REVIEW ARTICLE

European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma

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Abstract

Topical photodynamic therapy (PDT) is a widely used non-invasive treatment for certain non-melanoma skin cancers, permitting treatment of large and multiple lesions with excellent cosmesis. High efficacy is demonstrated for PDT using standardized protocols in non-hyperkeratotic actinic keratoses, Bowen's disease, superficial basal cell carcinomas (BCC) and in certain thin nodular BCC, with superiority of cosmetic outcome over conventional therapies. Recurrence rates following PDT are typically equivalent to existing therapies, although higher than surgery for nodular BCC. PDT is not recommended for invasive squamous cell carcinoma. 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. Reduced discomfort has been observed with novel protocols including shorter photosensitizer application times and in daylight PDT for actinic keratoses.
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[Correction added on 30 November 2012, after first online publication: conflict of interest statement was amended.]

Disclaimer

The following guidelines are based on the best evidence available at the time of publication and caution should be exercised when interpreting data where there is a limited evidence base. It may be necessary to depart from the guidelines in the interests of specific patients and circumstances.

Introduction

This guideline seeks to promote safe and effective practice across Europe for the delivery of topical photodynamic therapy (PDT) in dermatological indications and reflects evidence derived from a systematic literature review (using MEDLINE), and previous therapy guidelines.[1,2] There is a substantial literature on novel indications for topical PDT and these are reviewed in Part II.[3]

Topical PDT has, to date, been approved for the treatment of certain non-melanoma skin cancers (NMSC). Currently, only three photosensitizing agents are licensed for use in Europe (Table 1). One is methyl aminolaevulinate (MAL) Metvix®/Metvixia® (Galderma, Lausanne, Switzerland). MAL is used along with red light to treat non-hyperkeratotic actinic keratoses (AK), Bowen's disease (BD), superficial and nodular basal cell

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carcinomas (BCC), although approvals vary between countries. A patch containing 5-ALA (Alacare®; 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, and BF-200 ALA (Ameluz®; Biofrontera AG, Leverkusen, Germany) is licensed for PDT in combination with red light. Another formulation of 5-ALA, Levulan (DUSA Pharmaceuticals, Wilmington, MA, USA), is approved in North 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 aminolaevulinic acid (ALA) made in hospital pharmacies, so caution is advised in comparison of results.

Photosensitizers

PDT for dermatological indications, first described over 20 years ago, typically involves the topical application of the photosensitizer prodrug, ALA or its methylated ester MAL, which are converted by the haem biosynthetic pathway predominantly to protoporphyrin IX (PpIX) and activated by light of an appropriate wavelength, producing reactive oxygen species, especially singlet oxygen, resulting in apoptosis and necrosis of target tissue.[4] Selective uptake of the prodrugs is probably due to altered surface permeability over lesions and different rates of porphyrin metabolism, with activated lymphocytes also accumulating photosensitizer.[5,6]

ALA is hydrophilic whereas 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 and nodular BCC failed to show a difference in response.[7,8] Recently, the nanoemulsion BF-200 ALA, which improves ALA stability and skin penetration, was compared with MAL for thin/moderate thickness face/scalp AK, with a higher patient complete clearance of 78% vs. 64% respectively.[9]

A self-adhesive, skin-coloured thin 5-ALA patch, directly applied to AK lesions without crust removal was superior to cryotherapy in clearing mild/moderate AK.[10]

Enhancing penetration of a photosensitizer using iontophoresis or chemical enhancers may increase the efficacy of PDT, but remains experimental. Elevating skin temperature during ALA application may also improve efficacy as PpIX production is a temperature-dependent process.[11]

MAL-PDT is delivered using a standardized protocol of two treatments 1 week apart for BCC and BD, but with only one initial treatment for AK, repeated at 3 months only if required.[12] MAL is typically applied for 3 h, but Levulan ALA although licensed for an 18–24 h application, is widely used with shorter application intervals around 1 h.[13] A shorter 1-h incubation for MAL-PDT in AK is also an option with no significant difference in clearance rates when compared (1 h:76%, 3 h:85%).[14]

Several novel topical photosensitizers including hypericin and silicon phthalocyanine have been assessed in a variety of cutaneous neoplasms, but await commercialization.[15–17]

Light sources and dosimetry

A range of light sources can be used for topical PDT including lasers, filtered xenon arc, metal halide or fluorescent lamps and light emitting diodes (LED). Large fields can be treated using narrowband LED devices, e.g. the Aktilite 128 (Galderma, Lausanne, Switzerland) and the Omnilux (Phototherapeutics Ltd, London, UK). These red LED sources match the 630/635-nm activation peak of PpIX while excluding the extraneous wavelengths present in broadband lights, thus permitting shorter illumination times. Filtered intense pulsed lights (IPLs) have been successfully used in PDT for AK, although phototoxic effects may not match cut-off filter notations provided by their manufacturers.[18] 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.[9,19]

Protoporphyrin IX has its largest absorption peak in the blue region at 410 nm with smaller absorption peaks at 505, 540, 580 and 630 nm. Most light sources for PDT seek to utilize the 630-nm red absorption peak, to improve tissue penetration. However, a blue fluorescent lamp (peak emission 417 nm) is used in Levulan-PDT.

Fractionation (discontinuous illumination) can improve tumour responsiveness by permitting tissue reoxygenation during 'dark' periods. Studies support the superiority of fractionation to conventional illumination in ALA-PDT for superficial BCC (97% vs. 89%), but not in Bowen's disease.[20,21] Overall clearance of 95% after 2 years was achieved for 552 NMSC lesions following ALA-PDT using two light fractions of 20 and 80 J/cm^2; at 4 and 6 h.[22] Another group has shown superior clearance of fractionated lesions by ALA-PDT (using the same protocol) at 3 months of 96% AK compared with 89% for lesions treated twice 7 days apart, with 12-month clearance rates of 94% and 85%.[23] An alternative ALA-PDT fractionation protocol of two doses of 75J/cm^2; at 4 and 5 h was associated with initial clearance of 94% nBCC, but with a cumulative failure rate of 30% by 3 years.[24]

PDT using daylight (MAL for 0.5 h, then daylight for 2.5 h) has been shown to be as effective as conventional red light MAL-PDT in AK, but with minimal or no therapy-related pain.[25] The same group has demonstrated no inferiority by reducing daylight exposure to 1.5 h in a study of thin AK, an observation replicated in another study of all severity grades of AK, although with poorer response rates for moderate and thick AK and variation in response between centres.[26,27] A recent international consensus highlighted the convenience of daylight PDT for patients with multiple AK requiring field therapy, but careful scheduling is required, giving consideration to time of the year when suitable daylight and tolerable weather conditions prevail, with use of an appropriate sunscreen to the entire sun-exposed area.[28]

There is also an option for ambulatory PDT where patients wear a portable LED light source with low irradiance over 100 min. In two small pilot studies, the device has been effective

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in treating BD and sBCC, clearing 11 of 17 lesions with minimal pain in most.[29,30]

Lesion preparation

Gentle removal of overlying crust and scale is commonly performed for moderate thickness/hyperkeratotic AK, BD and sBCC when using 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,[11,14] whereas others have not noted increased drug uptake following lesion preparation of BD and BCC (in a study of 4- and 6-h ALA application possibly indicating reduced need with longer application times) and lesion preparation is not necessary when using a novel ALA patch.[10,31,32]

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 PDT operators perform a more significant preparation with debulking curettage, 3 weeks prior to ALA-PDT, clearing 92% of nBCC in a single treatment, although no comparison without prior curettage was made.[33] In a small comparison study of PDT (ALA and MAL) with or without debulking immediately before application of pre-photosensitizer, residual nBCC was more often observed in lesions that were not debulked.[7] Additional preparation techniques reported include microneedling, skin vapourization with CO_2 laser or ablative fractional resurfacing.[34–36]

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 deeper photosensitizer penetration before photoactivation. Occlusion is standard practice in MAL-PDT of AK, Bowens and BCC, but is not performed when using Levulan-ALA. When daylight was compared with conventional PDT, no difference in efficacy was noted between 0.5-h and 3-h occlusion intervals and recent studies recommend no occlusion, yet report equivalent efficacy in AK.[26]

Fluorescent diagnosis

The detection of skin surface fluorescence, either subjectively using simple handheld Wood's lamp (long wave UVA) or semiquantitatively using CCD camera systems coupled to digital imaging, is used to help delineate lesions and can be useful in identifying persistent/recurrent disease.[37,38] PpIX fluorescence imaging to determine tumour boundaries during Mohs micrographic surgery has shown inconsistent results regarding improvement in surgical efficacy.[39] Fluorescence diagnosis was not substantially superior to clinical assessment in a study of 28 BCC where tumours were excised on the basis of fluorescence outline with failure of correlation of the margin with histopathological tumour border in six lesions.[40]

Extent of photobleaching during PDT, but not total initial protoporphyrin IX fluorescence, is predictive of lesion clearance.[41] In another study, fluorescence diagnosis in keratinocyte intraepidermal neoplasias was unable to discriminate between lesions or proliferative activity.[42] Intensity of pain has been associated with fluorescence and may anticipate patients more likely to require anaesthesia.[43]

Actinic Keratoses (Strength of Recommendation A, Quality of Evidence I)

Thin and moderate thickness AK on the face and scalp respond well to topical PDT, with typical clearance rates of 89–92% 3 months after therapy, equivalent or superior to cryotherapy, depending on protocol.[44–46] One-year sustained lesion clearance rates of 78% and 63–69% have been reported following ALA-PDT (up to two treatments) and patch ALA-PDT (single treatment) respectively.[32,47]

Current licensed use recommends that for AK, MAL-PDT be given as a single treatment and repeated if required after 3 months, reflecting equivalent efficacy in a comparison study with double therapy 7 days apart.[45] A large randomized intraindividual study of face/scalp AK in 119 patients used this protocol to compare MAL-PDT with cryotherapy.[46] After the initial cycle of treatments, PDT cleared more lesions (87% vs. 76%), but with equivalent outcome after non-responders were retreated (89% vs. 86%).

Efficacy of PDT for AK on acral sites is reduced by approximately 10% to that for face/scalp lesions, probably in part due to a higher proportion of less-responsive thicker lesions on these sites. When compared, MAL-PDT was less effective than cryotherapy for acral AK (lesion clearance 78% vs. 88% at 6 months).[48] In a right/left comparison study with imiquimod, ALA-PDT cleared significantly more moderate AK lesions (58% vs. 37%), and equivalent numbers of thin AK on the hands/forearms (72% lesions).[49]

As reviewed above, several novel methods of delivering PDT have been used to treat AK, including the adhesive patch, daylight, ambulatory light sources and fractionated light protocols. Licensed recently, PDT using the BF-200 ALA was superior to MAL with clearance of 90% vs. 83% of thin/moderate thickness face/scalp AK (complete clearance rates of 78% vs. 64%) 12 weeks after one or two PDT treatments.[9]

PDT may be a useful therapy for patients with actinic cheilitis. Clearance was achieved in 26/40 patients after ALA-PDT (two treatments 2 weeks apart), although with histological recurrence in nine during 18 months of follow-up.[50] Two sessions of MAL-PDT 1 week apart achieved clinical clearance in 7/15 patients, although histological clearance was evident in only 4/7.[51] A recent study achieved superior results using sequential MAL-PDT then imiquimod 5% cream with complete clinical cure of 80% and histological cure of 73%.[52]

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Guidelines identify PDT as effective both as a lesion and field-directed treatment for AK and suggest PDT has a role where AK are multiple and/or confluent, at sites of poor healing, or where there has been a poor response to other topical therapies.[53,54] In a randomized comparison of patient tolerance to MAL-PDT or topical imiquimod for multiple face/scalp AK, a significantly higher level of satisfaction was observed following PDT.[55]

Bowen's Disease (Strength of Recommendation A, Quality of Evidence I)

Invasive SCC (Strength of Recommendation D, Quality of Evidence II-iii)

A patient can expect clearance of 86–93% of BD lesions (squamous cell carcinoma in situ) 3 months beyond one or two cycles of MAL-PDT using red light, respectively, (two treatments 7 days apart as one cycle) with sustained clearance at 24 months of 68–71%, equivalent to conventional therapy, but with superior cosmesis.[56,57] Another study observed 76% clearance rate after two sessions of MAL-PDT and median follow-up of 16 months.[58]

MAL-PDT is effective in treating lesions over 3 cm, with 96% lesions cleared 3 months after one cycle of two treatments 7 days apart, with only three recurrences by 1 year.[59] PDT has been reported to clear digital, subungual and nipple BD and where it arises in a setting of poor healing (lower leg, epidermolysis bullosa and radiation dermatitis).[2] PDT may offer an alternative for treating penile intraepithelial neoplasia, with one large series using both ALA- and MAL-PDT in 10 patients showing clearance in 7, but later recurrence in 4.[60]

Therapy guidelines recommend PDT as the treatment of choice for both large and small plaques of BD on poor-healing sites, representing the majority of lesions, and a good choice for large lesions in good-healing sites.[61] There is reduced efficacy of PDT for microinvasive and for 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 that 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.[57]

Superficial Basal cell carcinoma (Strength of Recommendation A, Quality of Evidence I)

Nodular Basal cell carcinoma (Strength of Recommendation A, Quality of Evidence I)

Clearance rates at 3 months of 92–97% following MAL-PDT for primary superficial BCC are observed with protocols of either one single initial treatment or two treatments 7 days apart, followed by a repeat two-treatment cycle at 3 months, if required.[62,63] 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. A weighted initial clearance rate of 87% was noted for sBCC treated by ALA-PDT in a review of 12 studies, compared with 53% for nodular lesions.[64]

Thicker lesions appear less responsive to PDT and lesions in the H-zone also have reduced sustained clearance rates.[65,66] Clearance at 3 months of 91% of primary nBCC following MAL-PDT is reported, with 76% still clear at 5 years.[12,67]

Comparison of ALA-PDT with cryotherapy for BCC showed equivalent efficacy with superior cosmesis.[68] Clearance rates were also equivalent for MAL-PDT vs. cryotherapy for sBCC, 97% and 95% at 3 months, respectively, with overall clearance after 5 years identical at 76% of lesions initially treated, but with superior cosmesis post-PDT.[62]

MAL-PDT was equivalent to surgery (92% vs. 99% initial clearance, 9% and 0% recurrences at 1 year) for sBCC, but inferior to surgery for nBCC when recurrence rates were compared (91% vs. 98% initial clearance, 14% and 4% recurrences at 5 years).[63] Cosmetic outcome was superior following PDT compared with surgery. In a randomized pilot study of PDT with minimal curettage pre-ALA application vs. conventional surgery, there was no evidence of superiority of PDT over surgery.[69] Overall histologically confirmed response rates of 73% were reported following MAL-PDT for nBCC, using the standard licensed protocol, although 89% of facial BCC cleared.[70] 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, although no debulking of the tumour mass was performed.[71]

Fractionated ALA-PDT was equivalent to surgery in initially clearing nBCC, but with a 30% failure rate over 3 years after PDT when a 75J/75J protocol was used, although in another study, 80% of nBCC remained clear at 2 years using a 20J/80J fractionated dosing described above.[22,24]

A 6-year clinical and histological follow-up of 53 BCCs, originally less than 3.5-mm thick, and treated by one or two sessions of ALA-PDT using the penetration enhancer dimethylsulphoxide and with prior lesion curettage, reported 81% of sites as disease free.[72]

PDT is a potentially useful option for patients with naevoid BCC syndrome (NBCCS), with series and cases reported and a large cohort of 33 patients treated by topical or systemic PDT, depending on whether lesions were less than/greater than 2 mm in thickness when assessed by ultrasound.[2,73] MAL-PDT for NBCCS can improve patient satisfaction and reduces the need for surgical procedures.[74]

Topical PDT is recommended for primary superficial and thin low-risk nodular BCC, but is a relatively poor choice for high-risk lesions including morphoeic BCC.[75] PDT is best considered for nodular lesions where surgical excision is relatively contraindicated, or where patient preference, reflecting past therapy history, comorbidities and/or cosmetic considerations result in a willingness to accept higher risk of recurrence. It is advised that patients receiving topical PDT for nodular BCC are reviewed for evidence of recurrence for at least 1 year.

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Table 1: Treatment protocols for licensed indications

	Indication	Preparation/drug application	Illumination recommendations	Protocol	Reference
16.0% MAL Metvix® /Metvixia® (Galderma)	Thin, non-hyper keratotic AK (face/scalp), Bowens, superficial/ nodular BCC	Remove scales/crusts, slightly roughen surface (remove intact epidermis overlying nBCC) Apply a layer of cream approx 1-mm thick via spatula to lesion and surrounding 5–10 mm of skin. Cover with occlusive dressing for 3 h, then wipe clean with saline	After 3 h, remove dressing, wipe clean with saline, then illuminate using red light of spectrum 570–670 nm, total dose 75 J/cm^2 (red light with narrower spectrum can be used)	AK – one treatment, assess 3 months, BD 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/Metvix+160 + mg+g+cream/ (accessed 24/12/11)
8 mg 5-ALA (2 mg/cm^2;) medicated plaster (Alacare®, Spirig AG)	Mild AK (≤1.8 cm in diameter) face/bald scalp (hairless areas)	Apply medicinal plaster up to a maximum of six patches on six different lesions. Incubate for 4 h.	After 4 h, remove plaster and expose to red light with a narrow spectrum device (spectrum of 630 ± 3 mm, total light dose of 37 J/cm^2).	Single use treatment, reassess after 3 months, retreat remaining lesions with alternative therapies.	Full details @ http://www.mhra.gov.uk /home/groups/par/documents /websiteresources /con057372.pdf (published 28.9.2009)
78 mg/g 5-ALA gel (Ameluz®; Biofrontera Bioscience)	Mild to moderate AK (Olsen 1 and 2), face /scalp	Remove scales/crusts, gently roughen surface, degrease skin. Apply a layer of cream approx 1-mm thick via spatula or protected fingertips to lesion and surrounding 5–10 mm of skin. Cover with occlusive dressing for 3 h, then wipe off remnant gel.	After 3 h, remove dressing, wipe clean, then illuminate using red light either with a narrow spectrum (~630 nm, light dose 37 J/cm^2;) or a broader, continuous spectrum (570–670 nm, light dose 75- 200 J/cm^2).	One treatment, reassess after 3 months, remaining lesions may be retreated.	Full details @ http://www.ema.europa.eu/ema /index.jsp?curl=pages/medicines /human/medicines/002204 /human_med_001528.jsp&mid =WC0b01ac058001d124 (published 09/01/2012)
20% ALA solution (Levulan Kerastick™; DUSA Pharmaceuticals)	Minimal /moderate thickness 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 14–18 h, 10 J/cm^2 light dose BLU-U (1000 s), 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/levulan-product-information.html (accessed 24/12/11)

ALA, aminolaevulinic acid; AK, actinic keratoses; BCC, basal cell carcinomas; BD, Bowen's disease; MAL, methyl aminolaevulinate.

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Adverse effects

Pain/burning sensation is often experienced during PDT, although varying widely in severity, usually developing within minutes of commencing light exposure and probably reflects nerve stimulation and/or tissue damage by reactive oxygen species, possibly aggravated by hyperthermia. Most patients tolerate PDT without anaesthesia, but pain is more likely to be experienced if large fields are treated, especially on well-innervated areas (face, scalp, hands, perineum), and is more common when treating AK than Bowen's/BCC.[76-79] Patients with sensitive skin types appear more prone to pain. The second treatment of a two-therapy cycle may be more painful.[80]

PDT with MAL has been stated to be less painful than ALA-PDT in comparison trials of scalp AK, although longer application time of ALA (5–6 h vs. 3 h) may have contributed[7,81] Greater pain was observed in comparison of ALA- with MAL-PDT in tape-stripped normal skin.[82] In a recent comparison of ALA and MAL in PDT for NMSC, both applied for 4 h, MAL-PDT was less painful on the head, but not on the trunk and extremities.[83] In a single-centre retrospective study comparing BP-200 ALA with MAL-PDT for AK, patients treated using MAL had a lower mean pain score and fewer treatment interruptions, although a similar level of pain was observed in a large randomized blinded comparison of BF-200 ALA with MAL for AK.[9,84]

The topical anaesthetics, tetracaine gel, a mixture of lignocaine 2.5% and prilocaine 2.5% or morphine gel, have not been shown to reduce pain significantly during PDT.[85–87] Cold-air analgesia, using a device to blow air at a temperature of −35°C, reduced pain duration and severity in a study of ALA-PDT for BD and BCC, although cooling may slow the photodynamic reaction.[88] Transcutaneous nerve stimulation appears to have limited effect.[89]

Nerve blocks are useful for large field treatments (e.g. forehead, entire scalp), more effective than cold-air analgesia in a split-face controlled study of MAL-PDT during treatment of multiple AK in the frontal region.[90–92]

PDT using low-intensity light (daylight, ambulatory) is less painful, but results in prolonged treatment times. PDT using a variable pulsed light was associated with reduced pain compared with standard red light MAL-PDT, whereas MAL-PDT using visible light plus water-filtered infrared A was equivalent in efficacy, but was almost painless.[93,94]

Erythema and oedema are common post-PDT, with erosion, crust formation and healing over 2–6 weeks, but ulceration is rare. Urtication of treatment sites has been described and is probably an exaggeration of the normal inflammatory response to PDT.[95] Following PDT, localized photosensitivity can remain for up to 48 h, ALA degrading with a half-life of about 24 h, and MAL-induced PpIX clearing from normal skin within 24–48 h.[96,97] Postinflammatory hypo- and hyperpigmentation are rarely observed.[98] Hair loss is also possible, given concomitant sensitization of pilosebaceous units, but is more often observed with PDT for indurated BCC than AK.[99] A clinically obvious scar is rarely observed following PDT.

There is a risk of sensitization to MAL that might give an exaggerated response to patients receiving further PDT with the same drug formulation.[100–103]

Two case reports of melanoma within the field of previous PDT and of SCC developing following PDT (supplemented by topical 5-fluorouracil) for penile intraepithelial neoplasia could represent evidence of progression, but the melanomas may well have arisen coincidentally, and the SCC development may be due to incomplete response of the PIN to two therapy modalities.[104-106]

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Appendix I

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 good evidence to support the rejection of the use of the procedure

Appendix II

Quality of evidence

I. Evidence obtained from at least one properly designed, randomized control trial
II-i Evidence obtained from well-designed control trials without randomisation
II-ii Evidence obtained from well-designed cohort or case-control analytic 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 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 comprehensiveness of follow-up or conflicts in evidence).

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