NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of photodynamic therapy for non-melanoma skin tumours (including premalignant and primary, non-metastatic skin lesions)

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2005.

Procedure name

- Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary, non-metastatic skin lesions)

Specialty societies

Specialist advice was sought from:

- British Association of Dermatologists.
- British Association of Plastic Surgeons.

Description

Indications

Non-melanoma skin tumours include primary (non-metastatic) malignant lesions such as basal cell carcinoma and squamous cell carcinoma, and premalignant lesions such as Bowen's disease and actinic (or solar) keratoses.

Basal cell carcinoma (also known as rodent ulcer) is the most common form of skin cancer in humans. There are several clinical and histological sub-types, including nodular and superficial, and these may behave differently. Basal cell carcinoma is generally a slow-growing, locally invasive epidermal skin tumour that rarely spreads to other distant parts of the body. Although it is not usually life threatening, the tumour can cause extensive tissue destruction if it is not treated adequately.

Squamous cell carcinoma is the second most common type of skin cancer in the UK. It arises from cells in the epidermis and spreads into the surrounding skin. It can also spread to nearby lymph nodes and may be life-threatening in rare cases.

Bowen's disease (also known as squamous cell carcinoma *in situ*) is a very early form of non-melanoma skin cancer. If it is not treated, it can progress to invasive squamous cell carcinoma.

Actinic keratoses are small lumps of hard skin that are usually harmless but they have the potential to develop into invasive squamous cell carcinoma. Although the risk of progression is small, it is impossible to predict which lesions will progress to squamous cell carcinoma.

Current treatment and alternatives

Current treatments for basal cell carcinoma include topical chemotherapy, curettage, surgical excision, cryotherapy and radiotherapy. Squamous cell carcinoma is usually removed surgically. Actinic keratoses and Bowen's disease are usually treated with curettage, cryotherapy or topical chemotherapy.

What the procedure involves

Before photodynamic therapy (PDT), the lesion is prepared by removing overlying crust and scale. Cream containing a photosensitising agent is applied to the lesion and a margin of surrounding skin. The area is covered with a light occlusive dressing and left for a few hours. Excess cream is then removed and the lesion is illuminated by light of an appropriate wavelength to activate the photosensitiser, producing targeted tumour destruction. Occasionally, the photosensitising agent may be given intravenously. More than one lesion may be treated in a session and the treatment may be repeated. There are different photosensitising agents which may have different safety and efficacy profiles.

Potential benefits of photodynamic therapy include good cosmetic outcomes and treatment of superficial lesions that are too large for surgery.

Efficacy

One randomised controlled trial of patients with basal cell carcinoma reported that there was no statistically significant difference in lesion response between PDT and surgery (91% [48/53] and 98% [51/52] of patients respectively). Another randomised controlled trial reported that 25% (11/44) of patients had a positive biopsy at 12 months after PDT compared with 15% (6/39) of patients after cryotherapy ($p > 0.05$). Both of these studies reported statistically significantly better cosmetic outcomes after PDT than the comparator.

Two randomised controlled trials compared PDT and cryotherapy in patients with actinic keratosis; one reported a similar lesion response rate for PDT and cryotherapy (69% [252/367] and 75% [250/332] of lesions respectively) whereas the other study reported that 91% (267/295) of lesions treated with PDT responded at three months, compared with 68% (278/407) of lesions treated with cryotherapy ($p < 0.001$). Both studies reported that a significantly higher proportion of patients had good or excellent cosmetic outcomes after PDT.

A case series of 59 patients with basal cell carcinoma reported that the overall cure rate was 79% (277/350) of lesions after a mean follow-up of 35 months.

The Specialist Advisors stated that there were some concerns about recurrence rates and that the treatment may be more appropriate for superficial lesions than for deeper tumours. In addition, the treatment may be particularly useful for large,

superficial lesions of Bowen's disease, actinic keratosis and basal cell carcinoma, especially where there are multiple lesions and where repair would otherwise require extensive surgery.

Safety

Adverse events were mainly transient local reactions. Three studies reported that the total rate of adverse events ranged from 43% (44/102) to 90% (38/42) of patients. The most common complication was a burning sensation of the skin, and this affected between 31% (16/52) and 64% (27/42) of patients. Two studies reported ulceration rates of 0% (0/20) and 12% (5/42). One large case series reported minor pigmentary changes and superficial scarring each in 2% (10/483) of lesions. Other adverse events included pain, erythema, crusting, itching, oedema and blisters.

The Specialist Advisors agreed that the procedure is generally safe and well tolerated. It is theoretically possible that the treatment could induce carcinogenicity but this is likely to be a low risk.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to photodynamic therapy for non-melanoma skin tumours. The search strategy is described in Appendix A. The following selection criteria were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with non-melanoma skin tumours.
Intervention/test	Photodynamic therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on six randomised controlled trials and two case series (see Table 1). Two randomised controlled trials included patients with basal cell carcinomas: one compared PDT with surgery and the other compared PDT with cryotherapy.[1,2] Three randomised controlled trials included patients with actinic keratosis; one of these compared active PDT with cryotherapy, one compared active PDT with placebo PDT and one study compared active PDT, placebo PDT and crysurgery.[3,4,5] The final randomised controlled trial included patients with Bowen's disease.[6] One case series included 207 patients with 483 non-melanoma skin lesions and the second included 59 patients with basal cell carcinomas followed up for a mean period of 35 months.[7,8]

Other studies that are considered to be relevant to the procedure but have not been summarised in Table 1 are listed in Appendix B.

Existing reviews on this procedure

A British Photodermatology Group workshop published guidelines for topical photodynamic therapy in 2002.[9] The report concluded that there are several possible light sources and optimal disease-specific irradiance, wavelength and total dose characteristics have yet to be established. The treatment was considered to be effective in actinic keratoses on the face and scalp, Bowen's disease and superficial basal cell carcinomas, but a relatively poor option for nodular basal cell carcinomas and squamous cell carcinomas. The guidelines describe the treatment as intrinsically very safe.

A Cochrane Review on interventions for basal cell carcinoma of the skin was published in 2004.[10] Two randomised controlled trials using photodynamic therapy were identified. The first compared PDT with two freeze-thaw cycle cryotherapy and is described in Table 1.[2] The second study compared two different light sources and reported no statistical difference between them with regard to clinical response or cosmetic results.[11]

The review concluded that there has been very little good-quality research on the efficacy of the different treatment modalities. Surgery and radiotherapy appeared to be the most effective treatments, with surgery showing the lowest failure rates. Few studies compared surgery with other treatments.

Two Cochrane Reviews are in progress and are due to be published at the end of 2005. One is on photodynamic therapy for localised squamous cell carcinoma of the skin and the other is assessing interventions for actinic keratosis.[12,13]

Table 1 Summary of key efficacy and safety findings on photodynamic therapy for non-melanoma skin tumours

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Rhodes L (2004)[1]

Randomised controlled trial

1999–2000

Multicentre study

101 patients with basal cell carcinoma (110 lesions):
• 52 patients (55 lesions) PDT
• 49 patients (55 lesions) surgery

Mean age:
• PDT = 69 years (range 40 to 95)
• Surgery = 67 years (range 38 to 82)

Inclusion criteria: age ≥ 18 years, previously untreated histologically confirmed primary nodular basal cell carcinoma suitable for simple excision surgery

Exclusion criteria: > 10 eligible lesions; lesions in the midface region, orbital areas, and ears; lesions < 6mm or > 15 mm (face or scalp), > 20 mm (extremities or neck), > 30 mm (trunk); pigmented or morpheaform lesions; porphyria; Gorlin syndrome; history of arsenic exposure; participation in any other investigational study within 30 days; likely to be poor complier; immunosuppressive medication; pregnancy or breastfeeding

Photosensitiser: methyl aminolevulinate (Metvix, Photocure ASA, Oslo, Norway)

Follow-up: 24 months</td>
<td>Primary outcome measure was clinically assessed lesion clearance at 3 months after treatment. Secondary end points were sustained response at 12 months and cosmetic outcome at 3 and 12 months

Lesion response at 3 months
<table>
<tr><td></td><td>PDT</td><td>Surgery</td></tr>
<tr><td>Overall</td><td>91% (48/53)</td><td>98% (51/52)</td></tr>
<tr><td>By site of lesion</td><td></td><td></td></tr>
<tr><td>Face / scalp</td><td>95% (20/21)</td><td>97% (31/32)</td></tr>
<tr><td>Trunk / neck</td><td>85% (23/27)</td><td>100% (15/15)</td></tr>
<tr><td>Extremity</td><td>100% (5/5)</td><td>100% (5/5)</td></tr>
<tr><td>By longest diameter of lesion (mm)</td><td></td><td></td></tr>
<tr><td>6–14</td><td>90% (36/40)</td><td>98% (42/43)</td></tr>
<tr><td>15–19</td><td>91% (10/11)</td><td>100% (6/6)</td></tr>
<tr><td>20–30</td><td>100% (2/2)</td><td>100% (3/3)</td></tr>
</table>
Estimated treatment difference = 4.8% (95% confidence interval, -3.4% to 13.0%, p = 0.25).

Tumour free at 12 months:
• PDT = 83% (44/53)
• Surgery = 96% (50/52), p = 0.15

At 24 months, 5 recurrences of previously cleared lesions were seen in the PDT group vs 1 in the surgical group.

Excellent or good cosmetic outcome (patient rated)
<table>
<tr><td></td><td>PDT</td><td>Surgery</td><td>P value</td></tr>
<tr><td>3 months</td><td>95% (39/41)</td><td>84% (37/44)</td><td>0.10</td></tr>
<tr><td>12 months</td><td>98% (41/42)</td><td>84% (36/43)</td><td>0.03</td></tr>
<tr><td>24 months</td><td>97% (28/29)</td><td>75% (27/36)</td><td>0.04</td></tr>
</table>
</td>
<td>Complications
Total adverse events:
• PDT = 52% (27/52)
• Surgery = 29% (14/49), p = 0.03

Burning sensation of skin:
• PDT = 31% (16/52)
• Surgery = 0% (0/49)

Pain in skin:
• PDT = 14% (7/52)
• Surgery = 6% (3/49)

Erythema:
• PDT = 14% (7/52)
• Surgery = 2% (1/49)

Skin infection:
• PDT = 0% (0/52)
• Surgery = 6% (3/49)

Crusting:
• PDT = 4% (2/52)
• Surgery = 0% (0/49)

Itching:
• PDT = 4% (2/52)
• Surgery = 0% (0/49)</td>
<td>Randomisation described.

One additional patient was randomised to each of the groups but withdrew consent and did not receive the study treatment.

Patients randomised to PDT treatment received 1 or 2 PDT cycles comprising 2 sessions of PDT, 1 week apart.

Local anaesthesia was provided with surgery but not with PDT.

Four patients (2 in each group) were excluded from 3-month results because of withdrawal or violation of the study protocol.

Losses to follow-up at 24 months:
• PDT = 7.7% (4/52)
• Surgery = 4.1% (2/49)

Three patients died during the first 12 months of the study. No deaths were considered to be related to the study treatment.

Study was powered to detect a 15-percentage point difference at 3 months. A 15-percentage point advantage in favour of surgery at 12 months cannot be excluded. Study was not powered to examine long-term recurrence rate.</td>
</tr>
</table>

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Wang I (2001)[2] Randomised controlled trial Sweden 88 patients with basal cell carcinomas (88 lesions): • 53% (47/88) PDT • 47% (41/88) cryotherapy (2 freeze-thaw cycles) Age range: 42 to 88 years Inclusion criteria: histopathologically verified basal cell carcinomas (superficial and nodular) suitable for PDT as well as cryotherapy, age between 20 and 90 years Exclusion criteria: pregnancy/lactation; severe malignancies; daily intake of vitamins E or C, beta-carotene, iron preparations, non-steroidal anti-inflammatory agents or strong analgesics in higher than specified doses; morphoeic growth; porphyria; abdominal pain of unknown aetiology; photosensitivity; treatment of the lesion with topical steroids type III or IV within the previous month Photosensitiser: δ-aminolaevulinic acid (Johnson & Johnson, Norderstedt, Germany) Follow-up: 12 months	**Primary outcome measure was the result of punch biopsies taken 12 months after first treatment** Retreatments: • PDT = 30% (13/44) • Cryotherapy = 3% (1/39) Positive biopsy for all lesions at 12 months: • PDT = 25% (11/44) • Cryotherapy = 15% (6/39) $p > 0.05$ (not significant) Positive biopsy for superficial lesions: • PDT = 38% (8/21) • Cryotherapy = 7% (1/15) Positive biopsy for nodular lesions: • PDT = 13% (3/23) • Cryotherapy = 21% (5/24) Clear border recurrence at 12 months: • PDT = 2% (1/44) • Cryotherapy = 3% (1/39) There was a significantly shorter healing time after PDT compared with cryotherapy, in terms of leakage and oedema Excellent or good cosmetic results (in terms of hypopigmentation, hyperpigmentation, scarring and tissue defect): • PDT = 93% (39/42) • Cryotherapy = 54% (20/37) $p < 0.001$ One patient in the PDT group did not respond to treatment and was referred for surgery	**Complications** PDT: • aching, radiating out from the treatment site = 2% (1/47) Cryotherapy: • infection at the treatment site = 2% (1/41) The differences in pain scores were not statistically significant.	Randomisation process described. Each patient was included in the trial based on one tumour. No local anaesthesia was administered. One patient in the cryotherapy group turned out to have a squamous cell carcinoma rather than a basal cell carcinoma. The histopathological diagnosis was not verified for one patient in the PDT group. One patient in each group died after the 3-month follow-up visit (both unrelated to the basal cell carcinoma or its treatment). Recurrences based on histopathology rather than clinical examination. Some positive biopsies were from lesions that were judged to be cured by clinical examination. Punch biopsies only cover a small portion of the lesion but they were always taken from the most suspicious areas. The authors conclude that PDT is the treatment modality of choice for large and superficial lesions.

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Szeimies R (2002)[3]

Randomised controlled trial

1999

Austria, Germany, Italy, Netherlands and Switzerland

202 patients with actinic keratosis (732 lesions):
• 50% (102/202) PDT
• 50% (100/202) cryotherapy

Mean age (years):
• PDT = 71 (range 42 to 88)
• Cryotherapy = 72 (range 45 to 89)

Follow-up: 3 months

Inclusion criteria: clinical diagnosis of actinic keratosis with up to 10 lesions suitable for cryotherapy and no treatment within the previous 4 weeks

Exclusion criteria: patients receiving regular ultraviolet therapy, pigmented lesions in the target area or porphyria

Photosensitiser: methyl 5-aminolevulinate (Metvix, PhotoCure ASA, Oslo, Norway)</td>
<td>Primary outcome measure was lesion response at 3 months.

Overall lesion complete response rate:
• PDT = 69% (252/367) (95% confidence interval 64% to 74%)
• Cryotherapy = 75% (250/332) (95% confidence interval 70% to 80%)

Higher response rates were observed in thin lesions than in the thicker lesions.

Excellent or good overall cosmetic outcome after 3 months for patients with 75% or more of the lesions in complete response:
<table><tr><th></th><th>PDT (n = 54)</th><th>Cryotherapy (n = 68)</th></tr><tr><td>Patient assessed</td><td>98% (53/54)</td><td>91% (62/68)</td></tr><tr><td>Investigator assessed</td><td>96% (52/54)</td><td>81% (55/68)</td></tr></table>p = 0.035

95% confidence intervals for the difference in excellent or good cosmetic outcomes between the treatments were 4.8% to 26.0% (investigator assessment) and 0.7% to 14.6% (patient assessment)</td>
<td>Complications
Total local adverse reactions:
• PDT = 43% (44/102)
• cryotherapy = 26% (26/100)

Burning sensation:
• PDT = 32% (33/102)
• cryotherapy = 9% (9/100)

Skin pain:
• PDT = 10% (10/102)
• cryotherapy = 13% (13/100)

Crusting:
• PDT = 5% (5/102)
• cryotherapy = 6% (6/100)

Three patients discontinued treatment because of local reactions (1 PDT and 2 cryotherapy)</td>
<td>Randomisation was stratified with respect to number of lesions.

The PDT was repeated after 1 week in lesions not located on the face or scalp.

8% (31/384) lesions were given a second treatment.

In the PDT group, 2% (2/102) were lost to follow-up, 1% (1/102) discontinued because of an adverse event, 1% (1/102) was given cryotherapy after the PDT.

In the cryotherapy group, 2% (2/100) were lost to follow-up, 2% (2/100) discontinued because of adverse events, and 1% (1/100) used topical 5-fluorouracil intermittently.</td>
</tr>
</table>

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Pariser D (2003)[4]

Randomised controlled trial

USA

80 patients with actinic keratoses (502 lesions):
• 52% (42/80) PDT
• 48% (38/80) placebo cream and illumination

Mean age: 65 years (range 31 to 84)

Inclusion criteria: age ≥ 18 years, 4 to 10 previously untreated mild to moderate non-pigmented actinic keratoses on the face and scalp (at least 3 mm in diameter)

Exclusion criteria: immunosuppression for idiopathic, disease-specific or therapeutic reasons; porphyria; pigmented actinic keratosis lesions; known allergy to photosensitiser; known hypersensitivity to nut products; current or prior (within 30 days) participation in other clinical studies; pregnancy; lactation; inadequate contraceptive measures during treatment and 1 month thereafter in women of childbearing potential; any conditions that may be associated with a risk of poor protocol compliance

Photosensitiser: methyl aminolevulinate (Metvix, PhotoCure, Oslo, Norway)

Follow-up: 3 months</td>
<td>Primary outcome measure was the percentage of patients in whom 100% of lesions had responded completely after 3 months

Patient complete response rate at 3 months:
• PDT = 82% (32/39)
• Placebo = 21% (8/38)
p = 0.001

Lesion response rate:
• PDT = 89% (209/236)
• Placebo = 38% (92/241)

Excellent or good overall cosmetic outcome after 3 months for patients with 75% or more of the lesions in complete response:
<table><tr><th></th><th>PDT (n = 32)</th></tr><tr><td>Patient assessed</td><td>91% (29/32)</td></tr><tr><td>Investigator assessed</td><td>97% (31/32)</td></tr></table></td>
<td>Complications
Any adverse event:
• PDT = 90% (38/42)
• Placebo = 58% (22/38)

Burning sensation of the skin:
• PDT = 64% (27/42)
• Placebo = 10% (4/38)

Erythema:
• PDT = 52% (22/42)
• Placebo = 21% (8/38)

Crusting:
• PDT = 38% (16/42)
• Placebo = 16% (6/38)

Pain on the skin:
• PDT = 24% (10/42)
• Placebo = 0% (0/38)

Blisters:
• PDT = 19% (8/42)
• Placebo = 5% (2/38)

Oedema:
• PDT = 14% (6/42)
• Placebo = 3% (1/38)

Stinging skin:
• PDT = 14% (6/42)
• Placebo = 3% (1/38)

Skin ulceration:
• PDT = 12% (5/42)
• Placebo = 0% (0/38)

Treatment was discontinued for 1 patient as a result of local phototoxicity reactions</td>
<td>Randomisation described.

Double-blind study.

Treatment was repeated 1 week later for each patient.

The investigator who performed the clinical assessment did not participate in the treatment.

Per protocol efficacy analysis.

Three patients did not complete the study (all in the active PDT group); 2 discontinued as a result of adverse events and 1 was lost to follow-up.</td>
</tr>
</table>

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma

Study details	Key efficacy findings	Key safety findings	Comments
Freeman M (2003)[5] Randomised controlled trial Australia 200 patients with actinic keratosis (855 lesions): • 44% (88/200) active PDT • 12% (23/200) placebo PDT • 44% (89/200) cryotherapy Mean age (years): • active PDT = 64 (range 33 to 86) • placebo PDT = 66 (range 49 to 89) • cryotherapy = 65 (range 38 to 86) Inclusion criteria: clinical diagnosis of mild-to-moderate non-pigmented actinic keratosis of the face or scalp, suitable for cryotherapy, with the largest diameter of each lesion being ≥ 5 mm Exclusion criteria: 'Severe' lesions (defined as very thick and/or obvious actinic keratosis), pigmented actinic keratosis, extrafacial sites Photosensitiser: methyl aminolevulinate (Metvix, Photocure ASA, Oslo, Norway) Follow-up: 3 months	**Primary outcome measures were lesion response rate, overall cosmetic outcome and cosmetic outcome in individual lesions at 3 months** Lesion response rate (per protocol analysis): • active PDT = 91% (267/295) • placebo PDT = 30% (18/61) • cryotherapy = 68% (278/407) (Response was statistically significantly higher for active PDT compared with both placebo PDT [$p < 0.001$] and cryotherapy [$p < 0.001$]) Excellent cosmetic outcome (as assessed by investigator): • active PDT = 83% (73/88) • cryotherapy = 51% (45/89), $p < 0.001$ Excellent cosmetic outcome (as assessed by patient): • active PDT = 76% (67/88) • cryotherapy = 56% (50/89), $p < 0.001$ Hypopigmentation in individual lesions: • active PDT = 5% (15/295) • cryotherapy = 29% (118/407) Hyperpigmentation, scar formation or tissue defects were present in fewer than 6% of the lesion sites in both treatment groups	**Complications of active PDT (2 sessions per patient)** • Burning sensation, stinging, painful skin = 46.0% (81/176) • Erythema = 23.9% (42/176) • Oedema = 8.5% (15/176) • Skin peeling = 5.7% (10/176) • Skin bleeding = 5.1% (9/176) • Blisters = 3.4% (6/176) • Itching = 5.1% (9/176) • Crusting = 2.3% (4/176)	Randomisation method described. An additional four patients were randomised but withdrawn before treatment. All efficacy results were analysed for both the intention to treat and per protocol populations. The results of the intention to treat analyses were similar to those of the per protocol populations. Each patient was treated with two sessions of PDT, 7 days apart. The study was open with regard to PDT versus cryotherapy and double-blind with regard to active versus placebo PDT. One patient in the active PDT group discontinued the study due to a burning sensation.

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma

Study details	Key efficacy findings	Key safety findings	Comments
Salim A (2003)[6] Randomised controlled trial UK 40 patients with Bowen's disease (66 lesions) • 50% (20/40) PDT • 50% (20/40) topical chemotherapy (5-fluorouracil) Mean age: 76 years (range 65 to 88) Inclusion criteria: one to three lesions of previously untreated, histologically proven, Bowen's disease measuring 0.5 to 4.0 cm No exclusion criteria were reported Photosensitiser: 5-aminolaevulinic acid (Porphin, Crawford Pharmaceuticals Ltd, Milton Keynes, UK) Follow-up: 12 months	**Primary outcome measure was lesion clearance** Initial complete clinical clearance: • PDT = 88% (29/33) • Topical chemotherapy = 67% (22/33) Recurrences at 12-month follow-up: • PDT = 6% (2/33) • Topical chemotherapy = 18% (6/33) Overall clearance rate at 12 months: • PDT = 82% (27/33) • Topical chemotherapy = 48% (16/33) Odds ratio for success of PDT in comparison with topical chemotherapy = 4.78 (95% confidence interval 1.56 to 14.62, p = 0.006)	**Complications** Widespread dermatitic reactions: • PDT = 0% (0/20) • Topical chemotherapy = 20% (4/20) (3 of these patients discontinued treatment) Ulceration/erosion of lesions: • PDT = 0% (0/20) • Topical chemotherapy = 15% (5/33) Pain: • PDT = 73.7% (14/19) • Topical chemotherapy = 66.7% (10/15) Median pain scores in the two treatment groups were not significantly different (p = 0.32)	Randomisation described. Local anaesthetic was offered to patients experiencing pain during PDT. All patients were reviewed at 6 weeks and treatment was repeated if required. No losses to follow-up. Five lesions treated with topical chemotherapy were withdrawn prior to completion of a single treatment cycle.

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Clark C (2003)[7] Case series UK 207 patients with 483 non-melanoma skin lesions Median age: 76 years (range 20 to 100) Indications: Bowen's disease, superficial basal cell carcinoma, actinic keratosis, nodular basal cell carcinoma, angiosarcoma, metastatic breast carcinoma, vulval Paget's disease, viral warts, keloid, erosive pustular dermatosis of scalp, erosive mucosal lichen planus, disseminated superficial actinic porokeratosis. Median follow-up: 48 weeks Photosensitiser: 5-aminolaevulinic acid (Crawford Pharmaceuticals Ltd, Milton Keynes, UK)	**Primary outcome measure was lesion clearance** Complete lesion clearance (after 1 to 4 treatments): • Bowen's disease = 91% (117/129) • Superficial BCC = 97% (84/87) • Actinic keratosis = 91% (21/23) Recurrence rate at follow-up: • Bowen's disease = 10.3% (12/129) • Superficial BCC = 4.8% (4/87) • Actinic keratosis = 4.8% (1/23)	**Complications** Moderate pain = 40.8% (252/618) Severe pain = 17.5% (108/618) 'Almost all patients experienced a burning pain at the treatment site' Expected immediate adverse effects included erythema, oedema, erythematous flare, urticaria and exudation. Minor pigmentary change = 2% (10/483) Superficial scarring = 2% (10/483) Severe pain was experienced in a higher proportion of treatments using high-output broadband and laser sources than in treatments using a low-output xenon arc source.	Patient selection not described. Histological confirmation of Bowen's disease or superficial basal cell carcinoma was obtained and, in general, only superficial BCC with a depth less than 2 mm was treated. Treatment was repeated 3 monthly up to a maximum of 4 treatments. If patients experienced severe discomfort or large areas were being treated, topical anaesthetic was applied. Four different light sources were used.

Abbreviations used: PDT = photodynamic therapy, BCC = basal cell carcinoma			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Soler A (2001)[8] Case series 1995–1997 Norway 59 patients with basal cell carcinomas (310 lesions) Mean age: 69 years (range 45 to 89) Inclusion criteria: at least one lesion verified by cytology or histology as basal cell carcinoma (nodular or superficial), no treatment within previous 6 months Exclusion criteria: Gorlin's syndrome, immunosuppressive treatment before or after PDT Photosensitiser: methyl 5-aminolaevulinate (PhotoCure ASA, Oslo, Norway) Mean follow-up: 35 months	**Primary outcome measures were long-term complete response rate, recurrence rate, cosmetic outcome and extent of dermal fibrosis at 2 to 4 years after treatment** Initial cure rate (at 3 to 6 months) = 89% (310/350) Overall long-term complete response = 89% (277/310) Overall recurrence rate = 11% (33/310) Overall cure rate (including the initial non-responders and recurrent lesions) = 79% (277/350) 'Excellent' cosmetic appearance = 83% (230/277) Depigmentation = 14% (38/277) Redness = 2% (5/277) Atrophy = 1% (4/277) Hyperpigmentation = 1% (4/277) Dermal fibrosis = 4% (1/23) Nearly half of the recurrent lesions were located at high-risk areas (nose, nasolabial area, temple, periorbital region, scalp, ear)	**Complications** Not reported	Retrospective study. All tumour sites with initial complete response were re-examined after 2 to 4 years. An additional 40 lesions were treated during the initial study period but were not included in the long term follow-up results as they only showed a partial response. 10% (31/310) of lesions had been treated more than 6 months previously (surgery = 13, radiation = 9, PDT = 8, cryotherapy = 5, topical chemotherapy = 1). 6% (19/310) of lesions were treated with 2 sessions of PDT, 1% (3/310) was treated with 3 sessions and 0.3% (1/310) received 4 sessions of PDT. Nodular lesions were debulked with curettage prior to PDT treatment.

Validity and generalisability of the studies

- One randomised controlled trial excluded lesions in the midface area, orbital areas and ears.[1]
- Four studies excluded patients on the basis of the number of lesions.[1,3,4,6]
- Four studies excluded patients on the basis of the size of the lesions.[1,4,5,6]
- One study only included patients with nodular basal cell carcinoma.[1]
- The studies used different photosensitising agents, which may have different safety and efficacy profiles.
- Some studies treated all patients with two sessions of PDT, whereas others treated only selected patients with repeat sessions.
- One study used the results of punch biopsies to assess the response.[2] The other studies reported the response based on clinical examination.
- One study reported that the levels of pain experienced during treatment varied according to the light source used.[7]

Specialist Advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- The technique is established practice but new photosensitisers have been developed.
- The key efficacy outcome is clearance of the lesion – either complete clinical clearance or negative biopsy.
- Photodynamic therapy is a topical treatment and it is possible that it may treat only the superficial component of the tumour, leaving deeper nodular disease to continue developing.
- Photodynamic therapy may be appropriate for treating large superficial lesions, especially where multiple and where repair would otherwise require extensive surgery.
- Photodynamic therapy is a rapidly evolving field.
- Treatment protocols differ in terms of light delivery techniques and dosimetry.
- Selection of appropriate lesions is important.
- The procedure is likely to have a minor to moderate impact on the NHS, in terms of numbers of patients eligible for treatment and use of resources.

Issues for consideration by IPAC

- None of the studies in the main extraction table (Table 1) included patients with squamous cell carcinoma.

References

1 Rhodes LE, de Rie M, Enstrom Y et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma. *Archives of Dermatology* 2004; 140: 17–23.

2 Wang I, Bendsoe N, Klinteberg CAF et al. Photodynamic therapy vs cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *British Journal of Dermatology* 2001; 144: 832–40.

3 Szeimies RM, Karrer S, Radakovic-Fijan S et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *Journal of the American Academy of Dermatology* 2002; 47: 258–62.

4 Pariser DM, Lowe NJ, Stewart DM et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *Journal of the American Academy of Dermatology* 2003; 48: 227–32.

5 Freeman M, Vinciullo C, Francis D et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix®) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *Journal of Dermatological Treatment* 2003; 14: 99–106.

6 Salim A, Leman JA, McColl JH et al. Randomised comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *British Journal of Dermatology* 2003; 148: 539–43.

7 Clark C, Bryden A, Dawe R, et al. Topical 5-aminolaevulinic acid photodynamic therapy for cutaneous lesions: outcome and comparison of light sources. *Photodermatology, Photoimmunology & Photomedicine* 2003; 19: 134 – 41.

8 Soler AM, Warloe T, Berner A et al. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. *British Journal of Dermatology* 2001; 145: 467–71.

9 Morton CA, Brown SB, Collins S et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *British Journal of Dermatology* 2002; 146: 552–67.

10 Bath FJ, Bong J, Perkins W et al. Interventions for basal cell carcinoma of the skin (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.

11 Soler Am, Angell-Petersen E, Warloe T, et al. Photodynamic therapy of superficial basal cell carcinoma with 5-aminolevulinic acid with dimethylsulfoxide and ethylenediaminetetraacetic acid: a comparison of two light sources. *Photochemistry and Photobiology* 2000; 71: 724–9.

12 Westby M, Bath F, Herd R, et al. Photodynamic therapy for localised squamous cell carcinoma of the skin. (Protocol). *The Cochrane Database of Systematic Reviews* 2003, Issue 2.

13 Gupta AK, Inniss K, Wainwright R, et al. Interventions for actinic keratoses. (Protocol). *The Cochrane Database of Systematic Reviews* 2003, Issue 4.

Appendix A: Literature search for photodynamic therapy for non-melanoma skin tumours

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	2005 Issue 1	6/04/2005
Embase	1980 to 2005 Week 14	6/04/2005
Medline	1966 to March Week 4 2005	6/04/2005
Premedline	April 5 2005	6/04/2005
CINAHL	1982 to April Week 1 2005	6/04/2005
British Library Inside Conferences (limited to current year only)		6/04/2005
National Research Register	2005 Issue 1	6/04/2005

Search strategy used in Medline

1. (photodynamic adj2 therap$).tw.
2. pdt.tw.
3. exp *carcinoma, squamous cell/
4. *carcinoma, basal cell/
5. (skin adj2 cancer$).tw.
6. (skin adj2 tumo?r$).tw.
7. or/3-6
8. 1 or 2
9. 7 and 8
10. skin/
11. skin$.tw.
12. 10 or 11
13. 9 and 12
14. limit 13 to humans
15. limit 14 to yr=1990 - 2005

Appendix B: Additional papers on photodynamic therapy for non-melanoma skin tumours not included in the summary tables

The following table outlines studies that are considered potentially relevant to the overview but were not included in the main data extraction table and is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Bakos RM, Bakos L, ferlin E, et al. Photodynamic therapy with delta-aminolevulinic acid for superficial keratinocytic neoplasms. *Anais Brasileiros de Dermatologia* 2003; 78: 197–207.	52 patients.	Case series. Single session of treatment. Superficial BCC, actinic keratoses and Bowen's disease.	55% lesions completely resolved, 30% partial remission, 16% failures.
Cairnduff F, Stringer M, Hudson E at al. Superficial photodynamic therapy with topical 5-aminolaevulinic acid for superficial primary and secondary skin cancer. *British Journal of Cancer* 1994; 69: 605–8.	36 areas of Bowen's disease, 16 basal cell carcinomas.	Case series.	Complete response rate: Bowen's disease = 89% Basal cell carcinoma = 50%
Dijkstra AT, Majoie IML, Van Dongen JWF, et al. Photodynamic therapy with violet light and topical delta-aminolaevulinic acid in the treatment of actinic keratoses, Bowen's disease and basal cell carcinoma. *Journal of the European Academy of Dermatology & Venereology* 2001; 15: 550–4.	38 patients.	Case series.	Complete remission after single treatment = 82% of superficial BCCs (100% after 2 treatments), 50% of nodular BCCs, 90-100% of solitary lesions of Bowen's disease.
Dragieva G, 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.	40 patients.	Non-randomised study, comparing response in transplant recipients with controls.	Cure rates were comparable at 4 weeks, but significantly lower in transplant recipients than in controls at 48 weeks.
Ericson MB, Sandberg C, Stenquist B, et al. Photodynamic therapy of actinic keratosis at varying fluence rates: assessment of photobleaching, pain and primary clinical outcome. *British Journal of Dermatology* 2004; 151: 1204–12.	37 patients. 7 week follow-up.	Comparative study, comparing different fluence rates.	Lower fluence rates resulted in more favourable treatment response.
Fink-Puches R, Soyer HP, Hofer A, et al. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. *Archives of Dermatology* 1998; 134: 821–6.	47 patients. Median follow-up = 19 months for BCC, 8 months for SCC.	Case series. Superficial BCC and superficial squamous cell carcinoma.	Overall recurrence rate at follow-up = 44% for BCC and 69% for SCC.
Grapenglasser S, Gudmundsson F, Larkö O et al. Pain caused by photodynamic therapy of skin cancer. *Clinical and Experimental Dermatology* 2002; 27: 293–7.	60 patients.	Case series.	Patients with actinic keratosis had more pain than those with Bowen's disease or BCC.
Horn M, Wolf P, Wulf H, et al. Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. *British Journal of Dermatology* 2003; 149: 1242–9.	94 patients. 24 month follow-up.	Case series. Patients with 'difficult to treat' superficial and/or nodular BCC.	Overall lesion recurrence rate at 24 months = 18% (12/66). Good or excellent cosmetic outcome = 94%.

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Kubler AC, Haase T, Staff C, et al. Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck. *Lasers in Surgery & Medicine* 1999; 25: 60–8.	18 patients. Mean follow-up = 15 months.	Case series. Systemic photo-synthesiser.	Complete response in 93% (90/97) of lesions.
Lui H, Hobbs L, Tope WD et al. Photodynamic therapy of multiple nonmelanoma skin cancers with verteporfin and red light-emitting diodes. *Archives of Dermatology* 2004; 140: 26–32.	54 patients. 24 month follow-up.	Comparison of different light doses. BCC and Bowen's disease.	Negative biopsy results at 6 months ranged from 69% to 93%. Complete clinical response ranged from 51% to 95%.
Morton CA, Whitehurst C, Moseley H et al. Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. *British Journal of Dermatology* 1996; 135: 766–71.	19 patients.	Randomised controlled trial. Bowen's disease.	PDT had a lower recurrence rate and fewer adverse effects.
Morton CA, Whitehurst C, Moore JV et al. Comparison of red and green light in the treatment of Bowen's disease by photodynamic therapy. *British Journal of Dermatology* 2000; 143: 767–72.	16 patients. 12 month follow-up.	Comparison of red and green light. Bowen's disease.	Green light was less effective than red light (72% clearance versus 94%, p = 0.002).
Naidenov N, Denchevo R, Tsankov N. Recurrence rate of basal cell carcinoma after topical aminolevulinic acid-based photodynamic therapy. *Acta Dermatovenerologica Croatica* 2004; 12: 157–61.	60 patients.	Case series. Single PDT procedure.	Recurrence rate = 35%. Lowest recurrence rates were seen for superficial BCCs.
Pagliaro J, Elliott T, Bulsara M et al. Cold air analgesia in photodynamic therapy of basal cell carcinomas and Bowen's disease: an effective addition to treatment: a pilot study. *Dermatologic Surgery* 2004; 30: 63–6.	26 patients with 2 lesions.	Comparative study.	Concurrent cold air analgesia improved the tolerability of PDT.
Soler AM, Angell-Petersen E, Warloe T et al. Photodynamic therapy of superficial basal cell carcinoma with 5-aminolevulinic acid with dimethylsulfoxide and ethylendiaminetetraacetic acid: a comparison of two light sources. *Photochemistry and Photobiology* 2000; 71: 724–9.	83 patients. 6 month follow-up.	Comparison of laser and broad-band halogen light. Superficial BCC.	No significant differences in cure rate or cosmetic outcome.
Soler AM, Warloe T, Tausjo J, et al. Photodynamic therapy of residual or recurrent basal cell carcinoma after radiotherapy using topical 5-aminolevulinic acid or methylester aminolevulinic acid. *Acta Oncologica* 2000; 39: 605–9.	20 patients. Mean follow-up = 22 months.	Case series. Residual or recurrent BCC.	At follow-up, 82% (18/22) lesions in complete remission.
Soler AM, Warloe T, Tausjo J, et al. Photodynamic therapy by topical aminolevulinic acid, dimethylsuphoxide and curettage in nodular basal cell carcinoma: a one-year follow-up study. *Acta Dermato-Venereologica* 1999; 79: 204–6.	58 patients. Mean follow-up = 17 months.	Case series. Nodular BCC.	95% (113/119) of lesions still in complete response at follow-up. 5% recurrence.
Varma S, Wilson H, Kurwa HA, et al. Bowen's disease, solar keratoses and superficial basal cell carcinomas treated by photodynamic therapy using a large-field incoherent light source. *British Journal of Dermatology* 2001; 144: 567–74.	88 patients. 12 month follow-up.	Case series. Two treatments.	Complete clearance at 12 months = 69% for Bowen's disease, 82% for BCC, 72% for solar keratoses.
Wilson BD, Mang TS, Stoll H, Jones C, Cooper M, Dougherty TJ. Photodynamic therapy for the treatment of basal cell carcinoma. Archives of Dermatology 1992; 128(12):1597-1601.	37 patients (151 lesions)	Case series. Primary or recurrent BCC - mostly widespread or large single tumours.	Complete response rate 88% with one treatment application.

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Xu S, Wang X, Xu W et al. Evaluation of photodynamic therapy of skin cancers with δ-aminolevulinic acid. Chinese Medical Journal 2002; 115: 1141–5.	88 patients. 1 to 3 year follow-up.	Case series. Includes BCC, squamous cell carcinoma and Bowen's disease.	Recurrence rates = 11% for BCC, 22% for squamous cell carcinoma.