	Galderma	Galder
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	no	no	none
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1	Board membership	Roche Meda, Leo	EADV AND SIDEMAST BOARD MEMBER	no	none
2	Consultancy	Roche Meda, Leo	Cantabria, Beiersdorf, Leo, Roche	no	Abbvie Novart Galder
3	Employment	no	no	no	none
4	Expert testimony	no	no	no	Spirig,
5	Grants/grants pending	no	Pfizer, Novartis	no	Spirig,
6	Payment for lecture including service on speakers bureaus	Roche, Leo	Beiersdorf, Pierre Fabre, Abbott	Galderma	Almira Galder Novart
7	Payment manuscript preparation	no	no	no	LEO
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10	Payment for development of educational presentations	no	no	no	Octaph
11	Stock/stock options	no	no	no	none
12	Travel/accommodation/meeting expenses unrelated to activities listed**	Roche, BMS, Galderma	Galderma, ISDIN	no	none
13	Other	no	no	no	Biofro Roche Clinuv investi

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Other relationships

1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	no	no	none

		R Hunger	***S Karrer***	***P Lehmann***	***S Pia***
1	Grant	no	no	no	no
2	Consulting fee or honorarium	no	S. Karrer has received honoraria for lectures for Galderma	Galderma	no
3	Support for travel to meetings for the study or other purposes	no	no	Galderma Janssen Cilag	no
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	no	no	no
5	Payment for writing or reviewing the manuscript	no	no	no	no
6	Provision of writing assistance, medicines, equipment, or administrative support	no	no	no	no
7	Other	n/a	n/a	no	n/a

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work

1	Board membership	no	no	Galderma	Gald Abb Nov
2	Consultancy	MSD, Leo Pharma	no	no	Abb Nov Gald Pfiz
3	Employment	no	no	no	no
4	Expert testimony	no	no	no	no
5	Grants/grants pending	no	no	no	no
6	Payment for lecture including service on speakers bureaus	Allmiral	no	no	no
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11	Stock/stock options	no	no	no	no
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Other relationships

1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	no	no	no

		Claas Ulrich	**LR Braathen**
1	Grant	Galderma, Spirig	no
2	Consulting fee or honorarium	Galderma, Almirall, Novartis	no
3	Support for travel to meetings for the study or other purposes	Spirig	Galderma
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1	Board membership	Galderma, Novartis	no
2	Consultancy	Galderma, Novartis	no
3	Employment	no	no
4	Expert testimony	no	no
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6	Payment for lecture including service on speakers bureaus	Galderma, Pfizer, Novartis, Almirall, Meda, Spirig	Galderma
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13	Other	no	no

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1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	no

C A Morton[1], R-M Szeimies[2], A. Sidoroff[3], A-M Wennberg[4], *N Basset-Seguin*[5], *P Calzavara-Pinton*[6], *Y Gilaberte*[7], *G Hofbauer*[8], *R E Hunger*[9], *S Karrer*[10], *P Lehmann*[11], *S Piaserico*[12], *Claas Ulrich*[13], LR Braathen[14]

1. Department of Dermatology, Stirling Community Hospital, Stirling, FK8 2AU, UK

2. Dept. of Dermatology & Allergology, Klinikum Vest GmbH, Knappschaftskrankenhaus Recklinghausen, Dorstener Strasse 151, D-45657 Recklinghausen, Germany

3. Department of Dermatology and Venereology, Medical University Innsbruck, Austria

4. Department of Dermatology, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden

5. Department of Dermatology, Hôpital Saint Louis, Paris, France

6. Department of Dermatology, Spedali Civili, Brescia, Italy

7. Department of Dermatology, Hospital San Jorge, Huesca, Spain

8. Department of Dermatology, Zurich University Hospital, Zürich, CH-8091, Switzerland

9. Department of Dermatology Bern, CH-3010 Bern, Switzerland

10. Department of Dermatology, University Hospital Regensburg,Regensburg, Germany

11. Department of Dermatology, HELIOS Klinikum Wuppertal, Germany

12. Unit of Dermatology, Department of Medicine, University of Padova, Italy

13. Skin Cancer Centre, Hautklinik der Charitie, Chariteplatz 1, 10117 Berlin, Germany

14. Dermatology, Bern

Correspondence: colin.morton@nhs.net

Disclaimer

These guidelines consider all current and emerging indications for the use of topical PDT in Dermatology. In addition to undertaking a systematic literature review, these guidelines include evidence reviewed in previous therapy specific PDT guidelines published in 2007[1], 2008[2] and 2013[3,4], as well as disease-specific EDF guidelines on actinic keratosis (2011[5]) and basal cell carcinoma (2012[6]). These S2 guidelines have been prepared by the PDT subgroup of the European Dermatology Forum (EDF)'s guidelines committee.

It presents consensual expert recommendations on the use of topical photodynamic therapy in dermatological indications, reflecting current published evidence.

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Keywords: 5-aminolaevulinic acid, dermatology, guidelines, methyl aminolaevulinate, non-melanoma skin cancer, topical photodynamic therapy.

1. Introduction

Photodynamic therapy (PDT) involves the activation of a photosensitizing drug by visible light to produce reactive oxygen species within target cells, resulting in their destruction.[7,8] In addition, various pro- and anti-inflammatory as well as immunomodulatory effects have been observed. In Dermatological indications, PDT is usually performed by topical application of precursors of the heme biosynthetic pathway, in particular 5-aminolaevulinic acid (5-ALA) or its ester, methyl aminolaevulinate (MAL), converted within target cells into photoactivatable porphyrins, especially protoporphyrin IX (PpIX). After an incubation period, light of an appropriate wavelength activates the photosensitizer promoting the photodynamic reaction. Before light illumination, it is possible to detect skin surface fluorescence, assisting detection and delineation of both visible and incipient lesions.

Three agents are currently licensed for use in Europe: Methyl aminolaevulinate (160mg/g) (MAL) Metvix®/Metvixia® (Galderma, Paris, France) is used along with red light to treat non-hyperkeratotic actinic keratosis (AK), squamous cell carcinoma *in-situ* (SCC *in-situ*/Bowen's disease), superficial and nodular basal cell carcinomas (sBCC, nBCC), although approvals vary between countries. A patch containing 5-ALA (Alacare® (Galderma-Spirig AG, Egerkingen, Switzerland)) is approved for the treatment of mild AK in a single treatment session in combination with red light without pretreatment of the lesion. Furthermore for AK, a nanoemulsion (Ameluz® (Biofrontera AG, Leverkusen, Germany)) is licensed for PDT in combination with red light for the treatment of mild and moderate AK. A 20% formulation of 5-ALA, Levulan (DUSA Pharmaceuticals, USA), is approved in N. America and certain other countries for AK, in a protocol that uses blue light. Many original studies of topical PDT used non-standardized preparations of ALA made in hospital pharmacies, so direct comparison of early studies may not be valid.

Topical PDT is approved for the treatment of certain non-melanoma skin cancers (NMSC) in the immunocompetent with superiority of cosmetic outcome over conventional therapies. Recurrence rates are typically equivalent to existing therapies, although inferior to surgery in nodular BCC. Topical PDT can be used both, as lesional or as area/field-therapy, and has the potential to delay/reduce the development of new AK, although direct evidence of prevention of invasive squamous cell carcinoma remains limited.

PDT has also been studied for its place in the treatment as well as potential to prevent, superficial skin cancers in immunosuppressed patients, although sustained clearance rates are lower than when used in immunocompetent individuals. Additional potential cancer indications for topical PDT include local patch/plaque cutanous T-cell lymphoma and extra-mammary Paget's Disease. In addition, PDT can improve acne and several other inflammatory/infective dermatoses, and improves several aspects of photoageing. PDT is further used in combination with other drugs intended for treatment in NMSC or together with chemical/physical treatments which enable a better drug penetration. Despite extensive experience beyond NMSC, there are currently no licensed approvals for its wider use, in part due to ongoing studies seeking optimized protocols, but also the substantial costs involved in widening the labeled indications for the photosensitizing agents.

Treatment is generally well tolerated but tingling discomfort or pain is common during PDT. New studies identify patients most likely to experience discomfort and permit earlier adoption of pain-minimization strategies. Alterations in the way PDT is delivered, including the use of daylight or shorter photosensitiser application times, are associated with decreased discomfort, whilst efficacy appears to be maintained at least in the treatment of actinic keratoses.

2. Method of action

2.1 Photosensitizers

ALA is hydrophilic whilst MAL is more lipophilic, and hence MAL may penetrate more deeply into lesions although studies that have compared these agents when used to treat AK, nodular BCC or acne, failed to show a difference in response.[9-11] A novel gel formulation of ALA with nanoemulsion, BF-200 ALA (Ameluz®), which improves ALA stability and skin penetration, was recently compared with MAL (and placebo) in treating AK with PDT in a multicentre randomized trial.[12] BF-200 ALA-PDT achieved significantly higher complete clearance of lesions (patients had 4-8 thin/moderate thickness AK face/scalp) of 78% vs. 64% 12 weeks after last treatment (see below).

A self-adhesive, skin-coloured thin 5-ALA patch (Alacare®), directly applied to AK without the need of lesion preparation, has been shown to be superior to cryotherapy in the treatment of mild and moderate thickness AK, providing a clean and uniform method of application of photosensitizer although possibly limited by licence restriction in use to a maximum of six 2cm^2 patches at one treatment to mild AK only.[13]

Enhancing penetration of a photosensitizer may increase the efficacy of PDT, but currently there is no licensed approval for a protocol that uses a penetration enhancer (e.g. dimethyl sulfoxide, azone, glycolic acid, oleic acid) or iontophoresis to increase the penetration of ALA. Elevating skin temperature during ALA application may also improve efficacy as PpIX production is a temperature-dependant process.[14]

In nodular BCC of up to 2mm thickness, a 3-hour application of 160mg/g MAL showed the highest selectivity for tumour, and this procedure is licensed in the form of two treatments one week apart for BCC.[15] It is also licensed as a double treatment for SCC *in-situ* (Bowen's disease), but in AK one initial treatment is recommended, with only non-responders receiving a second treatment at three months. In contrast to MAL, the drug-light interval used in ALA-PDT varies widely. The 20% ALA formulation used with the Blu-U™ system (blue fluorescent lamps) is licensed for a drug light interval of 18-24 hours but is widely used with application times of around 1 hour for AK**.**[16] A shorter incubation time of 1 hour with MAL for AK is also an option given that in a comparison of 1h vs. 3h, overall lesion response rates (after 1 or 2 PDT treatments) were 76% vs. 85% respectively.[17]

Additional topically applied photosensitizers have been assessed, but require further clinical study. A study compared topical indocyanine green with indole-3-acetic acid in the treatment of acne and found the agents equally effective.[18] Topical hypericin has been studied in AK, SCC *in-situ*, BCC, cutaneous T-cell lymphoma and psoriasis with relatively disappointing results, although protocols have yet to be optimized.[19,20] Similarly, topical silicon phthalocyanine PDT has been demonstrated to trigger apoptosis in a variety of cutaneous neoplasms.[21] The cationic photosensitizer PPA904 [3,7-bis(*N*,*N*-dibutylamino) phenothiazin-5-ium bromide] has been topically applied to chronic wounds and demonstrated significant reduction in bacterial load with a trend towards wound healing observed in a recent blinded, randomized, placebo-controlled, single-treatment, Phase IIa trial. [22]

2.2 Light sources and dosimetry

A range of light sources can be used for topical PDT including filtered xenon arc and metal halide lamps, fluorescent lamps and light emitting diodes (LED) and even lasers although coherent light is not required. Large fields can be treated using narrowband LED devices e.g. the Aktilite 128 (Galderma, Paris, France), BF-Rhodo LED (Biofrontera, Leverkusen, Germany) and Omnilux PDT (Phototherapeutics, London, UK) each with an output that matches the 630/635 nm activation peak of PpIX whilst excluding the extraneous wavelengths present in broadband sources e.g. PhotoDyn 750/505 (Hydrosun, Germany) and

Waldmann PDT 1200L (Waldmann, Germany), permitting shorter irradiation times. Filtered intense pulsed lights (IPLs) have been successfully used in PDT for AK, acne and photorejuvenation although they emit different spectra because of different filter technologies, resulting in a need to derive specific protocols to achieve identical radiant exposures.[23] There is evidence that narrow spectrum light sources are associated with relatively higher response rates when compared with broad-spectrum devices, with complete patient clearance rates of 85% and 68% for BF-200 ALA-PDT or MAL-PDT respectively, compared with 72% and 61% when broad spectrum devices were used.[12,24]

Protoporphyrin IX has its largest absorption peak in the blue region at 410nm with smaller absorption peaks at 505, 540, 580 as well as 630nm. Most light sources for PDT use the 630nm absorption peak in the red region, in order to improve tissue penetration, although, a blue fluorescent lamp (peak emission 417nm) is recommended in Levulan-PDT. Light dosimetry for approved skin cancer indications are summarized in Table 1. Dosimetry for emerging inflammatory/infective dermatoses is not yet standardized, but often uses less intense illuminations although multiple treatments are typically employed. Consideration of high dose and low dose regimens for PDT in acne have been reviewed although an optimal has not been established.[25]

Discontinuous illumination (fractionation) may improve the efficacy of PDT by permitting tissue re-oxygenation during 'dark' periods. Studies that seek to optimize the therapeutic advantage of split light doses, support superiority of the fractionation approach to conventional illuminations in ALA-PDT for superficial BCC, but not in SCC *in-situ*.[26,27] Overall clearance of 95% after 2 year follow-up has been reported in a large series of 552 lesions (AK, SCC *in-situ*,sBCC, nBCC) following ALA-PDT using two light fractions of 20 and 80 J/cm² at 4 and 6 hours separated by a 2 hour dark interval.[28] Another group has confirmed these high efficacy results for AK treated by ALA-PDT, showing superior clearance of fractionated lesions (using the same protocol) at 3 months of 96% compared with 89% for lesions treated to standard protocol (2 treatments 7 days apart) with 12 month clearance rates only slightly lower at 94% and 85% respectively.[29] An alternative ALA-PDT fractionation protocol of two doses of 75J/cm² at 4 and 5 hours was associated with an initial 94% clearance rate for nBCC, but with a cumulative failure rate of 30% by 3 years.[30]

To date, no significant improvement in efficacy has been demonstrated using light fractionation in MAL-PDT, considered to be due to differences in localization between the agents, with an altered response of endothelial cells to ALA and MAL-PDT noted in-vivo.[31]

Daylight can also be used as light source for PDT with application of MAL for 0.5 hour, followed by exposure to daylight for up to 2.5 hours.[32] Blue light accounts for a high proportion of the effective light, and is as effective as conventional red light MAL-PDT in treating AK with that additional benefit of only minimal therapy-related pain. No inferiority was observed by reducing the daylight exposure to 1.5 hours although response was greater for thin compared with moderate thickness AK.[33,34] Daylight-PDT has recently been assessed for treating basal cell carcinomas.[35]

There is also an option for patients to wear a portable LED device, permitting ambulatory PDT to reduce the need for hospital attendance**.**[36] Efficacy has been reported in three studies with the largest achieving 84% lesion clearance, predominantly sBCC and SCC *in-situ*, 1 year following 2 treatments, one week apart, with minimal pain.[36-8]

Dosimetry in PDT is defined by photosensitizer dose, drug-light interval, wavelength/band, irradiance (mW/cm^2) and fluence (J/cm^2) of light. Total effective fluence, taking into account incident spectral irradiance, optical transmission through tissue, and absorption by photosensitizer, has been proposed as a method for more accurate dosimetry, but in practice, light dosage can only be estimated from the energy fluence[39].

2.3 Lesion preparation

Protocols for topical PDT in Europe conventionally recommend some form of lesion preparation to enhance photosensitizing agent absorption and light penetration in MAL-PDT and nano-emulsion ALA-PDT. Studies using a novel ALA plaster for mild and moderate thickness AK did not require prior preparation with results consistent with standard protocols.[13,14] However, gentle removal of overlying crust and scale is commonly performed for moderate thickness/hyperkeratotic AK, as well as in SCC *in-situ* and superficial BCC when using currently approved MAL-PDT. Occlusion of lesions with a keratolytic the night before treatment can facilitate easier crust removal. Tape-stripping, microdermabrasion or laser ablation, or gentle curettage can also be used to reduce hyperkeratosis. Some practitioners have observed reduced efficacy if lesions are not debrided prior to PDT[14,17] while others have not noted increased drug uptake following lesion preparation of SCC *in-situ* and BCC (in a study of 4 and 6 hour ALA application possibly indicating reduced need with longer application times).[41]

Lesion preparation is probably more important when treating nodular BCC by PDT with recommended practice to gently remove overlying crust with a curette/scalpel in a manner insufficient to cause pain, and thus not requiring local anaesthesia. Some practitioners

perform a more formal lesion debulking days/weeks prior to PDT, with 92% of BCC clearing following a single session of ALA-PDT in one study.[42] In a small comparison study of PDT (ALA and MAL) with or without debulking immediately pre-photosensitizer application, residual nodular BCC was more often observed in BCCs that were not debulked.[10]

Additional techniques of skin preparation have been reported including microneedling, skin vapourization with CO_2 laser, or ablative fractional resurfacing prior to PDT.[43-6]

Practitioners typically cover treatment sites with light occlusive dressings, on the presumption that full exposure to ambient light during the incubation period will lead to increased activation of PpIX superficially reducing the opportunity for deeper photosensitizer penetration before photoactivation. PDT with occlusion is standard practice in MAL-PDT of AK, SCC *in-situ* and BCC, but is not performed when using Levulan PDT for facial AK. The most recent studies of daylight PDT also do not require initial occlusion.[34]

3. Treatment protocols

3.1 Standard topical PDT

Recommended protocols for ALA-PDT and MAL-PDT using currently licensed photosensitizing agents for non-melanoma skin cancer indications are summarized in Table 1. Protocols employed in emerging indications are discussed with each indication.

3.2 Daylight PDT

Daylight PDT, although to date without current licensed approval, is performed with initial widespread application of an organic sunscreen (with an absorption spectrum that doesn't significantly overlap that of PPIX) followed approximately 15 minutes later by lesion preparation, then MAL to treatment area, without occlusion. After 30 minutes application, patients are exposed to daylight for 1.5-2.0 hours when treating AK, the most widely studied indication using this technique.[34,47]

3.3 Ambulatory PDT

The treatment protocol for ambulatory PDT, using an approved inorganic light-emitting diode device, involves gentle scraping of lesion followed by application of a thin even layer of photosensitizing drug (ALA or MAL) to include a 5mm rim of surrounding normal skin and secured by a translucent dressing.[38] The light emitting 'plaster' is then applied the lesion and the patient can return home or to work. The device automatically switches on after the incubation period (3-4 hours depending on photosensitizing agent) to

deliver a total dose of 75J/cm^2 at 7mW/cm^2. Another approach is the integration of an optical fiber in a flexible textile structure which allows uniform light distribution even of curved surfaces. The textile structure is coupled to a portable laser light source adjustable to the appropriate wavelengths.[48] Current trials are studying the feasibility in PDT of actinic keratosis.

4. Fluorescent diagnosis

The detection of skin surface fluorescence has been examined as a non-invasive method for detection of tumour boundaries. Given that fluorescence can be demonstrated following application of ALA and MAL, just prior to therapeutic illumination of lesions, it may assist in lesion definition as well as in identifying persistent/recurrent disease that may not be clinically obvious.[49] Compared with relatively subjective assessment of fluorescence using the Wood's lamp, a CCD camera system can provide semi-quantitative measurements of PpIX within dermatological lesions**.** PpIX fluorescence imaging to determine tumour boundaries during Mohs micrographic surgery has been assessed with inconsistent results regarding improvement in surgical efficacy.[50] Fluorescence diagnosis has not been shown to be substantially superior to simple clinical assessment of tumour margins.[51]

Measurement of fluorescence during MAL-PDT has shown extent of photobleaching, but not total initial protoporphyrin IX fluorescence, to be predictive of lesion clearance.[52] In another study, fluorescence diagnosis in keratinocyte intraepidermal neoplasias was unable to discriminate between lesions or proliferative activity, although hyperkeratosis was an important determinant of macroscopic fluorescence intensity.[53] Intensity of pain has been associated with fluorescence intensity and can offer guidance to PDT practitioners, helping anticipate patients more likely to require active pain management.[54]

5. Current indications

5.1 Actinic keratoses (*Strength of Recommendation A, Quality of Evidence 1*)

Topical PDT has been widely studied for thin and moderate thickness AK on the face and scalp with clearance rates of licensed products of 81-92% three months after treatment to current protocols.[12,13,24,55-57] One year lesion clearance rates of 78% and 63-79% have been reported following ALA-PDT (up to 2 treatments) and patch ALA-PDT (single treatment) respectively.[40,58]

No advantage was observed in performing an initial double treatment of MAL-PDT, 7 days apart, for thin AK compared with a single treatment with clearance of 89% and 93%

respectively.[56] A single treatment cleared fewer moderate thickness AK, 70% compared with 84% if an initial double treatment was used, but response rate improved after a repeat treatment at 3 months to 88%. A randomized intra-individual study of 1501 face/scalp AK in 119 patients used this protocol to compare MAL-PDT with cryotherapy.[57] After the initial cycle of treatments, PDT resulted in a significantly higher cure rate than cryotherapy (87% vs. 76%), but with equivalent outcome after non-responders were retreated (89% vs. 86%).

ALA-PDT using a 20% formulation and blue light, cleared 75% or more of all lesions (4-7 face/scalp AK/patient) in 77% patients in pivotal randomized placebo-controlled trials using the 14-18 hour ALA application interval.[55] Following a second treatment, where required, clearance rate increased to 89% at week 12.

ALA-PDT using the BF-200 nano-emulsion was superior to MAL in clearing thin and moderate thickness AK from face/scalp in patients with multiple AK, with clearance of 90% vs. 83% of lesions (respective complete clearance rates of 78% vs. 64%) 12 weeks after one or two PDT treatments.[12] Another randomized study observed overall clearance of 81% of lesions following BF-200 ALA PDT compared with a 22% placebo response. Significantly superior patient and lesion clearance rates were noted in this study in the subset of patients treated using a narrowband red LED source (96% and 99% respectively) compared with broadband light.[24] In a recent follow-up to these two studies, similar recurrence rates were observed following BF 200 ALA-PDT and MAL-PDT with lesion recurrence rates of 22% and 25% respectively at 12 months, with 47% of ALA-PDT and 36% of MAL-PDT patients remaining completely clear.[59] The subgroup that was illuminated with narrow wavelength LED lamps reached sustained clearance rates of 53-69% for BF-200 ALA studies, with 41% remaining clear after MAL-PDT using narrowband light.

ALA-PDT using the self-adhesive patch cleared 82%-89% of mild or moderate AK in patients with 3-8 face/scalp lesions, superior to the 77% clearance rate in a comparator group receiving cryotherapy.[13] Twelve months after the single treatment, patch ALA-PDT remained superior in efficacy to cryotherapy.[40]

MAL-PDT using daylight is as effective, but less painful, than conventional PDT with a randomized intra-individual trial of patients with multiple AK on face/scalp demonstrating a reduction, after a single treatment, of 79% on the daylight side compared with 71% when standard LED illumination was used.[32] Subsequent multicentre studies have demonstrated that daylight exposure of 1.5 hours is as effective as the 2.5 hours, but that lesion response is highest for thin lesions (76%) compared with clearance rates of 61% and 49% for moderate and thick AK respectively.[33,34] A study assessing the impact of latitude on delivery of daylight

PDT identified that daylight PDT can be performed throughout summer and until mid-September in Reykjavik and Oslo, late October in Copenhagen and Regensburg, mid-November in Turin, and all year in Israel.[60] During these months it should be possible to achieve protoporphyrin IX weighted daylight doses above 8J/cm^2, and a maximum daytime temperature of 10°C, to permit effective treatment.

Topical PDT is less effective for AK on acral sites, probably in part due to a higher proportion of thicker lesions on these sites. A study comparing MAL-PDT with cryotherapy for AK on the extremities demonstrated inferior efficacy with PDT, with clearance of 78% of lesions at 6 months compared with 88% for cryotherapy.[61] However, in a right/left comparison study with imiquimod, ALA-PDT cleared significantly more moderate thickness AK lesions (58% vs. 37%), and equivalent numbers of thin AK on the hands/forearms (72% lesions).[62]

Actinic cheilitis has also been successfully treated by PDT, although the literature remains limited to case reports and series. A large series of 40 patients saw complete clinical response at 3 months in 26 following ALA-PDT (2 treatments 2 weeks apart) although with histological evidence of recurrence in 9 patients (35%) over 18 months of follow-up.[63] Two sessions of MAL-PDT one week apart achieved complete clinical cure in 47% of 15 patients and partial response in a further 47% although histological clearance was evident in only 4 of the 7 patients who appeared clinically clear.[64] In a recent retrospective analysis of real-life practice of off-label PDT across 20 Italian Dermatology departments, actinic cheilitis was one of the most successful indications, clearing 27 of 43 (63%) patients with complete response maintained at follow-up at 4.2 +/-5.9 months.[65] Sequential MAL-PDT then imiquimod 5% cream achieved complete clinical cure of 80% and histological cure of 73% in a study of 30 patients, suggesting improved outcome using combination treatment.[66]

Therapy guidelines identify PDT as effective both as a lesion and field-directed treatment and suggest PDT has a role where AK are multiple/clustered, at sites of poor healing, or where there has been a poor response to other topical therapies.[67,68] PDT remains a predominantly hospital-based therapy in most countries whilst many patients with AK are treated by primary care physicians. The high quality of cosmesis consistently observed in PDT studies for NMSC indications including AK, combined with increasing emphasis on patient choice over therapy, may see increased demand for topical PDT. In a randomized comparison of patient tolerance to MAL-PDT and topical imiquimod for multiple face/scalp AK, a high level of satisfaction was observed with both therapies, with PDT slightly superior.[69]

5.2 Squamous cell carcinoma *in-situ* (Bowen's disease)/Invasive SCC

Squamous cell carcinoma in-situ (*Strength of Recommendation A, Quality of Evidence 1*)
Invasive SCC (*Strength of Recommendation D, Quality of Evidence 11-iii*)

Lesion clearance rates of 88-100% are reported for SCC *in-situ* 3 months after one or two cycles of MAL-PDT, with 68-89% of treated lesions remaining clear over follow-up periods of 17-50 months.[70-74]

MAL-PDT using a broadband red light was compared with clinician's choice of cryotherapy or topical 5-fluorouracil (5-FU) in a large European study with 225 patients with 275 SCC *in situ*.[70] The lesion complete response rates 3 months after the last treatment (1-2 treatment cycles) were similar with all regimens (93% for MAL-PDT, 86% for cryotherapy, 83% for 5-FU) but PDT gave superior cosmetic results. Initial clearance rate following PDT increased from 73% after first cycle of treatment to 93% after the second cycle to non-responders. Although 1-year sustained lesion clearance rates showed MAL-PDT to be superior to cryotherapy; rates for the three therapies were similar after 2 years with 68% of lesions cleared following PDT, 60% after cryotherapy and 59% after 5-FU.[71] A similar 3-month efficacy rate of 88% was observed in an open study of MAL-PDT (only one cycle of two treatments, 7 days apart), for 41 SCC *in situ*, using the narrowband red LED sources now in routine use, with sustained clearance at 24 months of 71%[72] Further open studies of 51 and 43 lesions treated by the same MAL-PDT protocol (only one cycle of two treatments) observed 76% and 89% sustained clearance after a mean follow-up period of 17 and 50 months, respectively.[73,74]

MAL-PDT has been shown to be effective in treating lesions over 3cm in diameter, with 22/23 lesions showing complete clinical response 3 months after one treatment cycle of two sessions 7 days apart, with only 3 lesions recurring over a 1year follow-up.[75] An open study using ALA-PDT specifically for large diameter and multiple SCC *in situ* lesions showed that 88% (35/40) of large SCC *in situ*, all with a diameter greater than 2 cm, cleared following one to three treatments, although four patches recurred within 1 year.[76] In 10 further patients with multiple (three or more) SCC *in situ*, 98% (44/45) of patches cleared, although four lesions recurred over 1 year.

ALA-PDT has been widely studied in SCC *in-situ*, although not a licensed indication. Recently, 90% of 19 lesions initially cleared an open study in patients unsuitable or unwilling to have surgery, with 77% still clear at 2 years, but only 53% at 5 years following only one session of ALA-PDT with a non-formulary ALA and with two penetration enhancers added.[77]

ALA-PDT has been compared with cryotherapy and with 5-FU.[78,79] PDT proved superior in efficacy and adverse events in comparison with 5-FU, as well as being less painful compared with cryotherapy. No significant benefit from light fractionation was observed in a pilot comparison study of single illumination of ALA-PDT at 4 hours versus split illumination at 4 and 6 hours, clearing 80% and 88% of lesions, respectively.[27] In another study of fractionated ALA-PDT by this group, a sustained clearance rate of 84% at 2 years was observed.[28]

Body site does not appear to impact efficacy of PDT with protoporphyrin IX accumulation identical in SCC *in situ* located on acral and non-acral sites.[80] Topical PDT has been reported to clear digital, subungual and nipple Bowen's disease and where it arises in a setting of poor healing (lower leg, epidermolysis bullosa and radiation dermatitis).[81-87] PDT may offer an alternative for treating penile intraepithelial neoplasia, with one large series, using ALA- and MAL-PDT in 10 patients noted clearance in 7, but later recurrence in 4.[88]

Ambulatory PDT has been particularly studied for small plaques of SCC in-situ and superficial basal cell carcinomas.[37] An overall 84% response rate at 1 year was observed in a recent study using ambulatory PDT in NMSC lesions including 10 SCC *in-situ*.[38] Red narrowband LED light is used most often, for PDT treatment of SCC *in-situ*, however, a square wave intense pulsed light, with reduced dose variability, cleared all nine lesions in one case series with all remaining clear after a follow-up period of 4 months.[89]

Although one patient with clinically diagnosed SCC *in-situ* treated with PDT was diagnosed with melanoma at the same site a few months following treatment, it is uncertain if the treatment contributed, given the lack of initial histology.[90]

Therapy guidelines recommend PDT as the treatment of choice for both large and small plaques of SCC *in-situ* on poor healing sites, representing the majority of lesions, and a good choice for large lesions in good healing sites.[91] In a patient-reported outcome study, satisfaction with ALA-PDT for *SCC in situ* was high, with 90% of respondents indicating a very favourable impression of the treatment, although with burning sensation described in 21%.[92]

There is reduced efficacy of PDT for micro-invasive and nodular invasive SCC where 24 month clearance rates of 57% and 26% have been reported. The degree of cellular atypia is a negative prognostic factor, suggesting poorly differentiated keratinocytes are less sensitive to PDT. In view of its metastatic potential and reduced efficacy rates, PDT currently cannot be recommended for invasive SCC.[72]

5.3 Basal cell carcinoma

Superficial Basal cell carcinoma (*Strength of Recommendation A, Quality of Evidence 1*)
Nodular Basal cell carcinoma (*Strength of Recommendation A, Quality of Evidence 1*)

MAL is currently the only photosensitizing agent approved for the treatment of superficial and/or nodular BCC, indicated where patient is unsuitable for other available therapies due to possible treatment related morbidity and poor cosmetic outcome; such as lesions on the mid-face or ears, on severely sun damaged skin, large lesions, or recurrent lesions.

Initial clearance rates of 92-97% for primary superficial BCC were achieved with protocols of either 1 single initial treatment or 2 treatments 7 days apart, followed by a repeat two-treatment cycle at 3 months, if required.[93,94] Recurrence rates of 9% at 1 year were noted in both studies, with 22% of initially responding lesions recurring over 5 years of follow-up (no new recurrences beyond 36 months). 91% of primary nodular BCC were clinically clear 3 months following MAL-PDT, with a sustained lesion clearance response rate of 76% after 5 years of follow-up, also with no new recurrences beyond 36 months.[15,95]

Histologically confirmed response rates were observed in a further two randomized studies of MAL-PDT for nodular BCC, using the standard protocol. Treatment site excisions (at 6 months for responders, 3 months for non-responders) revealed clearance in 73%, most effective for facial lesions where 89% achieved complete histological response.[96] A poorer response was reported in a large series of 194 BCC, with an 82% clearance rate for sBCC, but only 33% of nodular lesions clearing following MAL-PDT by standard protocol**.** The authors describe no debulking of the tumour prior to PDT.[97]

PDT for BCC is conventionally delivered using LED light sources, but two recent studies report the use of daylight (for 2.5 hours) or an ambulatory in-organic LED source for illumination with the advantage of virtually pain-free treatments. In the pilot study of daylight MAL-PDT, 90% of 30 lesions were clear 3 months after a single cycle of two treatments one week apart, although 6 recurrences during follow-up left a 12 month clearance rate of 74%[35] In the largest trial to date of ambulatory PDT in NMSC, including 14 superficial BCC with 1year follow-up, an 84% clinical clearance rate was observed (included SCC in-situ).[38]

MAL-PDT was equivalent to surgery (92% vs. 99% initial clearance, 9% and 0% recurrences at 1 year) for superficial BCC but inferior to excision for nodular BCC when recurrence rates are compared (91% vs. 98% initial clearance, 14% and 4% recurrences at 5 years).[94,95] Cosmetic outcome is superior following PDT compared with surgery.

Clearance rates were equivalent when MAL-PDT was compared with cryotherapy for the treatment of superficial BCC, 97% and 95% at 3 months respectively, with overall

clearance after 5 years identical at 76% of lesions initially treated, but with superior cosmesis following PDT.[94] A single-blind randomized non-inferiority comparison of MAL-PDT (2 treatments one week apart) with imiquimod cream (daily five times weekly for 6 weeks) or topical 5-fluorouracil (twice daily for 4 weeks) for superficial BCC achieved tumour-free rates at 12 months of 73%, 83%, and 80% respectively, indicating that using these protocols, 5-fluorouracil is non-inferior and imiquimod superior to one cycle of MAL-PDT.[98]

ALA has also been widely used in treating BCC, with a weighted initial clearance rate of 87% noted for superficial BCC treated by ALA-PDT in a review of 12 studies, compared with 53% for nodular lesions.[99] When ALA-PDT was compared with cryotherapy for both superficial and nodular BCC, there was no significant difference in efficacy (histo-pathologically verified recurrence rates at 12 months: PDT 25%, cryotherapy 15%) although healing times were shorter and cosmesis superior with PDT.[100]

In a randomized comparison trial of single versus fractionated ALA-PDT (i.e. application of a first dose of light after 4 hour, followed by a 2 hour rest and a consecutive illumination in order to facilitate resynthesis of PPIX for a more efficient cell killing) for superficial BCC, 5 years after treatment, fractionated PDT produced a superior response (88% vs. 75% respectively).[26] Fractionated ALA-PDT was equivalent to surgery in initially clearing lesions but with a 31% failure rate over a median of 5 years after PDT, compared with only 2% following surgery when a 75J/75J protocol was used although 80% of lesions remained clear at 2 years using the 20J/80J fractionated dosing described above.[28,101] Success of treatment depended on tumour thickness, with probability of recurrence-free survival over 5 years 94% if tumour less than or equal to 0.7mm, compared with 65% for thicker lesions. In a randomized pilot study of PDT with minimal curettage pre-ALA application versus conventional surgery, there was also no evidence of superiority of PDT to surgery.[102]

Responsiveness of BCC is influenced by lesion thickness, with reduced efficacy with increasing tumour thickness in a study using ALA-PDT.[103] Lesions in the H-zone also have reduced sustained clearance rates.[104]

A six-year clinical and histological follow-up of 53 BCCs, originally less than 3.5mm thick, and treated by one or two sessions of ALA-PDT using the penetration enhancer dimethylsulfoxide and with prior lesion curettage, reported 81% of treated sites remained disease free at 72 months.[105]

Patients with naevoid basal cell carcinoma syndrome (NBCCS) can benefit from PDT with several series and cases reported. A large cohort of 33 patients were treated by topical or systemic PDT depending on whether lesions were less than/greater than 2mm in thickness

when assessed by ultrasound, with an overall local control rate at 12 months of 56.3%.[106] A recent short report observed that MAL-PDT for NBCCS improves patient satisfaction and reduces the need for surgical procedures.[107]

Topical PDT is recommended as a good treatment for primary superficial BCC, and fair treatment for primary low-risk nodular BCC, proposed as the treatment of choice for large low risk primary superficial BCC. PDT is also a good choice against alternative therapies for small primary and recurrent small and large superficial BCC, but is a relatively poor choice for high risk lesions including morphoeic BCC.[108] Given recurrence rates that are higher than surgery, PDT is best considered for thin nodular lesions where surgical excision is relatively contraindicated, or where patient preference, reflecting past therapy history, co-morbidities and/or cosmetic considerations result in a willingness to accept higher risk of recurrence.

6. Emerging indications

6.1 Treatment of non-melanoma skin cancer in organ transplant recipients

(*Strength of Recommendation B, Quality of Evidence I*)

Organ transplant recipients (OTR) have an increased incidence of SCC of 50- to 100-fold compared to the general population, with surgery for full excision recommended.[109,110] Photodynamic therapy, along with other non-surgical techniques, are suggested for treating AK or SCC *in-situ in* OTR, with PDT permitting physician-directed treatment of multiple lesions and field therapy.[110]

A prospective study compared the efficacy of PDT for AK and SCC *in-situ* in immunocompetent patients (IC) with OTR for one or two 5-ALA PDT treatments.[111] At four weeks, complete remission was indistinguishable in both groups (IC 94% vs. OTR 88%), but differed at 12 weeks (IC 89% vs. OTR 68%) and 48 weeks (IC 72% vs. OTR 48%).[111] Higher complete remission was observed when two session of MAL-PDT were performed: At three months complete remission varied between 71% and 90%.[112,113] Reduced efficacy of PDT in OTR may result from the large number of intraepithelial lesions, more prominent hyperkeratosis, and an altered, secondary local immune response. Location of lesions also appears important for the outcome: Response for AK to PDT on the hands ranged between 22 and 40%.[112,113] Only one study has compared MAL PDT to another topical modality: complete remission differed at one month with 89% for MAL-PDT and 11% for topical 5-fluorouracil, with more pain, but also better cosmesis following MAL-PDT.[114]

6.2 Prevention of non-melanoma skin cancer in organ transplant recipients (*Strength of Recommendation B, Quality of Evidence I*)

The increase in incidence of OTR to SCC has been attributed to impairment of the cutaneous immunosurveillance due to systemic immunosuppressive medication with cyclosporine and azathioprine known also to induce specific effects enhancing the potential for de-novo formation of NMSC.[115-8]

Only one clinical trial has examined the impact of regularly applied photoprotection on the incidence of NMSC in OTR. In spite of equal numbers of AK at baseline, a marked difference in favour of the intent-to-treat sunscreen group was recorded after 24 months and the lesion count was significantly lower as compared to the initial visit.[119]

There is emerging literature on the potential for topical PDT to delay/prevent certain NMSC lesions, although the strength of evidence for specific prevention of SCC remains weak. MAL-PDT (one treatment) significantly delayed the development of new lesions in an intra-patient randomised study of 27 OTR with AK (9.6 vs. 6.8 months for control site).[120] By 12 months, 62% of treated areas were free from new lesions compared to 35% in control areas. In a multicentre intra-patient study of multiple treatments of MAL-PDT compared with no treatment in 81 OTR, there was an initial significant reduction in new lesions (65 vs. 103 in the control area), mainly AK, but this effect was lost by 27 months.[121] Following two treatments, 1 week apart, PDT was repeated at 3, 9 and 15 months suggesting further treatments are required to maintain a protective effect. No significant difference in the occurrence of SCC was observed in a study of blue light ALA-PDT versus no treatment after 2 years follow-up in 40 OTR.[122] However, another study of blue-light ALA-PDT, repeated at 4-8 week intervals for 2 years, observed a reduction in the incidence of SCC in 12 OTRs, compared with the number developing in the year prior to treatment, with a mean reduction at 12 and 24 months of 79% and 95%.[123]

6.3 Field cancerization (*Strength of Recommendation B, Quality of Evidence I*)

The concept of field cancerization was introduced by Slaughter in 1953.[124] In the skin, it suggests that the clinically normal appearing skin around AKs and SCCs have subclinical features of genetically damaged cells which can potentially develop into a neoplastic lesion. In general oncology it is defined as the pathological and genetic changes found in the tissue peripheral to a tumour, resulting from ‘preconditioning’ of the affected organ by various carcinogenic agents.[125]

The major carcinogen for skin cancer is UV radiation. One of the most common genetic abnormalities in NMSC is the presence of UV induced Tp53 mutations.[126] It has been shown that these Tp53 mutations are found very early as P53 mutated clones can be found in > 70% of patients over 50 years of age in sun exposed skin.[127] In animal models, these Tp53 mutated clones precede papilloma and squamous cell carcinoma formation and represent an early stage of skin carcinogenesis.[128] The presence of Tp53 mutations define at the molecular level the concept of UV induced field cancerization in the skin.[129]

Field cancerization can be suspected when multiple AK are present and is also illustrated in case of development of simultaneous multifocal epidermoid carcinomas on the scalp. The subclinical changes of field cancerization can be evaluated by reflectance confocal microscopy by showing some epidermal and dermal morphological changes including disruptive changes within individual corneocytes and parakeratosis; cellular and nuclear atypia, pleiomorphism, loss of the honeycomb pattern and architectural disarray.[130]

The disappearance of Tp53 mutated cells and cellular atypia in field cancerization area following PDT has been shown and emphasizes the interest of adapting the therapeutic strategy to target not only AK lesions but also the surrounding field.[131] Field therapies, such as PDT, imiquimod, 5-fluorouracil and ingenol mebutate are most appropriate for treating field cancerization. Organ transplant patients have multiple clones of Tp53 mutated cells on sun exposed skin[132] A recent expert consensus has noted that PDT might prevent new AKs and the transformation of AK to invasive SCC and has proposed to evaluate the interest of repeated cyclic PDT treatment in that population.[133]

The preventive potential of field PDT in immunocompetent individuals was studied in photodamaged patients with facial AK, where ALA-PDT demonstrated a significant delay over control sites of about 6 months until new AK developed.[134]

6.4. .*Cutaneous T-cell Lymphoma (CTCL)* (*Strength of Recommendation C, Quality of Evidence IIiii*)

The sensitization of skin-infiltrating malignant lymphocytes induces a selective fluorescence of plaques of mycosis fungoides/CTCL that is five times more intense than in normal skin.[135] Clinical evidence of PDT for CTCL is derived from case reports and series. The early reports used 20% ALA with no standardization of protocol and a variable number of treatment sessions. Their overall results indicate that ALA-PDT is effective and well tolerated with a clearance rate that, in a few studies, was close to 100% after one to five exposures without apparent differences related to the stage of the treated lesions.[136-141]

More recently, three case series[142-4] and a multicentre retrospective study used MAL-PDT delivered to the standard treatment regimen as for BCC, but repeated several times, if needed. In the first report, complete remission was observed in four of five patients with unilesional patch, plaque and nodular disease, with partial response in the remaining patient after a median of 6 treatments (range 1–9).[142] In the second report, 6 of 12 patients with plaque- type lesions had a complete clearance, five a partial response, and one no response to a mean of 5.7 MAL-PDT treatments.[143] In these two reports, no recurrences were seen after 6-24 months. In the most recent trial, 10 patients with unilesional patch- and plaque- stage CTCL were treated with 2-6 MAL-PDT treatments at one-week intervals. Both clinical and histological clearance was seen in five patients and a partial remission in two. During follow-up (8–31 months), 6/7 patients with complete or partial remission did not show a relapse.[144]

In a retrospective observational study of medical records of 19 patients with unilesional plaque stage MF or isolated MF lesions in body flexures has reported a much lower efficacy with a complete remission only in five patients with two relapsing during follow-up.[65] In a further retrospective study of 12 patients with up to paucilesional MF, a 75% one-month response rate (6 complete responders, 3 partial) was observed following monthly MAL-PDT repeated for 6 months, with regression of lymphocytic infiltrate in 8/9 lesions biopsied (only one lesion biopsies/patient).[145] Response rates were similar between patches and plaques but higher in sun-protected areas.

The above reports and series indicate the potential for topical PDT in localized patch/plaque CTCL, although it may be less practical and more costly than standard phototherapy for multiple lesions. Current evidence indicates that topical PDT should be restricted to localized disease, with a possible indication for lesions in the body folds that can not be exposed to phototherapy.

6.5 Acne (*Strength of Recommendation B, Quality of Evidence I*)

P. acnes produces small amounts of porphyrins permitting a direct photodynamic effect without external sensitizer, with the action spectrum for reduction of *P acnes* following the absorption spectrum of porphyrins[146] However, the addition of topical ALA enhances porphyrin synthesis, with ALA taken up by the pilosebaceous unit.[147] PDT promotes transient antimicrobial and anti-inflammatory effects, inhibition and destruction of sebaceous glands, as well as enhanced epidermal turnover promoting reduced follicular obstruction.[148]

Hongcharu *et al* treated the backs of 22 acne patients by PDT.[149] They compared ALA-PDT, ALA alone, light alone and a control area using a broad-band lamp (550-700 nm). The results revealed a significant reduction of inflammatory acne and decreased sebum excretion in the ALA-PDT group only, 10 weeks after one treatment, with the sebaceous glands damaged and smaller. In an uncontrolled open study Itoh *et al*, 13 patients with facial acne all improved when treated with ALA-PDT using a halogen lamp (600-700 nm, 13 J/cm2).[150]

An open, randomized, controlled study was performed by Pollock *et al* on the back of 10 patients with acne compared ALA-PDT, ALA alone, light alone and a control site using one treatment of a diode laser (635 nm, 25 mW/cm2, 15 J/cm^2) weekly for 3 weeks. They found a significant reduction of inflammatory acne with ALA-PDT, but no reduction of P. acnes count nor in sebum excretion.[151]

Wiegell *et al* used MAL and a narrowband red LED light, (635nm, 37 J/cm^2) to treat 21 patients.[152] Following 2 treatments, 2 weeks apart, there was a 68% reduction in inflammatory lesions after PDT, versus 0% in a control group of 15 patients. There was no reduction in non-inflammatory lesions in both groups. In a subsequent split-face study, Wiegell compared a single treatment of ALA- with MAL-PDT, using a lower fluence rate.[11] A similar reduction in inflammatory lesions was observed between the groups but ALA-PDT showed more prolonged and severe side effects.

In another split-face study, Hörfelt *et al* compared MAL-PDT versus placebo (light only) in 30 patients with facial acne also using red LED (635nm, 37 J/cm^2, 68 mW/cm^2).[153] Two treatments were given 2 weeks apart. Twelve weeks after treatment a 54% versus 20% reduction in inflammatory parameters was noted between active and control groups, along with non-significant reductions in non-inflammatory lesions of 40% and 20% respectively. In another study, Hörfelt *et al* compared light doses using a single treatment of ALA-PDT and broadband light, with all 15 patients responding, but with no change in P. acnes count nor sebum excretion rate, although higher doses induced more pain.[154] In a critical analysis of PDT studies in acne high-dose ALA- and MAL-PDT were considered to produce similar effects, with photosensitizer incubation of three or more hours associated with longer remission and red light more likely to promote sebaceous gland destruction compared to blue or pulsed light.[25] Pain is usually encountered during treatment and can be severe. Acute effects also include desquamation and reversible hyperpigmentation. PDT may emerge as an

alternative to oral antibiotics, especially for inflammatory acne of moderate severity although it may be feasible to treat acne conglobate.[155-6]

Treatment protocols are yet to be optimized for the use of PDT in acne, balancing efficacy, tolerability and cost-effectiveness, especially if multiple treatments are required. Current scientific data indicate a clear potential in the therapeutic arsenal of acne, although for the present PDT for acne should be considered experimental.

6.6 Refractory hand/foot warts and genital warts

Refractory hand/foot warts (*Strength of Recommendation B, Quality of Evidence I*)

Refractory genital warts (*Strength of Recommendation B, Quality of Evidence I*)

The efficacy of topical PDT in the treatment of viral warts has been demonstrated in several studies. Clearance rates of recalcitrant hand and foot warts of 50-100% have been reported, usually repetitive treatments (up to 6 treatments) were applied. A randomized pilot study with ALA-PDT with 30 patients showed superior clearance to cryotherapy.[157] A controlled randomized trial with 232 recalcitrant warts showed 18 weeks after treatment a 56% clearance rate for ALA-PDT compared to 42% for placebo-PDT.[158] Pain during and after illumination was the main side effect. Several further case reports and series including a study for recalcitrant periungual warts confirmed these results.[65,159-164] Furthermore, facial plane warts have also been treated successfully with PDT in two independent case series.[165-6] Despite these positive results very few practitioners routinely use PDT for hand and foot warts, probably due to the absence of optimized protocols.

There are several case reports and series reporting beneficial effects of topical PDT for the treatment of genital warts. The clearance rate for female patients varied from 66%[167] to 100%[168] whereas in male patients a response rate of 73% was reported.[169] A larger study with 164 patients with urethral condylomata reported a clearance rate of 95% after one to four ALA-PDT treatments.[170] A randomized study comparing ALA-PDT with CO_2 laser evaporation in 65 patients with condylomata acuminata showed a 95% complete removal rate for PDT and 100% for CO_2 laser. However, the recurrence rate was lower following PDT (6.3 versus 19.1%).[171] A larger study with 90 patients confirmed these results including the lower recurrence rate for topical PDT (9% versus 17% for CO_2 laser).[172] A larger study using ALA-PDT as an adjuvant treatment to CO_2 laser evaporation however did not demonstrate a beneficial effect of ALA-PDT in this setting.[173]

6.7 PDT for Cutaneous Leishmaniasis. (*Strength of Recommendation B, Quality of evidence I)*

PDT has been successfully used in cutaneous leishmaniasis caused by different types of Leishmania, especially *L. major* and *L. tropica*. In a placebo-controlled, randomized trial on cutaneous Leishmaniasis caused by *L. major*, weekly treatment of 10% ALA topically applied for 4 h under occlusion, paromomycin ointment and a white paraffin-based ointment used as placebo were compared.[174] Three months after treatment, 94% in the PDT group were completely healed and 6% (2 lesions) were partially improved, compared with the paromomycin group (41% complete healing and 29% partially improved) and the placebo group (13% complete healing and 40% partially improved) ($p<0,001$). All patients in the PDT group were amastigote-free, compared with 65% in the paromomycin group and 20% in the placebo group ($p<0,001$). None of the patients in the PDT group showed deep and or disfiguring scars compared to 42% patients win the paromocymicin group and 11% in the placebo group.

PDT appears to be at least as effective as cryotherapy but with better cosmetic results. Five lesions were treated with ALA-PDT whereas the other 4 lesions were treated with cryotherapy. After weekly treatments, the PDT-treated lesions healed after 6 sessions whereas cryotherapy-treated lesions cleared after five. PDT obtained better cosmetic results than cryotherapy but was more painful.[175]

In addition to these comparative studies, there are case series using different PDT protocols (a total of 46 lesions in 19 patients). The most frequently photosensitizer was 10% ALA[176-177], applied locally under occlusion for 4 hours, and MAL 16%, applied for 3 hours in 2 isolated cases.[178-179] Broadband spectrum red light (570-700 nm) was the most frequently used, using fluences between 75 and 100 J/cm^2.[180] Response rates varied between 96.9-100 %. PDT was administered weekly and up to 5 sessions were needed, 3 or more treatments being more effective than 1 or 2. Side effects were mild, including erythema and burning sensation during illumination but treatments were well tolerated. Cosmetic results were excellent, and most lesions left only superficial scarring or slight post inflammatory hyperpigmentation [174,181]

Daylight PDT may also be effective for cutaneous leishmaniasis. Fourteen patients (49 lesions) with non-ulcerated lesions caused by *L. major* or *L. tropica* were treated with weekly daylight MAL-PDT. The overall cure rates were 86% after a mean of five treatments. The treatment was practically pain-free and left minimal scarring.[181]

Finally, a case report of relapse of long-standing cutaneous leishmaniasis used intralesional ALA-PDT three times at weekly intervals. There was no evidence of residual infection and the site remains clinically clear at 2 years follow up.[182]

PDT appears not to kill the Leishmania *parasite* directly, with a systemic immune response considered responsible for the clearance of cutaneous lesions.[183] Some species are deficient of some enzymes in the heme biosynthetic pathway. Leishmania species that can cause mucocutaneous (*L. braziliensis* complex) or visceral leishmaniasis (*L.donovani* complex) should not be treated with PDT.[184]

ALA- and MAL-PDT can be effective in treating cutaneous leishmaniasis, and should be considered as a first-line therapy, especially in aesthetically sensitive sites, as well as in patients with lesions resistant to other methods of treatment.

6.8 Photorejuvenation (*Strength of Recommendation A, Quality of Evidence1*)

When treating patients with widespread facial AK with PDT, it became evident that not only did AK clear but also signs of photoaging improved. Since then many clinical studies, recently reviewed, have been specifically investigating the photorejuvenating effects of PDT.[185] Although different treatment protocols with either ALA or MAL have been used, most studies have been able to confirm significant improvement in fine wrinkles, mottled pigmentation, sallow complexion, skin texture, tactile roughness, telangiectasias and facial erythema, whereas coarse wrinkles and sebaceous hyperplasia were not significantly altered. In the majority of the studies intense pulsed light devices (IPL) were used for illumination mainly combined with ALA (0.5-20% ALA preparations or 20% Levulan® Kerastick).[186-195] The advantage of using IPL is a probably synergistic effect since IPL by itself is capable of improving lentigines, hyperpigmentations, fine lines and telangiectasias. Split-face studies were able to prove the superiority of the combination with a photosensitizer plus IPL as compared to sole IPL treatment.[188,189,190,195] In contrast to continuous red light sources, IPL with significant shorter illumination times also have the benefit of being less painful which is an important issue when treating large areas such as the whole face.[196] Since parameters of IPL can be widely varied in regard to wavelength, pulse duration, pulse interval and energy density it is difficult to compare studies using different parameters. Furthermore, the optimal parameters for photodynamic rejuvenation using IPL devices from different manufacturers still have to be defined.[23] Parameters of IPL must be carefully chosen especially when treating men in the beard area to avoid destruction of the hair follicles.

Using red light instead of IPL for illumination has the advantage that licensed and recommended PDT protocols can be applied when AK are present in the treatment area. The approved protocol for MAL-PDT using a light emitting diode (LED) warrants that also AK are effectively treated in parallel with a significant improvement of the signs of photoaging.[131,197-200] Another PDT protocol licensed for AK in the USA is the combination of 20% ALA solution (Levulan® Kerastick) with blue light. Only a few studies confirm the efficacy of this combination for skin rejuvenation.[201-203] It remains unclear which protocol is most effective.

Combination therapies have been tried with the aim to improve the penetration of the photosensitizer and thus the efficacy of PDT. Perforation of the skin with a microneedle roller (300 micrometer needle length) prior to incubation with ALA and subsequent IPL treatment led to excellent cosmetic results.[43] In a split face study MAL-PDT was compared to MAL-PDT combined with 1.5 mm length microneedling after MAL application.[204] After microneedling assisted PDT side effects such as pain and crusting were more intense, but cosmetic results were superior and led to an improvement even of coarse wrinkles while AK clearance rates did not differ between both sides. The shorter needle lengths (0.3 mm) provide sufficient improvement in penetration of the photosensitiser by puncture of the stratum corneum. The longer needle lengths (1.5 mm) also exhibit synergistic effects in neocollagen formation by direct damage to the dermis.[185] MAL-PDT in combination with a non-ablative fractional laser resulted in a better improvement of fine wrinkles as compared to fractional laser alone.[205]

Several studies aimed to elucidate the molecular mechanisms behind the rejuvenating effects of PDT. An increase of type I collagen and a reduction of elastotic material in the dermis reversing the signs of photoaging could be demonstrated histologically after PDT.[131, 199 ,206-210] In cell culture studies with dermal fibroblasts it could be proven that PDT induced an increased production of collagen type I and also of collagen degrading matrix metalloproteinase (MMP)-3 via activation of extracellular signal-regulated kinase (ERK).[210] The authors hypothesize that an increase of MMP-3, which is crucial in connective tissue remodelling, may promote the degradation and removal of old, damaged collagen fibres, while the fibroblast is initiating formation of new ones to replace them. Clinically observed improvement of telangiectasias and facial erythema not only after IPL but also after LED illumination might be due to collagen deposition in the upper dermis which compresses the telangiectatic vessels towards the deeper dermis.[131] Immunohistochemical expression of TP-53, a marker for epidermal carcinogenesis, was reduced after PDT indicating that PDT might

reverse the carcinogenic process in photodamaged skin.[131,211] The fact that histological and molecular signs of photodamage were still present after one single PDT session and that some effects of PDT such as increased collagen production were reversible a few months after PDT implies that repeated PDT sessions might be necessary to achieve a sustained skin rejuvenating effect.[207]

There is good evidence to support the use of topical PDT as an effective and save method for skin rejuvenation with limited and well calculable side effects. Since AK are often also present in photodamaged skin licensed treatment protocols should be preferred to warrant simultaneous treatment of AK.

6.9 Other reported uses

Both topical ALA and MAL have been used to treat a variety of inflammatory and infective skin disorders.[2,4,212]. The vast majority of data regarding these indications is, however, based on limited case reports or short-term, non-randomized studies involving small patient numbers. The patient selection criteria, drug concentrations, and irradiation protocols were not uniform across these studies. Larger well-designed trials and studies characterized by established treatment modalities and standardized methodologies are certainly warranted.

Psoriasis (*Strength of Recommendation D, Quality of Evidence 1*)

A prospective randomized, double-blind phase *I*/II intrapatient comparison study evaluated the efficacy of topical ALA-PDT in 12 patients with chronic plaque psoriasis. Three psoriatic plaques were randomly treated in each patient using a light dose of 20 J/cm^2 and 0.1%, 1% or 5% ALA, respectively. Treatment was conducted twice a week until complete clearance or for a maximum of 12 irradiations. Therapeutic efficacy was assessed by weekly determination of the psoriasis severity index (PSI). The authors reported limited mean percentage improvement of 37.5%, 45.6%, and 51.2% in the 0.1%, 1% and 5% ALA-treated groups, respectively. Treatment was, however, frequently interrupted due to severe burning and pain.[213]

A retrospective study involving 17 patients affected with psoriasis reported that 6 (35.3%) had marked improvement following MAL-PDT treatment, while psoriatic lesions worsened in 2 patients (11.8%), probably as a result of Koebner phenomenon[212]. Five patients (29.4%) experienced severe pain and/or burning sensation. All the patients showing a marked response relapsed during the 2.8 ± 0.7 months of follow-up.

On the basis of current evidence, topical ALA-PDT and MAL-PDT treatments do not appear to be useful for psoriasis in view of disappointing efficacy, time-consuming treatment procedures, and unfavourable adverse event profiles.

Sebaceous gland hyperplasia (*Strength of Recommendation C, Quality of Evidence III*)

In 2003, Alster and Tanzi[214] reported on 10 patients receiving ALA-PDT and a pulsed dye laser (PDL) irradiation for the treatment of sebaceous hyperplasia. The patients received one or two treatments at 6-week intervals with topical 20% 5-ALA followed 1 hour later by 595nm PDL irradiation. Matched lesions - some treated with the PDL alone and others left untreated – from the same patient served as controls. The ALA and PDL combination cleared sebaceous gland hyperplasia lesions with just one treatment in 7 patients and 2 treatments in 3 cases. The combination of topical 5-ALA and PDL appear more efficacious in treating sebaceous gland hyperplasia compared to PDL alone. The treatments were found to be well tolerated and no severe adverse events were reported. These results were confirmed by a retrospective study on 5 patients with sebaceous gland hyperplasia treated with a conventional MAL-PDT protocol (3 hours, 37 J/cm^2, 633 nm).[212] A marked improvement was noted in 2 patients, with moderate response in 2.

Both MAL-PDT and short-contact ALA combined with PDL seem to offer therapeutic benefit in sebaceous gland hyperplasia, but the practical aspects of drug delivery and dosage need further study.

Hypertrophic and Keloid Scars (*Strength of Recommendation C, Quality of Evidence II-iii*)

A retrospective study concentrating on 6 patients with field cancerization found a significant improvement in the appearance of hypertrophic scars after two to three PDT treatments (ALA and MAL) [215] Similar results were described by Calzavara-Pinton et al. who studied 8 patients with hypertrophic scars.[212] A marked improvement was noted in 5 (63%) of these. The treatment was well tolerated and none of the patients had a relapse during the mean follow-up period of 14.1 months. Another study showed that the positive effect of MAL-PDT in the treatment of hypertrophic scars is associated with a degradation of collagen and an increase in elastin fibres, suggesting an induction of collagen degrading enzymes. [216]

Ud-Din et al. demonstrated in 20 patients with keloid disease (10 patients were treated only with PDT, 6 were treated with surgical debulking and subsequently with PDT, and 4 were treated with total surgical excision and subsequently PDT) that three treatments of MAL-PDT (37 J/cm^2) at weekly intervals were effective in reducing pruritus and pain and in

improving pliability of symptomatic keloids.[217] In the 10 patients where PDT was applied postoperatively, there were only one recurrences at the 9-month follow-up.

Lichen sclerosus (*Strength of Recommendation C, Quality of Evidence III*)

An early study by Hillemanns *et al*.[218] sought to determine if PDT could be a treatment option for patients suffering from vulvar lichen sclerosus. Twelve women underwent 1–3 cycles of PDT with an argon ion-pumped dye laser (630 nm) at 80 J/cm^2 and a irradiance of 40–70 mW/cm^2 for up to 40 min. Prior to irradiation, the area was occluded with 20% 5-ALA for 4–5 h. Ten of the 12 women showed significant improvement in pruritus that lasted from 3 to 9 months. The procedure was fairly well tolerated although 25% of the patients required opioid analgesia. Histological evaluation was not conclusive.

There have only been a few case reports that have evaluated PDT as treatment for recalcitrant vulvar lichen sclerosus. Romero *et al.*[219] reported improvement in one of two patients with severe recalcitrant lichen sclerosus after 2 monthly treatments of 20% ALA-PDT with 2 hour-occlusion followed by red light (633 nm) at 30 J/cm^2 and 80 mW/cm^2. Vulvar lesions healed well and symptoms were decreased. Sotiriou *et al.*[220] described symptomatic improvement in 5 patients treated once with 20% ALA for 3 hours followed by red light (570–670 nm, 40 J/cm^2, 80 mW/cm^2). There was only a minimal change in clinical appearance in the patients studied and no resolution on histological evaluation.

Although potentially effective in relieving symptoms associated with lichen sclerosus, topical PDT did not appear to be associated with an improvement in clinical nor histological response in the limited number of cases studied.

Granuloma annulare (*Strength of Recommendation C, Quality of Evidence III*)

Two to 3 PDT sessions using 20% ALA gel and red light (100 J/cm²) were performed in a group of 7 consecutive patients with granuloma annulare.[221] The overall response rate in these patients was 57% (complete healing in 2 patients, marked improvement in 2, and no improvement in 3). The response rate was similar (54%) in a group of 13 patients with granuloma annulare treated with MAL-PDT after a mean of 2.8 treatments.[212] After a follow-up of 7 months, all patients were still in remission. The treatment was well tolerated and neither extensive local inflammation nor unbearable pain were reported. Topical PDT may be considered for patients affected by granuloma annulare resistant to conventional treatments.

Necrobiosis lipoidica (*Strength of Recommendation D, Quality of Evidence III*)

Berking *et al*. [222] evaluated PDT in necrobiosis lipoidica in the context of a multicenter retrospective study assessing 18 patients. Only 1 patient showed a complete response after nine treatment sessions while 6 had a partial response after as many as 14.
In another multicenter retrospective study assessing 8 patients affected with necrobiosis lipoidica, MAL-PDT treatment was associated with a 37% response rate after a mean of 10 PDT sessions.[212] Overall, PDT seems to be less effective in treating patients with necrobiosis lipoidica than those suffering from granuloma annulare.

7. Reactions to PDT

7.1 Normal and abnormal reactions

Most of the studies and reviews on PDT focus on efficacy, whereas normal and abnormal reactions to PDT are rarely specifically addressed.[223-4] The following reactions should be considered and communicated to patients before the PDT procedure. Their description is based on review papers and special reports on PDT side effects.[71, 225-6] Pain is discussed below.

The most prominent and common skin reactions to PDT are erythema and oedema due to the basic photodynamic/phototoxic action of the procedure. Especially when large areas are treated patients must be advised so that they can adjust their every day activities in the period following the treatment. This expected reaction may last about 4 to 7 days and may be ameliorated by application of emollients. Following this phototoxic reaction significant scaling may occur, which is often accompanied by itching lasting for up to two weeks. Application of emollients may lead to a significant control of this reaction.[71,,226]

Pustulation occurs in 20-30% of cases, where field cancerization has been treated and patients may be concerned they have acquired a troublesome skin infection. Patients should be reassured that this is a normal reaction to PDT which will not affect the outcome. Serial biopsies have shown that the pustulation is due to a rupture of the follicle wall with subsequent influx of leucocytes. Accordingly, the pustules are sterile and may last for 10-14 days.[224,226,227]

A less common skin reaction is crusting, which occurs mostly after treating thicker lesions e.g. superficial BCC or SCC *in-situ*. Less common unwanted effects include erosions, which mainly occur after treating widespread field cancerization on the arms, trunk and legs.[71]

Hyper- or hypopigmentation is uncommon, mainly occurring after treatment of BCC or SCC *in-situ* on the trunk or extremities, perhaps influenced by curettage pre-treatment. [71,223,224,226] Widespread erosions and pustules may cause significant anxiety for the patients.

Patients should be informed in detail about these possible effects prior to treatment, since most of the unwanted effects are easily managed, heal without scarring and do not influence the therapeutic response.

The following rare abnormal reactions has been reported mainly in case reports and should be taken into account when performing PDT: contact allergy to methyl aminolaevulinate[228,229] urticaria after MAL-PDT[230], postoperative hypertension after MAL-PDT[231], localized bullous pemphigoid induced by PDT[232].

Generally patients tolerate PDT well, especially when they are well informed and prepared on what to expect subsequent to the procedure.

7.2 Pain/discomfort during PDT

Pain is the dominant short term side-effect associated with PDT.[2,233,234] The pain may be severe but the mechanisms are poorly understood, although pain may be predicted in many instances. Large lesions and AK diagnosis with severe sun damage may predispose to more pain. Male gender has also been suggested but this is probably due to the fact that men have larger areas affected i.e. AK in bald men.[235,236]

In a retrospective study of 658 treatments, the following parameters were associated with more pain: large treatment area, AK, and face and scalp areas.[237] Simple pain reduction strategies include a cooling fan, water spraying, lower light intensity and fractionated light delivery.[234,238] Daylight PDT is associated with no/minimal pain, although suitable weather conditions are required for patients to sit outside for 2 hours in comfort.[34] It has been argued that MAL hurts less than ordinary ALA.[11] Other studies have not confirmed this.[10] New formulations may show benefit both in terms of efficacy and side effects.[12]

Nerve block has proven to be effective to reduce severe pain. Paoli *et al* showed that nerve blocks provide effective pain relief during PDT for extensive facial AKs. Halldin *et al* have demonstrated that nerve blocks enable adequate pain relief during topical PDT of field cancerization on the forehead and scalp.[239,240] On a 10 grade Visual Analogue Scale (VAS) the pain felt without nerve block was 7.5 and with nerve block 1.3. The nerve blocks did not interfere with the effectiveness of PDT. Nerve blocks have been reported to be safe and easy to perform on an out-patient basis.

Serra-Guillen and coworkers have compared nerve blocks to cold air analgesia on AK on the frontotemporal zone and found nerve blocks more effective.[241] In a controlled open split-face trial of PDT in 34 patients with multiple AK in the frontal region, cold air analgesia was compared with nerve block. Nerve block was found to be superior. Nerve blocks are

typically initiated 10-15 minutes before irradiation. The anaesthetized area is mapped by asking the patient where cutaneous perception is perceived with a needle.

Pain may be a major problem during treatment with PDT. Simple measures include cold air or spraying with water. In severe cases nerve blocks have proven useful. Topical application of local anaesthetics does not work due to chemical incompatibilities with ALA or MAL.

8. Summary of recommendations

Strength of Recommendation	***Quality of Evidence***	***Indication***
A	***I***	**Actinic keratoses** **Squamous cell carcinoma in-situ** **Superficial Basal cell carcinoma** **Nodular Basal cell carcinoma** **Photorejuvenation**
B	***I***	**Non-melanoma skin cancer in organ transplant recipients** **Prevention of non-melanoma skin cancer in organ transplant recipients** **Field cancerization** **Acne** **Refractory hand/foot warts** **Refractory genital warts** **Cutaneous Leishmaniasis**
C	***IIi***	**Sebaceous gland hyperplasia**
C	***II-iii***	**CTCL** **Hypertrophic scars/Keloids**
C	***III***	**Granuloma annulare** **Lichen sclerosus**
D	***I***	**Psoriasis**
D	***11-iii***	**Invasive SCC**
D	***III***	**Necrobiosis lipoidica**

9. References

1. Braathen Lasse R, Szeimies Rolf M, Basset Seguin N *et al*. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. *J Am Acad Dermatol*, 2007; **56**: 125-43.

2. Morton CA, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy *Br J Dermatol* 2008; **159**:1245-66.

3. Morton, C.A., Szeimies, R.-M., Sidoroff, A. and Braathen, L.R., European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma. *JEADV* 2013; **27**: 536–544.

4. Morton, C.A., Szeimies, R.-M., Sidoroff, A. and Braathen, L.R., European guidelines for topical photodynamic therapy part 2: emerging indications – field cancerization, photorejuvenation and inflammatory/infective dermatoses. *JEADV* 2013; **27**: 672–679.

5.http://www.euroderm.org/images/stories/guidelines/guideline_Management_Actinic_Keratoses-update2011.pdf

6.http://www.euroderm.org/images/stories/guidelines/guideline_Basal_Cell_Carcinoma-update2012%20.pdf

7. Kennedy J C. Pottier, R H. Pross D C. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience *J Photochem Photobiol B*. 1990;**6**: 143-8.

8. Henderson BW, Dougherty TJ. How does photodynamic therapy work? *Photochem Photobiol* 1992; **55**: 145-57.

9. Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol* 2007; **157**: 87-91.

10. Kuijpers D, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. *J Drugs Dermatol* 2006; **5**: 642-5.

11. Wiegell S, Wulf, HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol* 2006; **54**: 647-51.

12. Dirschka T, Radny P, Dominicus R, *et al*. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratoses: results of a multicentre, randomized, observer-blind phase III study in comparison with registered methyl-5-aminolaevulinate cream and placebo. *Br J Dermatol* 2012; **166**: 137-46.

13. Hauschild A, Stockfleth E, Popp G, *et al*. Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies *Br J Dermatol*. 2009; **160**: 1066-1074.
14. Gerritsen MJP, Smits T, Kleinpenning MM *et al*. Pretreatment to enhance protoporphyrin IX accumulation in photodynamic therapy. *Dermatology*, 2009; **218**: 193-202.
15. Rhodes LE, de Rie M, Enstrom Y *et al*. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. *Arch Dermatol* 2004; **140**: 17-23.
16. Nester MS, Gold MH, Kauvar ANB *et al*. The use of photodynamic therapy in Dermatology: results of a consensus conference. *J Drugs Dermatol* 2006; **5**: 140-154.
17. Braathen, L R. Paredes, B E. Saksela, O.*et al*. Short incubation with methyl aminolevulinate for photodynamic therapy of actinic keratoses. *J Eur Acad Dermatol Venereol*. 2009; **23**:550-5.
18. Jang MS, Doh KS, Kang JS, *et al*. A comparative split-face study of photodynamic therapy with indocyanine green and indole-3-acetic acid for the treatment of acne vulgaris. *Br J Dermatol* 2011; **165**: 1095-1100.
19. Kacerovska D, Pizinger K, Majer F *et al*. Photodynamic therapy of nonmelanoma skin cancer with topical hypericum perforatum extract--a pilot study. *Photochem Photobiol* 2008; **84**: 779-85.
20. Rook AH, Wood GS, Duvic M, *et al*. A phase II placebo-controlled study of photodynamic therapy with topical hypericin and visible light irradiation in the treatment of cutaneous T-cell lymphoma and psoriasis *J Am Acad Dermatol* 2010; **63**: 984-90.
21. Baron ED, Malbasa CL, Santo-Domingo D *et al*. Silicon phthalocyanine (Pc 4) photodynamic therapy is a safe modality for cutaneous neoplasms: results of a phase 1 clinical trial. *Lasers Surg Med;* **42**: 728-35.
22. Morley, S., Griffiths, J., Philips, G., *et al*. L.E. Phase IIa randomized, placebo-controlled study of antimicrobial photodynamic therapy in bacterially colonized, chronic leg ulcers and diabetic foot ulcers: a new approach to antimicrobial therapy. *Br J Dermatol* 2013, **168**: 617–624.
23. Maisch T, Moor AC, Regensburger J, *et al*. Intense pulse light and 5-ALA PDT: phototoxic effects in vitro depend on the spectral overlap with protoporphyrin IX but do not match cut-off filter notations. *Lasers Surg Med*. 2011 ; **43**:176-82.

24. Szeimies RM, Radny P, Sebastian M, *et al*.. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. *Br J Dermatol*. 2010;**163**:386-94.
25. Sakamoto FH, Torezan L, Anderson RR Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part II. Understanding parameters for acne treatment with photodynamic therapy**.** *J Am Acad Dermatol.* 2010;**63**:195-211.
26. de Vijlder HC. Sterenborg HJ. Neumann HA. Robinson DJ. de Haas ER. Light fractionation significantly improves the response of superficial basal cell carcinoma to aminolaevulinic acid photodynamic therapy: five-year follow-up of a randomized, prospective trial. Acta Dermato-Venereologica. 2012;**92**:641-7.
27. de Haas ER, Sterenborg HJ, Neumann HA, Robinson DJ. Response of Bowen disease to ALA-PDT using a single and a 2-fold illumination scheme**.** *Arch Dermatol* 2007; **143**: 264-5.
28. de Haas ER, de Vijlder HC, Sterenborg HJ *et al*. Fractionated aminolevulinic acid-photodynamic therapy provides additional evidence for the use of PDT for non-melanoma skin cancer. *J Eur Acad Dermatol Venereol* 2008; **22**: 426-30.
29. Sotiriou E, Apalla Z, Chovarda E, *et al.* Single vs. fractionated photodynamic therapy for face and scalp actinic keratoses: a randomized, intraindividual comparison trial with 12 month follow-up *J Eur Acad Dermatol Venereol* 2012; **26**:36-40.
30. Mosterd K, Thissen MRTM, Nelemans P, *et al*. Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial *Br J Dermatol* 2008; **159**: 864-70.
31. de Bruijn HS, Meijers C, van der Ploeg-van den Heuvel A, *et al.* Microscopic localisation of protoporphyrin IX in normal mouse skin after topical application of 5-aminolevulinic acid or methyl 5-aminolevulinate *J Photochem Photobiol B.* 2008;**92**:91-7.
32. Wiegell SR, Haedersdal M, Philipsen PA, *et al*. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blind study. *Br J Dermatol* 2008; **158**: 740-6.
33. Wiegell, S R. Fabricius, S. Stender, I M. *et al*. A randomized, multicentre study of directed daylight exposure times of 1 1/2 vs. 2 1/2 h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp *Br J Dermatol* 2011, **164**:1083-90.
34. Wiegell,SR, Fabricius,S, Gniadecka M, *et al*, Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp - a randomized multicentre study. *Br J Dermatol* 2012;**166**:1327-32.

35. Wiegell SR, Skødt V, Wulf HC. Daylight-mediated photodynamic therapy of basal cell carcinomas - an explorative study. J Eur Acad Dermatol Venereol. 2013. doi: 10.1111/jdv.12076.

36. Moseley H, Allen JW, Ibbotson S *et al*. Ambulatory photodynamic therapy: a new concept in delivering photodynamic therapy. *Br J Dermatol* 2006; **154**: 747-50.

37. Attili SK, Lesar A, McNeill A *et al*. An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode light source in the treatment of nonmelanoma skin cancer. *Br J Dermatol* 2009; **161**: 170-3.

38. Ibbotson SH, Ferguson J. Ambulatory photodynamic therapy using low irradiance inorganic light-emitting diodes for the treatment of non-melanoma skin cancer: an open study. *Photodermatol Photoimmunol Photomed*. 2012;**28**:235-9.

39. Moseley H. Total effective fluence: a useful concept in photodynamic therapy. *Lasers Med Sci*. 1996; **11**: 139-43.

40. Szeimies RM, Stockfleth E, Popp G, *et al*. Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. *Br J Dermatol* 2010;**162**:410-4.

41. Moseley, H. Brancaleon, L. Lesar, AE. Ferguson, J. Ibbotson, SH, Does surface preparation alter ALA uptake in superficial non-melanoma skin cancer in vivo? *Photodermatol Photoimmunol Photomed*. 2008; **24**:72-5.

42. Thissen MR, Schroeter CA, Neumann HA. Photodynamic therapy with delta-aminolaevulinic acid for nodular basal cell carcinomas using a prior debulking technique. *Br J Dermatol* 2000; **142**: 338-9.

43. Clementoni, MT. B-Roscher, M. Munavalli, GS. Photodynamic photorejuvenation of the face with a combination of microneedling, red light, and broadband pulsed light. *Lasers in Surgery & Medicine*. 2010; **42**:150-9.

44. Kolde G, Rowe E, Meffert H. Effective photodynamic therapy of actinic keratosis and Bowen's disease using microneedle perforation. *Br J Dermatol* 2013;**168**:450-1.

45. Whitaker IS, Shokrollahi K, James W; *et al*, Combined CO_2 Laser With Photodynamic Therapy for the Treatment of Nodular Basal Cell Carcinomas *Ann Plast Surg* 2007;**59**:484-8.

46. Togsverd-Bo K, Haak CS, Thaysen-Petersen D, Wulf HC, Anderson RR and Hædersdal M. Intensified Photodynamic Therapy of Actinic Keratoses with Fractional CO_2 laser - a randomized *Br J Dermatol* 2012;**166**:1262-9.

47. Wiegell SR, Wulf HC, Szeimies R-M, et al. Daylight photodynamic therapy for actinic keratosis: an international consensus. J Eur Acad Dermatol Venereol 2012; **26**: 673-679.
48. Cochrane C, Mordon SR, Lesage JC, Koncar V. New design of textile light diffusers for photodynamic therapy. *Mater Sci Eng C Mater Biol Appl*. 2013;**33**:1170-5.
49.Fritsch C J Ruzicka T. Fluorescence diagnosis and photodynamic therapy in dermatology from experimental state to clinic standard methods *Envtl Path, Tox & Oncol* 2006;**25**;425-39.
50. Lee CY, Kim KH, Kim YH. The efficacy of photodynamic therapy in delineating the lateral border between a tumour and a tumour-free area during Mohs micrographic surgery *Dermatologic Surgery* 2010; **36**: 1704-10.
51. Neus S, ambichler, Thilo. Bechara, Falk G. Wohl, Stephan. Lehmann, Percy. Preoperative assessment of basal cell carcinoma using conventional fluorescence diagnosis *Arch Derm Res* 2009; **301**: 289-94.
52. Tyrrell JS, Campbell SM, Curnow A The relationship between protoporphyrin IX photobleaching during real-time dermatological methyl-aminolevulinate photodynamic therapy (MAL-PDT) and subsequent clinical outcome *Lasers Surg Med*; 2010; **42**: 613-9.
53. Smits, T. Kleinpenning, M M. Blokx, WAM. van de Kerkhof, PCM. van Erp, PEJ. Gerritsen, M-JP Fluorescence diagnosis in keratinocytic intraepidermal neoplasias. *J Am Acad Dermatol* 2007;**57**:824-31.
54. Wiegell SR, Skiveren PA, Philipsen PA and Wulf HC. Pain during photodynamic therapy is associated with protoporphyrin IX fluorescence and fluence rate. *Br J Dermatol* 2008; **158:** 727-33.
55. Piacquadio DJ, Chen DM, Farber HF *et al*. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded phase 3 multicenter trials. *Arch Dermatol* 2004;**140:**41-6.
56. Tarstedt M, Rosdahl I, Berne B *et al*. A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix®)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005; 85: 424-8.
57. Morton C, Campbell S, Gupta G *et al*. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; **155**: 1029-36.
58. Tschen EH, Wong DS, Pariser DM *et al.* The Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol* 2006; **155**: 1262-9.

59. Dirschka, T., Radny, P., Dominicus, R, *et al.* Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolaevulinate for the treatment of actinic keratosis. *Br J Dermatol*, **168**: 825–836.

60. Wiegell, S R. Fabricius, S. Heydenreich J, et al. Weather conditions and daylight-mediated photodynamic therapy: protoporphyrin IX-weighted daylight doses measured in six geographical locations. *Br J Dermatol* 2013, **168**:186-91.

61. Kaufmann, R., Spelman, L., Weightman, W., *et al.* Multicentre intraindividual randomized trial of topical methyl aminolaevulinate–photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. *Br J Dermatol* 2008; **158**:994–9.

62. Sotiriou, E., Apalla, Z., Maliamani, F, *et al*. Intraindividual, right–left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. *J Eur Acad Dermatol Venereol* 2009; **23**:1061–1065.

63. Sotiriou E, Apalla Z, Chovarda E. Panagiotidou D, Ioannides D. Photodynamic therapy with 5-aminolevulinic acid in actinic keratosis: an 18 month clinical and histological follow-up. *J Eur Acad Dermatol Venereol* 2010; **24**: 916-20.

64. Berking C, Herzinger T, Flaig MJ *et al*. The efficacy of photodynamic therapy in actinic chielitis of the lower lip: a prospective study of 15 patients. Dermatol Surg 2007; **33**: 825-30.

65. Calzavara-Pinton PG, Rossi MT, Sala R, *et al*. A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinate (MAL-PDT) in 20 Italian dermatology departments. Part 2: Oncologic and infectious indications. *J Photochem Photobiol Sci*. 2013; **12**: 158-165.

66. Sotiriou E, Lallas A, Gooussi C *et al.* Sequential use of photodynamic therapy and imiquimod 5% cream for the treatment of actinic cheilitis; a 12 month follow-up study. *Br J Dermatol* 2011; **165**: 888-92.

67. Stockfleth E *et al.* Guidelines on actinic keratosis. European Dermatology Forum: http://www.euroderm.org/edf/images/stories/guidelines/guideline_Management_Actinic_Keratoses-update2011.pdf.

68. De Berker, D., McGregor, J., Hughes, B. Guidelines for the management of actinic keratosis. *Br J Dermatol*, 2007; **156**:222-230.

69. Serra-Guillen, C., Nagore, E., Hueso, L., *et al*. A randomized comparative study of tolerance and satisfaction in the treatment of actinic keratosis of the face and scalp between 5% imiquimod cream and photodynamic therapy with methyl aminolaevulinate. *Br J Dermatol*, 2011;**164**:429–433.

70. Morton CA, Horn M, Leman J, *et al*. A randomized, placebo-controlled, European study comparing MAL-PDT with cryotherapy and 5-fluorouracil in subjects with Bowen's disease. *Arch Dermatol* 2006; **142**: 729-35.

71. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol* 2007; **156**:793-801.

72. Calzavara-Pinton PG, Venturini M, Sala R *et al.* Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. *Br J Dermatol* 2008; **159**:137-44.

73. Truchuelo M, Fernandez-Guarino M, Fleta B *et al.* Effectiveness of photodynamic therapy in Bowen's disease: an observational and descriptive study in 51 lesions. *J Eur Acad Dermatol Venereol* 2012; **26**:868-74.

74. Cavicchini S, Serini SM, Fiorani R *et al.* Long-term follow-up of metil aminolevulinate (MAL)-PDT in difficult-to-treat cutaneous Bowen's disease. *Int J Dermatol* 2011; **50**:1002-5.

75. Lopez N, Meyer-Gonzalez T, Herrera-Acosta E *et al*. Photodynamic therapy in the treatment of extensive Bowen's disease. *J Dermatolog Treat* 2012: **23**:428-30.

76. Morton CA, Whitehurst C, McColl JH *et al.* Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma. *Arch Dermatol* 2001; **137**:319-24.

77. Souza CS, Felicio LB, Ferreira J *et al.* Long-term follow-up of topical 5-aminolaevulinic acid photodynamic therapy diode laser single session for non-melanoma skin cancer. *Photodiagn Photodyn Ther* 2009; **6**:207-13.

78. Salim A, Leman JA, McColl JH *et al.* Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol* 2003; **148**:539-43.

79. Morton CA, Whitehurst C, Moseley H *et al.* Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. *Br J Dermatol* 1996; **135**:766-71.

80. Tyrrell JS, Morton C, Campbell SM *et al.* Comparison of protoporphyrin IX accumulation and destruction during methylaminolevulinate photodynamic therapy of skin tumours located at acral and nonacral sites. *Br J Dermatol* 2011; **164**:1362-8.

81. Wong TW, Sheu HM, Lee JY *et al.* Photodynamic therapy for Bowen's disease (squamous cell carcinoma in situ) of the digit. *Dermatol Surg* 2001; **27**:452-6.

82.Brookes PT, Jhawar S, Hinton CP *et al.* Bowen's disease of the nipple-a new method of treatment. *Breast* 2005; **14**:65-7.

83.Tan B, Sinclair R, Foley P. Photodynamic therapy for subungual Bowen's disease. *Australas J Dermatol* 2004; **45**:172-4.

84.Usmani N, Stables GI, Telfer NR *et al.* Subungual Bowen's disease treated by topical ainolevulinic acid-photodynamic therapy. *J Am Acad Dermatol* 2005; **53**:S273-6.

85.Souza CS, Felicio LB, Bentley MV *et al.* Topical photodynamic therapy for Bowen's disease of the digit in epidermolysis bullosa. *Br J Dermatol* 2005; **153**:672-4.

86.Guillen C, Sanmartin O, Escudero A *et al.* Photodynamic therapy for in situ squamous cell carcinoma on chronic radiation dermatitis after photosensitization with 5-aminolaevulinic acid. *J Eur Acad Dermatol Venereol* 2000; **14**:298-300.

87. Ball SB, Dawber RP. Treatment of cutaneous Bowen's disease with particular emphasis on the problem of lower leg lesions. *Australas J Dermatol* 1998; **39**:63-8.

88. Paoli J, Ternesten Bratel A, Lowhagen G-B *et al*. Penile intraepithelial neoplasia: results of photodynamic therapy. *Acta Derm Venereol* 2006; **86**: 418-21.

89. Downs AM, Bower CB, Oliver DA *et al.* Methyl aminolaevulinate-photodynamic therapy for actinic keratoses, squamous cell carcinoma in situ and superficial basal cell carcinoma employing a square wave intense pulsed light device for photoactivation. *Br J Dermatol* 2009; **161**:189-90.

90. Schreml S, Gantner S, Steinbauer J *et al.* Melanoma promotion after photodynamic therapy of a suspected Bowen's disease lesion. *Dermatology* 2009; **219**:279-81.

91. Cox, N., Eedy, D., Morton, C. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol* 2007;**156**:11– 21.

92. Hu A, Moore C, Yu E *et al.* Evaluation of patient-perceived satisfaction with photodynamic therapy for Bowen disease. *J Otolaryngol Head Neck Surg* 2010; **39**:688-96.

93. Basset-Séguin N, Ibbotson SH, Emtestam L*, et al*. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial E J Dermatol 2008; **18:**547-53.

94. Szeimies, R., Ibbotson, S., Murrell, D. *et al.* A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8–20mm), with a 12-month follow-up. *J Eur Acad Dermatol Venereol* 2008; **22**:1302–1311.

95. Rhodes, LE, de Rie MA, Leifsdottir R, *et al*.. Five year follow up of a randomized prospective trial of topical methyl aminolevulinate-photodynamic therapy versus surgery for nodular basal cell carcinoma. *Arch Dermatol*, 2007;**143**, 1131-1136.

96. Foley P, Freeman M, Menter A, *et al*. Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies *Int J Dermatol* 2009; **48**: 1236-45.

97. Fantini, F., Greco, A., Del Giovane, C., *et al*. Photodynamic therapy for basal cell carcinoma: clinical and pathological determinants of response. *J Eur Acad Dermatol Venereol* 2011;**25**:896–901.
98. Arits AH. Mosterd K. Essers BA. *et al*. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. Lancet Oncology. 2013;**14**:647-54.
99. Peng Q, Warloe T, Berg K *et al*. 5-Aminolevulinic acid-based photodynamic therapy. Clinical research and future challenges. *Cancer* 1997; **79**: 2282-308.
100. Wang I, Bendsoe N, Klinteberg CA *et al*. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol* 2001; **144**: 832-40.
101. Roozeboom MH, Aardoom MA, Nelemans P, *et al*. Fractionated 5-aminolaevulinic acid-photodynamic therapy after partial debulking vs. surgical excision in the treatment of nodular basal cell carcinoma: A randomized controlled trial with at least 5-year follow-up. *J Am Acad Dermatol.* 2013; **69**: 280-7.
102. Berroeta L, Clark C, Dawe RS *et al*. A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low risk nodular BCC. *Br J Dermatol* 2007; **157**: 401-403.
103. Morton CA, Whitehurst C, McColl JH, Moore JV, MacKie RM. Photodynamic therapy for basal cell carcinoma - Effect of tumour thickness and duration of photosensitiser application on response. *Arch Dermatol*, 1998, **134**, 248-9.
104. Vinciullo C, Elliott T, Francis D *et al*. Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005; **152**: 765-72.
105. Christensen, E., Skogvoll, E., Viset, T., Warloe, T.,Sundstrøm, S. Photodynamic therapy with 5-aminolaevulinic acid, dimethylsulfoxide and curettage in basal cell carcinoma: a 6-year clinical and histological follow-up. *J Eur Acad Dermatol Venereol* 2009; **23**:58–66.
106. Loncaster J, Swindell R, Slevin F, *et al*. Efficacy of photodynamic therapy as a treatment for Gorlin Syndrome-related basal cell carcinomas. *Clinical Oncology* 2009;**21**: 502-8.
107. Pauwels, C., Mazereeuw-Hautier, J., Basset-Seguin, N., *et al*. Topical methyl aminolevulinate photodynamic therapy for management of basal cell carcinomas in patients with basal cell nevus syndrome improves patient's satisfaction and reduces the need for surgical procedures. *J Eur Acad Dermatol Venereol* 2011;**25**:861–864.
108. Telfer, N., Colver, G. and Morton, C. Guidelines for the management of basal cell carcinoma. *Br J Dermatol*, 2008;**159**:35–48.

109. Hofbauer GF, Bouwes Bavinck JN, Euvrard S. Organ transplantation and skin cancer: basic problems and new perspectives. *Exp Dermatol*. 2010;**19**:473-82.
110. Hofbauer GF, Anliker M, Arnold A, *et al.* Swiss clinical practice guidelines for skin cancer in organ transplant recipients. SGDV working group for organ transplant recipients. *Swiss Med Wkly*. 2009;**139**:407-15.
111. Dragieva C, Hafner J, Dummer R *et al.* Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation* 2004;**77**:115–21.
112. Dragieva C, Prinz BM, Hafner J *et al*. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol* 2004;**151**:196–200.
113. Piaserico S, Belloni Fortina A, Rigotti P *et al*. Topical photodynamic therapy of actinic keratosis in renal transplant patients. *Transplant Proc* 2007;**39**:1847–50.
114. Perrett CM, McGregor JM, Warwick J *et al. T*reatment of post-transplant premalignant skin disease: A randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol* 2007;**156**:320–8.
115. Rangwala S, Tsai KY. Roles of the immune system in skin cancer. *Br J Dermatol.* 2011;**165**:953-65.
116. Thoms KM, Kuschal C, Oetjen E, *et al*. Cyclosporin A, but not everolimus, inhibits DNA repair mediated by calcineurin: implications for tumorigenesis under immunosuppression. *Exp Dermatol.* 2011;**20**:232-6.
117. Yarosh DB, Pena AV, Nay SL, Canning MT, Brown DA Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B irradiation. *J Invest Dermatol*. 2005;**125**:1020-5.
118. O'Donovan P, Perrett CM, Zhang X, *et al.* Azathioprine and UVA light generate mutagenic oxidative DNA damage. *Science*. 2005;**309**:1871-4.
119. Ulrich C, Jürgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol.2009;**161** Suppl 3:78-84.
120. Wulf HC, Pavel S, Stender I, Bakker-Wensveen CAHB. Topical photodynamic therapy for prevention of new skin lesions in renal transplant recipients. *Acta Derm Venereol* 2006; **86**: 25-28.

121. Wennberg AM, Stenquist B, Stockfleth E, *et al.* Photodynamic therapy with methyl aminolevulinate for prevention of new lesions in transplant recipients: a randomized study. *Transplantation* 2008; **86**: 423-9.
122. De Graaf YGL, Kennedy C, Wolterbeek R *et al*. Photodynamic therapy does not prevent cutaneous squamous-cell carcinoma in organ-transplant recipients: results of a randomized-controlled trial. *J Invest Dermatol* 2006; **126**: 569-574.
123. Willey A, Mehta S, Lee PK. Reduction in incidence of squamous cell carcinoma in solid organ transplant recipients treated by cyclic Photodynamic therapy. *Dermatol Surg* 2010; **36**: 652-8.
124. Slaughter D. P., Southwick H. W., Smejkal W. "Field cancerization" in oral stratified squamous epithelium. *Cancer (Phila.),* 1953;**6**: 963-968.
125. Vauthey JN, Walsh GL, Vlastos G, Lauwers GY. Importance of field cancerisation in clinical oncology. *Lancet Oncol*. 2000;**1**:15-6.
126. Basset-Séguin N, Molès JP, Mils V, Dereure O, Guilhou JJ. TP53 tumor suppressor gene and skin carcinogenesis. *J Invest Dermatol*. 1994;**103**:102S-106S.
127. Ren ZP, Pontén F, Nistér M, Pontén J. Two distinct p53 immunohistochemical patterns in human squamous-cell skin cancer, precursors and normal epidermis. *Int J Cancer.* 1996 Jun 21;**69**:174-9.
128. Berg RJ, van Kranen HJ, Rebel HG*, et al*. Early p53 alterations in mouse skin carcinogenesisby UVB radiation: immunohistochemical detection of mutant p53 protein in clusters of preneoplastic epidermal cells. *Proc Natl Acad Sci U S A*. 1996 ;**93**:274-8.
129. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. *Cancer Res*. 2003;**63**:1727-30.
130. Ulrich M, Krueger-Corcoran D, Roewert-Huber J, *et al*. confocal microscopy for noninvasive monitoring of therapy and detection of subclinical actinic keratoses. *Dermatology.* 2010;**220**:15-24.
131. Szeimies RM, Torezan L, Niwa A, *et al*. Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. *Br J Dermatol*. 2012;**167**:150-9.
132. de Graaf YG, Rebel H, Elghalbzouri A, *et al*. More epidermal p53 patches adjacent to skin carcinomas in renal transplant recipients than in immunocompetent patients: the role of azathioprine. *Exp Dermatol*. 2008;**17**:349-55.

133. Basset-Seguin N, Baumann Conzett K, Gerritsen MJP *et al*. Photodynamic therapy for actinic keratoses in organ transplant recipients. *J Eur Acad Dermatol Venereol* 2013;**27**:57-66.

134. Apalla Z, Sotiriou E, Chovarda E, *et al.* Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. *Br J Dermatol* 2010;**162**: 171–175.

135. Svanberg K, Andersson T, Killander D *et al.* Photodynamic therapy of non-melanoma malignant tumours of the skin using topical delta-amino levulinic acid sensitization and laser irradiation. *Br J Dermatol* 1994;**130**:743–51.

136. Edstrom DW, Porwit A, Ros AM. Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: clinical and histological response. *Acta Derm Venereol* 2001;**81**:184–8.

137. Orenstein A, Haik J, Tamir J *et al*. Photodynamic therapy of cutaneous lymphoma using 5-aminolevulinic acid topical application. *Dermatol Surg* 2000;**26**:765–9.

138. Wolf P, Fink-Puches R, Cerroni L, Kerl H. Photodynamic therapy for mycosis fungoides after topical photosensitization with 5-aminolevulinic acid. *J Am Acad Dermatol* 1994;**31**:678–80.

139. Ammann R, Hunziker T. Photodynamic therapy for mycosis fungoides after topical photosensitization with 5-aminolevulinic acid. *J Am Acad Dermatol* 1995;**33**:541.

140. Leman JA, Dick DC, Morton CA. Topical 5-ALA photodynamic therapy for the treatment of cutaneous T-cell lymphoma. *Clin Exp Dermatol* 2002;**27**:516–8.

141. Markham T, Sheahan K, Collins P. Topical 5-aminolaevulinic acid photodynamic therapy for tumour-stage mycosis fungoides. *Br J Dermatol* 2001;**144**:1262–3.

142. Zane C, Venturini M, Sala R, Calzavara.Pinton P. Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed* 2006; **22**:254–8.

143. Fernandez-Guarino M, Harto A, Perez-Garcia B, Montull C, De Las Heras E, Jaen P. Plaque-phase mycosis fungoides treated with photodynamic therapy: results in 12 patients. *Actas Dermosifilogr* 2010;**101**:785-91.

144. Kim ST, Kang DY, Kang JS, Baek JW, Jeon YS, Suh KS. Photodynamic Therapy with Methyl-aminolaevulinic Acid for Mycosis Fungoides. *Acta Derm Venereol* 2012;**92**:264–8.

145. Quéreux G, Brocard A, Saint-Jean M, **et al**. Photodynamic therapy with methyl-aminolevulinic acid for paucilesional mycosis fungoides: A prospective open study and review of the literature. *J Am Acad Dermatol.* 2013;**69**:890-7.

146. Kjeldstad B, Johnsson A. An action spectrum for blue and near ultraviolet inactivation of propionibacterium acnes; with emphasis on a possible porphyrin photosensitization.*Photochem Photobiol*. 1986;**43**:67-70.
147. Divaris DX, Kennedy JC, Pottier RH. Phototoxic damage to sebaceous glands and hair follicles of mice after systemic administration of 5-aminolevulinic acid correlates with localized protoporphyrin IX fluorescence. *Am J Pathol*. 1990;**136**:891-7.
148. Sakamoto FH, Lopes JD, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice Part 1 Acne: when and why consider photodynamic therapy? *J Am Acad Dermatol* 2010; **63**:183–193.
149. Hongcharu W, Taylor CR, Chang Y, *et al*. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J invest Dermatol*. 2000:**115**:183-92.

150. Itoh Y, Ninomiya Y, Tajima S, Ishibashi A. Photodynamic therapy of acne vulgaris with topical delta-aminolaevulinic acid and incoherent light in Japanese patients. *J Dermatol*. 2001: **144**:575-9.
151. Pollock B, Turner D, Stringer MR, *et al.* Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action. *Br J Dermatol*. 2004 ;**151**:616-22.
152.Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *Br J Dermatol*. 2006;**154**:969-76.
153. Hörfelt C, Funk J, Frohm-Nilsson M, Wiegleb Edström D, Wennberg AM. Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. *Br J Dermatol*.2006;**155**:608-13.
154. Hörfelt C, Stenquist B, Larkö O, Faergemann J, Wennberg AM. Photodynamic therapy for acne vulgaris: a pilot study of the dose-response and mechanism of action. *Acta Derm Venereol*. 2007;**87**:325-9.
155. Elman M, Lebzelter J. Light therapy in the treatment of acne vulgaris. *Dermatol Surg*. 2004 ;**30**:139-46.
156. Yang GL, Zhao M, Wang JM, *et al*. Short-term clinical effects of photodynamic therapy with topical 5-aminolevulinic acid for facial acne conglobate: an open, prospective, parallel-arm trial. *Photodermatol Photoimmunol Photomed* 2013;**29**:233-8.
157. Stender IM, Lock-Andersen J, Wulf HC. Recalcitrant hand and foot warts successfully treated with photodynamic therapy with topical 5-aminolaevulinic acid: a pilot study. *Clinical and experimental dermatology* 1999; **24**: 154-9.

158. Stender IM, Na R, Fogh H et al. Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial. *Lancet* 2000; **355**: 963-6.
159. Fernandez-Guarino M, Harto A, Jaen P. Treatment of recalcitrant viral warts with pulsed dye laser MAL-PDT. *Journal of dermatological treatment* 2011; **22**: 226-8.
160. Ohtsuki A, Hasegawa T, Hirasawa Y et al. Photodynamic therapy using light-emitting diodes for the treatment of viral warts. *Journal of dermatology* 2009; **36**: 525-8.
161. Schroeter CA, Kaas L, Waterval JJ et al. Successful treatment of periungual warts using photodynamic therapy: a pilot study. *JEADV* 2007; **21**: 1170-4.
162. Schroeter CA, Pleunis J, van Nispen tot Pannerden C et al. Photodynamic therapy: new treatment for therapy-resistant plantar warts. *Dermatologic surgery* 2005; **31**: 71-5.
163. Smucler R, Jatsova E. Comparative study of aminolevulic acid photodynamic therapy plus pulsed dye laser versus pulsed dye laser alone in treatment of viral warts. *Photomedicine and laser surgery* 2005; **23**: 202-5.
164. Chong WS, Kang GY. Dramatic clearance of a recalcitrant acral viral wart using methyl aminolevulinate-red light photodynamic therapy. *Photodermatology, photoimmunology & photomedicine* 2009; **25**: 225-6.
165. Lu YG, Wu JJ, He Y et al. Efficacy of topical aminolevulinic acid photodynamic therapy for the treatment of verruca planae. *Photomedicine and laser surgery* 2010; **28**: 561-3.
166. Mizuki D, Kaneko T, Hanada K. Successful treatment of topical photodynamic therapy using 5-aminolevulinic acid for plane warts. *Br J Dermatol* 2003; **149**: 1087-8.
167. Fehr MK, Hornung R, Degen A *et al*. Photodynamic therapy of vulvar and vaginal condyloma and intraepithelial neoplasia using topically applied 5-aminolevulinic acid. *Lasers in surgery and medicine* 2002; **30**: 273-9.
168. Yang YG, Zou XB, Zhao H et al. Photodynamic therapy of condyloma acuminata in pregnant women. *Chinese medical journal* 2012; **125**: 2925-8.
169. Stefanaki IM, Georgiou S, Themelis GC et al. In vivo fluorescence kinetics and photodynamic therapy in condylomata acuminata. *Br J Dermatol* 2003; **149**: 972-6.
170. Wang XL, Wang HW, Wang HS et al. Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol* 2004; **151**: 880-5.
171. Chen K, Chang BZ, Ju M et al. Comparative study of photodynamic therapy vs CO2 laser vaporization in treatment of condylomata acuminata: a randomized clinical trial. *Br J Dermatol* 2007; **156**: 516-20.

172. Liang J, Lu XN, Tang H et al. Evaluation of photodynamic therapy using topical aminolevulinic acid hydrochloride in the treatment of condylomata acuminata: a comparative, randomized clinical trial. *Photodermatology, photoimmunology & photomedicine* 2009; **25**: 293-7.
173. Szeimies RM, Schleyer V, Moll I et al. Adjuvant photodynamic therapy does not prevent recurrence of condylomata acuminata after carbon dioxide laser ablation-A phase III, prospective, randomized, bicentric, double-blind study. *Dermatologic surgery* 2009; **35:** 757-64.
174. Asilian A , Davami M. Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. *Clin Exp Dermatol* 2006;**31**:634-7.
175. Pizinger K, Cetkovska P, Kacerovska D , Kumpova M. Successful treatment of cutaneous leishmaniasis by photodynamic therapy and cryotherapy. *Eur J Dermatol* 2009;**19**:172-3.
176. Enk CD, Fritsch C, Jonas F, Nasereddin A, Ingber A, Jaffe CL et al. Treatment of cutaneous leishmaniasis with photodynamic therapy. *Arch Dermatol* 2003;**139**:432-4.
177. Ghaffarifar F, Jorjani O, Mirshams M, Miranbaygi MH , Hosseini ZK. Photodynamic therapy as a new treatment of cutaneous leishmaniasis. *East Mediterr Health J* 2006;**12**:902-8.
178. Sohl S, Kauer F, Paasch U , Simon JC. Photodynamic treatment of cutaneous leishmaniasis. *J Dtsch Dermatol Ges* 2007;**5**:128-30.
179. Gardlo K, Hanneken S, Ruzicka T , Neumann NJ. Photodynamic therapy of cutaneous leishmaniasis. A promising new therapeutic modality. *Hautarzt* 2004;**55**:381-3.
180. van der Snoek EM, Robinson DJ, van Hellemond JJ , Neumann HA. A review of photodynamic therapy in cutaneous leishmaniasis. *J Eur Acad Dermatol Venereol* 2008;**22**:918-22.
181. Enk CD. Treatment of cutaneous leishmaniasis with daylight activated PDT. In: t. A. C. o. t. E. S. f. P. Therapy editor. Madrid 2013.
182. Evangelou G, Krasagakis K, Giannikaki E, Kruger-Krasagakis S , Tosca A. Successful treatment of cutaneous leishmaniasis with intralesional aminolevulinic acid photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2011;**27:**254-6.
183. Akilov OE, Kosaka S, O'Riordan K , Hasan T. Parasiticidal effect of delta-aminolevulinic acid-based photodynamic therapy for cutaneous leishmaniasis is indirect and mediated through the killing of the host cells. *Exp Dermatol* 2007;**16**:651-60.

184. Reveiz L, Maia-Elkhoury AN, Nicholls RS, Romero GA , Yadon ZE. Interventions for American cutaneous and mucocutaneous leishmaniasis: a systematic review update. *PLoS One* 2013;**8**:e61843.
185. Karrer S, Kohl E, Feise K, *et al*. Photodynamic therapy for skin rejuvenation: review and summary of the literature – results of a consensus conference of an expert group for aesthetic photodynamic therapy. *J Dtsch Dermatol Ges* 2013; **11**: 137-148.
186. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic photorejuvenation. *Dermatol Surg* 2002; **28**: 742-744.
187. Avram DK, Goldman MP. Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. *J Drugs Dermatol* 2004;**3**(1 Suppl):S36–9.
188. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20% 5-aminolevulinic acid and intense pulsed light treatment: a split-face comparison study. *J Drugs Dermatol* 2005; **4**: 35–38.
189. Dover JS, Bhatia AC, Stewart B, Arndt KA. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. *Arch Dermatol* 2005; **141**:1247–1252.
190. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. *Dermatol Surg* 2006; **32:** 795–801; discussion 801–803.
191. Bjerring P, Christiansen K, Troilius A, Bekhor P, de Leeuw J. Skin fluorescence controlled photodynamic photorejuvenation (wrinkle reduction). *Lasers Surg Med* 2009; **41**: 327–336.
192. Kosaka S, Yasumoto M, Akilov OE, Hasan T, Kawana S. Comparative split-face study of 5-aminolevulinic acid photodynamic therapy with intense pulsed light for photorejuvenation of Asian skin. *J Dermatol* 2010; **37**: 1005–1010.
193. Haddad A, Santos ID, Gragnani A, Ferreira LM. The effects of increasing fluence on the treatment of actinic keratosis and photodamage by photodynamic therapy with 5-aminolevulinic acid and intense pulsed light. *Photomed Las Surg* 2011; **29**: 427-432.
194. Piccioni A, Fargnoli MC, Schoinas S, *et al*. Efficacy and tolerability of 5-aminolevulinic acid 0.5% liposomal spray and intense pulsed light in wrinkle reduction of photodamaged skin. *J Dermatol Treat* 2011; **22**: 247-253.
195. Xi Z, Shuxian Y, Zhong L, *et al*. Topical 5-aminolevulinic acid with intense pulsed light versus intense pulsed light for photodamage in Chinese patients. *Dermatol Surg* 2011; **37**: 31–40.

196. Babilas P, Knobler R, Hummel S, *et al*. Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: a prospective randomized controlled trial. *Br J Dermatol* 2007; **157**: 111-117.
197. Zane C, Capezzera R, Sala R, Venturini M, Calzavara-Pinton P. Clinical and echographic analysis of photodynamic therapy using methylaminolevulinate as sensitizer in the treatment of photodamaged facial skin. *Lasers Surg Med* 2007; **39**: 203–209.
198. Ruiz-Rodriguez R, Lopez L, Candelas D, Pedraz J. Photorejuvenation using topical 5-methyl aminolevulinate and red light. *J Drugs Dermatol* 2008; **7**: 633-637.
199. Issa MC, Pineiro-Maceira J, Vieira MT, Olej B, Mandarim-de-Lacerda CA, Luiz RR, Manela-Azulay M. Photorejuvenation with topical methyl aminolevulinate and red light: a randomized, prospective, clinical, histopathologic, and morphometric study. *Dermatol Surg* 2010; **36**:39-48.
200. Sanclemente G, Medina L, Villa JF, Barrera LM, Garcia HI. A prospective split-face double-blind randomized placebo-controlled trial to assess the efficacy of methyl aminolevulinate + red-light in patients with facial photodamage. *J Eur Acad Dermatol Venereol* 2011; **25**: 49-58.
201. Gold MH. The evolving role of aminolevulinic hydrochloride with photodynamic therapy in photoaging. *Cutis* 2002; **69**: 41-46.
202. Goldman MP, Atkin D, Kincad S. PDT/ALA in the treatment of actinic damage: real world experience. *J Las Med Surg* 2002; **14** (S): 24.
203. Touma D, Yaar M, Whitehead S, Konnikov N, Gilchrest BA. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol* 2004; **140**: 33–40.
204. Torezan L, Chaves Y, Niwa A, Sanches JA, Festa-Neto C, Szeimies RM. A pilot split-face study comparing methyl aminolevulinate-photodynamic therapy (PDT) with microneedling-assisted PDT on actinically damaged skin. *Dermatol Surg* 2013; **39**: 1197-1201.
205. Ruiz-Rodriguez R, López L, Candelas D, Zelickson B. Enhanced efficacy of photodynamic therapy after fractional resurfacing: fractional photodynamic rejuvenation. *J Drugs Dermatol* 2007; **6**: 818–820.
206. Marmur ES, Phelps R, Goldberg DJ. Ultrastructural changes seen after ALA-IPL photorejuvenation: a pilot study. *J Cosmet Laser Ther* 2005; **7**: 21–24.

207. Orringer JS, Voorhees JJ, Hamilton T, Hammerberg C, Kang S, Johnson TM, Karimipour DJ, Fisher G. Dermal matrix remodeling after nonablative laser therapy. *J Am Acad Dermatol* 2005; **53**: 775–782.

208. Park MY, Sohn S, Lee ES, Kim YC. Photorejuvenation induced by 5-aminolevulinic acid photodynamic therapy in patients with actinic keratosis: a histologic analysis. *J Am Acad Dermatol* 2010; **62**: 85–95.

209. Park JY, Jang YH, Kim YS, Sohn S, Kim YC. Ultrastructural changes in photorejuvenation induced by photodynamic therapy in a photoaged mouse model. *Eur J Dermatol* 2013; 23:471-7.

210. Jang YH, Koo GB, Kim JY, Kim YS, Kim YC. Prolonged activation of ERK contributes to the photorejuvenation effect in photodynamic therapy in human dermal fibroblasts. *J Invest Dermatol* 2013, **133**:2265-2275.

211. Bagazgoitia L, Cuevas Santos J, Juarranz A, Jaén P. Photodynamic therapy reduces the histological features of actinic damage and the expression of early oncogenic markers. *Br J Dermatol* 2011; **165**: 144–151.

212. Calzavara-Pinton PG, Rossi MT, Aronson E, Sala R; Italian Group For Photodynamic Therapy. A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinate (MAL-PDT) in 20 Italian dermatology departments. Part 1: inflammatory and aesthetic indications. *Photochem Photobiol Sci*. 2013;**12**(1):148-57.

213. Schleyer V, Radakovic-Fijan S, Karrer S, et al. Disappointing results and low tolerability of photodynamic therapy with topical 5-aminolaevulinic acid in psoriasis.A randomized, double-blind phase I/II study. *J Eur Acad Dermatol Venereol* 2006; **20**: 823–828.

214. Alster TS, Tanzi EL. Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia*. J Drugs Dermatol*. 2003;**2**(5):501–4.

215. Sakamoto F, Izikson L, Tannous Z, Zurakowski D, Anderson RR. Surgical scar remodelling after photodynamic therapy using aminolaevulinic acid or its methylester: a retrospective, blinded study of patients with field cancerization. *Br J Dermatol* 2012; **166**: 413–416.

216. Campbell SM, Tyrrell J, Marshall R, Curnow A. Effect of MAL-photodynamic therapy on hypertrophic scarring. *Photodiagn Photodyn Ther* 2010; **7**: 183–188.

217. Ud-Din S, Thomas G, Morris J, et al. Photodynamic therapy: an innovative approach to the treatment of keloid disease evaluated using subjective and objective non-invasive tools. *Arch Dermatol Res* 2013; **305**: 205-214.

218. Hillemanns P, Untch M, Pro□ve F, Baumgartner R, Hillemanns M, Korell M. Photodynamic therapy of vulvar lichen sclerosus with 5-aminolevulinic acid. *Obstet Gynecol.* 1999;**93**(1):71–4.

219. Romero A, Hernández-Núñez A, Córdoba-Guijarro S, Arias-Palomo D, Borbujo-Martínez J. Treatment of recalcitrant erosive vulvar lichen sclerosus with photodynamic therapy. *J Am Acad Dermatol.* 2007; **57**(2 Suppl):S46–7.

220. Sotiriou E, Apalla Z, Patsatsi A, Panagiotidou D. Recalcitrant vulvar lichen sclerosis treated with aminolevulinic acid-photodynamic therapy: a report of five cases. *J Eur Acad Dermatol Venereol.* 2008;**22**(11): 1398–9.

221. Weisenseel P, Kuznetsov AV, Molin S, Ruzicka T, Berking C, Prinz JC. Photodynamic therapy for granuloma annulare: more than a shot in the dark. *Dermatology* 2008;**217**:329-32.

222. Berking C, Hegyi J, Arenberger P, Ruzicka T, Jemec GB. Photodynamic therapy of necrobiosis lipoidica-a multicenter study of 18 patients. *Dermatology* 2009;**218**:136-9.

223. Soler AM, Warloe T, Berner A, Giercksky KE. A follow-up study of recurrrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. *Br J Dermatol* 2001; **145**: 467-471.

224. Pariser DM, Lowe NJ, Stewart DM et al. Photodynamic therapy with topical methyl aminolevulinate (Metvix®) is effective and safe in the treatment of actinic keratoses: results of a prospective randomized trial. *J Am Acad Dermatol* 2003; **48**: 227-232.

225. Lehmann P. Nebenwirkungen der topischen photodynamischen Therapie. *Hautarzt* 2007; **58**: 597-603.

226. Gholam P, Kroehl V, Enk AH. Dermatology life quality index and side effects after topical photodynamic therapy of actinic keratosis. *Dermatology* 2013; **226**: 253-259.

227. Schmutz JL, Barbaud A, Trechot P. Erosive pustulosis on the scalp following dynamic phototherapy. *Ann Dermatol Venereol* 2010; **137**: 86.

228. Harries MJ, Street G, Gilmour E, Rhodes LE, Beck MH. Allergic contact dermatitis to methyl aminolevulinate (Metvix) cream used in photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2007; **23**: 35-36.
229. Korshoj S, Solvsten H, Erlandsen M, Sommerlund M. Frequency of sensitization to methyl aminolaevulinate after photodynamic therapy. *Contact Dermatitis* 2009; **60**: 320-324.
230. Wolfe CM, Green WH, Hatfield HK, Cognetta AB jr. Urticaria after methyl aminolevulinate photodynamic therapy in a patient with nevoid basal cell carcinoma syndrome. *J Drugs Dermatol* 2012; **11**: 1364-1365.
231. Borroni RG, Cargno A, Rivetti N, Arbustini E, Brazzelli V. Risk of acute postoperative hypertension after topical photodynamic therapy for non-melanoma skin cancer. *Photodermatol Photoimmunol Photomed* 2013; **29**: 73-77.
232. Rakvit P, Kerr AC, Ibbotson SH. Localized bullous pemphigoid induced by photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2011; **27**: 251-253.
233. Mikolajewska P, Rømoen OT, Martinsen OG, Iani V, Moan J, Grimnes S, Juzeniene A.Bioimpedance for pain monitoring during cutaneous photodynamic therapy: Preliminary study. *Photodiagnosis Photodyn Ther*. 2011;**8**:307-13.
234. Zeitouni NC, Paquette AD, Housel JP, *et al*. A retrospective review of pain control by a two-step irradiance schedule during topical ALA-photodynamic therapy of non-melanoma skin cancer. *Lasers Surg Med.* 2013;**45**:89-94.
235. Grapengiesser S, Ericson M, Gudmundsson F, Larkö O, Rosén A, Wennberg AM. Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol*. 2002;**27**:493-7.
236. Sandberg C, Stenquist B, Rosdahl I, Ros AM, Synnerstad I, Karlsson M, Gudmundson F, Ericson MB, Larkö O, Wennberg AM. Important factors for pain during photodynamic therapy for actinic keratosis. *Acta Derm Venereol*. 2006;**86**:404-8.
237. Halldin CB, Gillstedt M, Paoli J, Wennberg AM, Gonzalez H. Predictors of pain associated with photodynamic therapy: a retrospective study of 658 treatments. *Acta Derm Venereol.* 2011;**91**:545-51.
238. Ericson MB, Sandberg C, Stenquist B, Gudmundson F, Karlsson M, Ros AM, Rosén A, Larkö O, Wennberg AM, Rosdahl I. Photodynamic therapy of actinic keratosis at varying fluence rates: assessment of photobleaching, pain and primary clinical outcome. *Br J Dermatol*. 2004;**151**:1204-12.
239. Paoli J, Halldin C, Ericson MB, Wennberg AM. Nerve blocks provide effective pain relief during topical photodynamic therapy for extensive facial actinic keratoses. *Clin Exp Dermatol*. 2008;**33**:559-64.

240. Halldin CB, Paoli J, Sandberg C, Gonzalez H, Wennberg AM. Nerve blocks enable adequate pain relief during topical photodynamic therapy of field cancerization on the forehead and scalp. *Clin Exp Dermatol*. 2008;**33**:559-64.
241. Serra-Guillen C, Hueso L, Nagore E, *et al*. Comparative study between cold air analgesia and supraorbital and supratrochlear nerve block for the management of pain during photodynamic therapy for actinic keratosis of the frontotemporal zone. *Br J Dermatol*. 2009;**161**:353-6.

Appendix 1: Strength of recommendations, Quality of evidence

Strength of recommendations

A There is good evidence to support the use of the procedure
B There is fair evidence to support the use of the procedure
C There is poor evidence to support the use of the procedure
D There is fair evidence to support the rejection of the use of the procedure
E There is no evidence to support the rejection of the use of the procedure

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial
II-i Evidence obtained from well-designed controlled trials without randomization
II-ii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length of compreheniveness of follow up, or conflicts in evidence

Table 1: Treatment protocols for licensed indications – Adapted from reference 3

	Indication	Preparation/drug application	Illumination recommendations	Protocol	Reference
16.0% MAL (Metvix(R) Lausanne, CH)	Thin, non-hyper keratotic AK (face/scalp), SCC *in-situ*, sBCC,nBCC	Remove scales/crusts, roughen surface (remove intact epidermis over nBCC) Apply a layer of cream approx 1mm thick via spatula to lesion and surrounding 5-10mm of skin. Cover with occlusive dressing for 3 hours, then wipe clean with saline	After 3 hours, remove dressing, wipe clean with saline, then illuminate using red light of spectrum 570-670nm, total dose 75 J/cm2 (red light with narrower spectrum, giving the same activation, can be used: ~630nm, tlight dose of 37 J/cm²)	AK – one treatment, assess 3 months, SCC *in-situ* and BCC – two sessions 7 days apart, reassess after 3 months. Remaining lesions may be retreated	Full details @ http://www.medicines.org.uk/emc/medicine/11913/SPC (accessed 12/11/13)
8 mg 5-ALA (2 mg/cm²) medicated plaster (Alacare(R), Galderma Spirig AG, Egerkingen, CH)	Mild AK (≤ 1.8 cm in diameter) face/bald scalp	Apply medicinal plaster up to a maximum of 6 patches on 6 different lesions. Incubate for 4 hours.	After 4 hours, remove plaster and expose to red light with a narrow spectrum device (spectrum of 630 ± 3 mm, total light dose of 37 J/cm2).	Single use treatment, reassess after 3 months, retreat remaining lesions with alternative therapies.	Full details @ http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1356931026870.pdf (accessed 12/11/13)
78 mg/g 5-ALA gel (Ameluz(R), Biofrontera Bioscience, Leverkusen, DE)	Mild to moderate AK face/scalp	Remove scales/crusts, gently roughen surface, degrease skin. Apply a layer of cream approx 1mm thick via spatula or protected fingertips to lesion and surrounding 5mm of skin. Cover with occlusive dressing for 3 hours.	After 3 hours, remove dressing, wipe clean, then illuminate using red light either with a narrow spectrum (~630 nm, light dose 37 J/ cm²) or a broader, continuous spectrum (570-670 nm, light dose 75-200 J/cm2).	One treatment, reassess after 3 mths, remaining lesions may be retreated	Full details @ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002204/WC500120044.pdf (accessed 12/11/13)
20% ALA solution (Levulan Kerastick™) (DUSA Wilmington, MA)	Minimal/ moderate AK, face/scalp	Lesions should be clean and dry. Following solution admixture, apply directly to lesions by dabbing gently with the wet applicator tip, and reapply once dry. Treatment site not occluded, but protect from sun/bright light	After 14-18hrs, 10 J/cm2 light dose BLU-U (1,000sec), positioning lamp as per manufacturer's instructions	One application and one dose of illumination per treatment site per 8-week treatment session	Full details @ http://www.dusapharma.com/kerastick.html (accessed 12/11/13)