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Appendices

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A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin

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Appendix 5

Pre-cancerous skin scoping

One hundred and thirty-three publications, with study designs that did not meet the inclusion criteria for the review, reported on patients with pre-cancerous skin conditions being treated with PDT. The references are listed below, in alphabetical order; they have not been categorised and may still contain a number of duplicate publications.

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Appendix 6

Skin cancer scoping

Two hundred and thirty-five publications, with study designs that did not meet the inclusion criteria for the review, reported on patients with skin cancer being treated with PDT. The references are listed below in alphabetical order; they have not been categorised and may still contain a number of duplicate publications.

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Appendix 7
Barrett's oesophagus scoping

Seven non-RCTs reported in 11 publications were identified, which reported on patients with Barrett's oesophagus being treated with PDT.[1–11] These were originally to be included in the main systematic review; however, as 24 publications reporting 11 RCTs were identified, these less robust non-randomised designs were subsequently excluded from the review.

A further 96 publications with study designs that did not meet the inclusion criteria for the review were identified.[12–107] The references are listed below in alphabetical order, they have not been categorised and may still contain a number of duplicate publications.

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Other scoping publications

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Appendix 8

Oesophageal cancer scoping

One hundred and fifty publications, with study designs that did not meet the inclusion criteria for the review, reported on patients with oesophageal cancer being treated with PDT. The references are listed below in alphabetical order; they have not been categorised and may still contain a number of duplicate publications.

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Appendix 9

Lung cancer scoping

One hundred and seventy-seven publications, with study designs that did not meet the inclusion criteria for the review, reported on patients with lung cancer being treated with PDT. Details are lacking for many of these publications, so the categorisations may not be reliable.

There are 10 observational comparative studies, with sample sizes ranging from 29 to 687, although the sample size is unclear for one-half of them.[1–10] For some of these studies, all of the patients receive PDT, for others it is series of patients undergoing treatment for lung cancer, only a proportion of which receive PDT.

Eleven publications are described as trials but without a comparator group (Phase I/II/pilot studies), with sample sizes ranging from 9 to 54.[11–21]

One hundred and nineteen publications report case series;[22–140] 19 have over 100 patients, eight publications report on case series with between 50 and 100 patients, and 71 report less than 50 patients. For 21 publications it is not clear what the sample size is. Many of these publications are by the same authors and appear to be updated series of patients or duplicate reports published in different journals. Therefore, these publications may double count patients to a certain degree.

Thirty publications report less than 10 patients,[141–170] 16 of which are single case reports.[142,143,146,147,149,151,152,155–157,161,163,164,166,167,169]

A further seven publications remain uncategorised (e.g. the paper is unavailable, it is unclear what is being reported, or possible duplicate publication).[171–177]

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Observational comparative studies

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Appendix 10

Biliary tract cancer scoping

Thirty publications, with study designs that did not meet the inclusion criteria for the review reported on patients with biliary tract cancer being treated with PDT. Details are lacking for many of these publications, so the categorisations may not be reliable.

There is one comparative study, which is published in Korean;[1] the information is taken from the English abstract, which provides no methodological details. This study, of patients with advanced hilar cholangiocarcinoma, is a retrospective analysis of 27 patients who were treated with PDT under percutaneous cholangioscopy plus additional percutaneous biliary drainage compared with 20 patients who were treated with endoscopic biliary drainage alone.

Twelve publications are described as trials but without a comparator group (Phase I/II/pilot studies), with sample sizes ranging from 1 to 44.[2–13] One of these, a Phase II trial of 24 patients with Bismuth III/IV cholangiocarcioma treated with PDT after sensitization with Ps, also reports a retrospective comparison with a historical control group of 20 patients who fulfilled the inclusion criteria for the prospective study.[4]

Seven publications report case series with at least 10 patients but all of them have less than 50 patients.[14–20] Ten publications report fewer than 10 patients,[21–30] three of which are single case reports.[21–23]

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Case reports (single case or fewer than 10 patients)

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Appendix 11

Brain cancer scoping

Forty-three publications, with study designs that did not meet the inclusion criteria for the review, reported on patients with brain cancer being treated with PDT. Details are lacking for many of these publications, so the categorisations may not be reliable.

There are two studies with some form of comparison group, but both studies are poorly reported and lack methodological details.[1–2]

One comparative study reports the results of a Phase II trial of PDD/PDT in 26 patients with WHO grade IV recurrent glioblastoma who were sensitised with mTHPC (FOSCAN) prior to fluorescent guided resection and intraoperative PDT after 4 days.[2] This group of patients was compared with a control group of matched patients, but no details of how they were matched are provided.

The other comparative study reported on 30 patients [27 glioma (nine of which were recurrences), two malignant meningioma, two metastatic brain cancer] treated with high-dose PDT (haematoporphyrin derivative and pumped dye laser) in addition to craniotomy with a radical or partial excision of the tumour.[1] The authors state that 30 comparable patients who were treated with surgery alone were selected at random as control subjects, but no details are provided so it is not clear how these patients were selected.

Thirteen publications are described as being trials but without a comparator group, the number of patients ranging from 3 to 186.[3–15] Some of the publications appear to be related, either potential duplicate publications or reporting different outcomes for the same patients.

Twenty-two publications report case series with at least 10 patients[16–37] and six publications report less than 10 patients,[38–43] two of which are single case reports.[38–43] Of the 22 publications, four had between 50 and 100 patients,[26,27,29,30] and only three had more than 100 patients (one of which included various treatments and so not all patients will have undergone PDT).[32,33,35]

Many of the publications appear to be from the same clinical groups (14 are authored by Muller *et al.* and six by Kostron *et al.*) and there may well be significant overlap in the results presented (updating as more patients have been treated). Muller *et al.* began two RCTs that were not completed (see Chapter 11, Stopped trials) and some of the publications authored by them appear to report characteristics of the cohort of trial patients, but not comparative results.

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Appendix 12

Head and neck cancer scoping

One hundred and twenty-nine publications, with study designs that did not meet the inclusion criteria for the review, reported on patients with head and neck cancer being treated with PDT. Details are lacking for many of these publications, so the categorisations may not be reliable.

There are three studies that appear to be comparative, although the precise design is not clear for any of them.[1–3]

Fifteen publications are described as trials but without a comparator group (Phase I/II pilot studies), with sample sizes ranging from 5 to 121.[4–18]

Eighty-seven publications report case series;[19–105] eight have over 100 patients,[26–28,33,61,87,94,105] but not all of these contain patients with only head and neck cancer; some studies report multiple cancer site series. Eleven publications report on case series, with between 50 and 100 patients, and 56 report less than 50 patients. For 12 publications it is not clear what the sample size is.[19,39,40,48,56,57,60,64,68,82,85,99] Many of these publications are by the same authors and appear to be updated series of patients, or duplicate reports published in different journals. Therefore, these publications may double count patients to a certain degree.

Nineteen publications report fewer than 10 patients,[106–124] seven of which are single case reports.[108,110,112,115,120,121,124]

A further five publications remain uncategorised.[125–129]

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Appendix 13

Actinic keratosis data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Braathen *et al.* (2008)[54] **Data source** Full published paper **Country** Not stated, 'Europe' **Language** English **Study design** RCT **No. of participants** Total: 119 randomised, 112 treated (384 lesions) Intervention: 28 (1 hr; 160 mg/g) Comparator: 30 (3 hr; 160 mg/g) 2nd Comparator: 25 (1 hr; 80 mg/g) 3rd Comparator: 29 (3 hr; 80 mg/g) **No. of recruiting centres** Eight **Follow-up period and frequency** FU at wk 1 and 2, then at 2, 3, 6 and 12 mth	**Treatment intention** Curative **Type(s) of lesion and histology** Primary AK **Main eligibility criteria** Patients of 18 yr or older with Fitzpatrick skin type I, II or II with primary previously untreated, non-pigmented and non-infiltrating AK lesions (up to four lesions). Extensive exclusion criteria were reported **Patient characteristics** % Male: 56, age not reported. The majority of patients had three or fewer lesions; most were located on the face/scalp and were thin or moderately thick **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT comparing incubation time (1 hr or 3 hr) and dose (160 mg/g or 80 mg/g) **Intervention** MAL–PDT (1 hr + 160 mg/g). Most lesions were prepared using dermal curette to remove scales and crusts. 1-mm-thick layer of MAL cream applied to each lesion and to 5 mm of surrounding area. Lesions covered with occlusive dressing for specified incubation period then wiped off with saline. Lesions were illuminated with red lamp light (wavelength 570–670 nm, intensity 70 – 190 mW/cm^2) to provide total light dose of 75 J/cm^2. The mean illumination time was around 9.5 min. Any lesions without CR at 2 or 3 mth were given 2nd PDT treatment. Any non-CR at 6 mth offered alternative treatment **Comparator** MAL–PDT (3 hr + 160 mg/g) as above **2nd comparator** MAL–PDT (1 hr + 80 mg/g) as above **3rd comparator** MAL–PDT (3 hr + 80 mg/g) as above	**Morbidity** Lesion response (based on 110 patients with 380 lesions, two patients with four lesions excluded due to wrong diagnosis). Overall lesion response (not clear if CR) 85% 3 hr + 160 mg/g 76% 1 hr + 160 mg/g 74% 3 hr + 80 mg/g 77% 1 hr + 80 mg/g. *Note:* About one-third of lesions were not debrided as per protocol. For the 3 hr + 160 mg/g group CR was higher for debrided lesions (89%) than non-debrided (78%) Lesion recurrence (evaluated in 97 patients with 299 lesions that had responded completely): The lowest recurrence rates occurred in the 3 hr + 160 mg/g group (11%) compared with between 26% and 45% for the other groups Patients who received two PDT sessions: Lesion recurrence was lower for the 1-hr and 3 hr + 160 mg/g groups (19% and 17%) than for the 80 mg/g groups (44–45%). For debrided lesions in the 3 hr + 160 mg/g recurrence was 10% vs 14% for non-debrided lesions **QoL and return to normal activity** Cosmetic outcome (assessed by VAS score at 12 mth) was rated at between 8.4 cm and 9.3 cm by both investigator and patients indicating an excellent cosmetic outcome **AEs** Most AEs were mild intensity and the majority were local. The most commonly reported AE was erythema with a median duration of 17 d. Other AEs included skin pain, pruritis, burning sensation on skin, oedema and suppuration. Four patients experienced SAEs but these were not considered to be treatment related Treatment-related AE %: 1 hr + 160 mg/g, 98% 3 hr + 160 mg/g, 99% 1 hr + 80m/g, 98% 3 hr + 80 mg/g, 96%	**Authors' conclusions** PDT using a 1-hr incubation with 160 mg/g MAL cream may have potential for treating relatively mild AK lesions and offers practical advantages, but regular substitution is not recommended **Brief study appraisal** As the authors acknowledge, there were some important flaws in the design of this study, including the lack of blinding of outcome assessors, and having response rate judgements made clinically rather than histologically. Although the mean incubation and illumination times were consistent according to the protocol, it was clear that a large proportion of patients received only 1 PDT session (when 2 are recommended) and around one-third of lesions had not been debrided. Given that the protocol does not appear to have been followed closely, or has not utilised PDT optimally, these results should be considered with caution. No *p*-values or formal tests of statistical significance appear to have been carried out, making it difficult to assess the real differences between treatment groups

d, day(s); hr, hour(s); mth, month(s); wk, week(s); yr, year(s).

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Study details	Population details	Treatment details	Results	Interpretation
Authors Dragieva *et al.* (2004)[42] Linked publications[161] **Data source** Full published paper **Country** Switzerland **Language** English **Study design** RCT **No. of participants** Total: 17 (34 lesional areas with 129 AK; two lesional areas per patient were randomised for treatment) Intervention: 17 lesional areas (62 AK) Comparator: 17 lesional areas (67 AK) **No. of recruiting Centres** One **Follow-up period and frequency** FU 1, 4, 8 and 16 wk after 2nd treatment. AEs also recorded at these times and before and after illumination	**Treatment intention** Curative **Type(s) of lesion and histology** Mild to moderate AK **Main eligibility criteria** Male and female organ transplant recipients (18 or over) with mild to moderate AK (confirmed by 4-mm punch biopsy from thickest region). Patients with porphyria or known allergy to compounds or excipients of the cream were excluded **Patient characteristics** % Male: 76 Age range: 44–76 yr Mean age: 61 yr Most lesions were located on the face or scalp. Lesions were either untreated or had received previous ineffective treatment over 1 mth ago **Concomitant treatment** 1 g of oral paracetamol 1 hr before illumination and a fan was used on the affected area	**Trial treatments** MAL–PDT vs PDT with placebo cream (within-participant comparison) **Intervention** MAL–PDT: Two consecutive treatments 1 wk apart, performed on areas of maximum size 4 × 4 cm. Superficial curettage followed by application of 1-mm-thick MAL cream then covered with an occlusive dressing for 3 hr. After removal of dressing and cleaning of area using saline solution, PDT was delivered at 80 mW/cm^2 (75 J/cm^2) by a non-coherent light source (emission spectrum 600–730 nm) **Comparator** PDT with placebo cream: As for MAL but with placebo cream	**Morbidity** Week 16: For the MAL–PDT group there was CR of 13/17 lesional areas (95% CI 9 to 16) and PR in 3/17. There was no reduction in size or number of AK in 1/17 MAL–PDT treated area and in all placebo-treated areas. Overall lesion CR rate for MAL–PDT was 56/62 and for placebo 0/67 ($p = 0.0003$) **QoL and return to normal activity** Not assessed **AEs** For the MAL–PDT group discomfort (using the VAS scale) was mild in 11/17 and moderate in 6/17 (1st illumination) – and mild in 6/17, moderate in 9/17 and severe in 2/17 (2nd illumination). Mild to moderate intensity AEs for the MAL–PDT group included erthyema, oedema and crusting. For placebo treated areas discomfort was mild in all cases	**Authors' conclusions** PDT with methyl aminolevulinate is safe and effective for AK in transplant recipients. It may also reduce the risk of transformation of AKs to invasive, and potentially fatal, SCC **Brief study appraisal** This study was generally of high quality in methods and reporting. As the population recruited were immunosuppressed transplant recipients the results may not be generalisable to other populations

Study details	Population details	Treatment details	Results	Interpretation
Authors Ericson *et al.* (2004)[43] **Data source** Full published paper **Country** Sweden **Language** English **Study design** RCT **No. of participants** Total: 40 (37 analysed) Intervention: Nine (broad filter, 50 mW/cm^2) Comparator: 10 (broad filter, 75 mW/cm^2) 2nd Comparator: Nine (narrow filter, 30 mW/cm^2) 3rd Comparator: Nine (narrow filter, 45 mW/cm^2) **No. of recruiting centres** Multicentre **Follow-up period and Frequency** 7 wk	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Clinically typical AK; either one AK lesion, minimum diameter of 20 mm, or three lesions within area exceeding 25 cm^2 **Patient characteristics** % Male: 80 Mean age: 71 yr Lesions were located on the face, scalp, neck and upper chest **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT 50 mW/cm^2 (broad filter) vs ALA–PDT 75 mW/cm^2 (broad filter) vs ALA–PDT 30 mW/cm^2 (narrow filter) vs ALA–PDT 45 mW/cm^2 (narrow filter). Total dose 100 J/cm^2 (all treatments) **Intervention** ALA–PDT: Crusts and scales were removed then 20% ALA cream was applied using an occlusive bandage and removed after 3 hr. The Photo Demarcation System 1, Prototype 5, was used to deliver 50 mW/cm^2, total dose 100 J/cm^2. Fluorescence imaging recordings (365 and 405 nm, 0.5 mW/cm^2) took place before treatment, during treatment (after 5, 10, 20 and 40 J/cm^2) and after finishing treatment (100 J/cm^2) **Comparator** ALA–PDT with 75 mW/cm^2 (broad filter); other treatment details as before **2nd comparator** ALA–PDT with 30 mW/cm^2 (narrow filter); other treatment details as before **3rd comparator** ALA–PDT with 45 mW/cm^2 (narrow filter); other treatment details as before	**Morbidity** There was a significant correlation between fluence rate and treatment outcome ($p < 0.02$); the highest number of patients with complete remission was in the 30 mW/cm^2 (narrow filter) group (8/9 patients). There was a non-significant trend towards a smaller proportion of remaining AK for the narrow filter ($p = 0.07$). No significant difference was found between 45 mW/cm^2 (narrow) and 50mW (broad) groups implying preferable treatment outcome was attributable to fluence rate not spectral emission **QoL and return to normal activity** Not assessed **AEs** There was no significant correlation between fluence rate and VAS score. The VAS value increased up to a peak after a cumulative light dose of 20 J/cm^2	**Authors' conclusions** Photobleaching rate and primary treatment outcomes are dependent on fluence rate. A low fluence rate (30 mW/cm^2) seems preferable when performing PDT of AK using non-coherent light sources **Brief study appraisal** The details of this small trial were poorly reported therefore the reliability of the conclusions is unclear; however, the authors acknowledge that a larger RCT is required

Study details	Population details	Treatment details	Results	Interpretation
Authors Fowler and Zax (2002)[44] Linked publications[162,163] **Data source** Full published paper. A summary of results of 2 trials with identical treatment protocols. Results for most outcomes were only available as combined data. Further data were obtained from drugs.com[162] **Country** Not stated **Language** English **Study design** RCT **No. of participants** Total: Reported as being 243, across two trials – 116 in trial ALA-018, and 125 in trial ALA-019 (which totals 241) Intervention: ALA-018: 87 ALA-019: 93 Comparator: ALA-018: 29 ALA-019: 32 **No. of recruiting centres** Multicentre **Follow-up period and frequency** 1, 4, 8, and 12 wk, then FU at intervals of approximately 3 to 6 mth, up to 48 mth	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Patients with 4–15 grade I or II AKs on the face or scalp. Excluded patients had a history of cutaneous photosensitisation, porphyria, hypersensitivity to porphyrins, photodermatosis or inherited or acquired coagulation defects **Patient characteristics** % Male: 90 Age range: 34–89 yr The number of treated lesions per patient ranged from 4 to 15 Treated areas were the face or scalp, but not both in the same patient **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT vs PDT with placebo cream **Intervention** ALA–PDT: Topical 20% ALA and 10 J/cm^2 of visible blue light (from the BLU-U illuminator, for 1000 s) were applied. Lesions that had not cleared were re-treated at 8 wk and all patients were re-evaluated at 12 wk. After 12-wk long-term lesion recurrence was based on complete chart review (including lesion photographs and treatment during most recent patient visits at wk 36–48) **Comparator** Not described	**Morbidity** *At wk 8, CR rate (100%), by no. of patients*: ALA-018: 60/87 (69%) ALA–PDT vs 4/29 (14%) placebo ALA-019: 59/93 (63%) ALA–PDT vs 4/32 (13%) placebo *At wk 8, > 75% clearance rate, by no. of patients*: ALA-018: 68/87 (78%) ALA–PDT vs 6/29 (21%) placebo ALA-019: 71/93(76%) ALA–PDT vs 8/32 (25%) placebo When results for the two trials were pooled, the CR rate, for number of lesions, was: Lesion grade I: 666/756 (88%) ALA–PDT vs 122/302 (40%) placebo Lesion grade II: 495/632 (78%) ALA–PDT vs 52/199 (26%) placebo 34% of patients were re-treated at 8 wk At wk 12 CR rate was 129/180 (72%) in the ALA–PDT group vs 7/61(11%) in placebo treated patients. A response rate of least 75% was reported in 158/180 (88%) of ALA–PDT patients vs 12/61(20%) placebo-treated patients. The clearance rate was higher for facial lesions than scalp lesions At 4 yr after PDT, of 32 lesions in four patients (PDT group), 69% (22) remained cleared, 9% (3) were 'recurrent' and 22% (7) were 'uncertain'. Further results were reported **QoL and return to normal activity** For ALA–PDT cosmetic response was rated as 'good' to 'excellent' by investigators in 92% of lesions; patients rated cosmetic response as 'good' to 'excellent' in 94% AK lesions; 85% of patients previously treated with 5-FU or cryotherapy indicated a preference for ALA–PDT for future management **AEs** Severe stinging and/or burning was reported by at least 50% of PDT patients; less than 3% stopped treatment. In 99% of PDT patients, some or all lesions were erythematous shortly after treatment vs 79% in the placebo group. In 35% of PDT patients some or all lesions were oedematous vs 0% in the placebo group. Both types of AE resolved or improved by 4 wk. More ALA patients also reported postPDT itching (26% vs 7%) Seven patients had an SAE – all were deemed remotely, or not related to, treatment	**Authors' conclusions** The excellent short- and long-term cosmetic results, low recurrence rate and high rate of patient and physician satisfaction associated with ALA–PDT indicate definite advantages over other existing treatment modalities for AK **Brief study appraisal** Few methodological details were reported, and details of the study population were unclear. The sources of information appeared contradictory in reporting that FU both ceased at 12 mth, and also continued for 4 yr. The 4-yr results were presented for just four patients and this, coupled with the lack of a clinically relevant comparison treatment, further questions the reliability of the authors' conclusions. (Attempts were made to contact authors for further details.)

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Study details	Population details	Treatment details	Results	Interpretation
Authors Freeman (2003)[45] Linked publications[164,165] **Data source** Full published paper **Country** Australia **Language** English **Study design** RCT **No. of participants** Total: 204 Intervention: 88 (360 AKs) (active PDT) Comparator: 23 (74 AKs) (placebo PDT) 2nd Comparator: 89 (421 AKs) (cryotherapy) **No. of recruiting centres** Nine **Follow-up period and frequency** FU of 3 mth (after a run-in period of up to 2 wk)	**Treatment intention** Curative **Type(s) of lesion and histology** Mild to moderate non-pigmented AK **Main eligibility criteria** Patients with mild to moderate non-pigmented AK of the face or scalp suitable for cryotherapy (with the largest diameter of each lesion at least 5 mm) **Patient characteristics** % Male: 56 active PDT; 70 placebo PDT; 61 cryotherapy Mean age: 64 Age range: 33–89 yr Cancer stage: Grade I: 209 active PDT; 35 placebo PDT; 232 cryotherapy Grade II: 151 active PDT; 39 placebo PDT; 45 cryotherapy. All patients were Caucasian, most had Fitzpatrick skin type I or II **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs PDT with placebo cream vs conventional cryotherapy **Intervention** MAL–PDT: Scales and crusts were removed and lesion surface roughened with a curette. MAL cream (160 mg/g) was applied (1 mm thickness) under occlusion for 3 hr then PDT with red light (570–670 nm), intensities of 50–250 mW/cm^2, total dose 75 J/cm^2. 2 identical lamps (Curelight, Photocure ASA, Oslo) illuminated fields with maximum 5.5cm diameter, mean exposure time 10 min with a maximum of six treatment sites (mapped with acetate sheets and AKs marked) per patient. Anatomical landmarks and polaroid photography also used. This PDT procedure was repeated after 7 d **Comparator** PDT with placebo: As for MAL–PDT but with colour-matched cream base instead of MAL **2nd comparator** Cryotherapy: AKs were outlined and lesions were frozen uniformly with a 1- to 2-mm rim. The locally accepted regimen was used, i.e. the protocol specified a single-timed freeze–thaw cycle with no exact freeze time (the time from formation of an ice ball to commencement of thawing). Lesions with a mean diameter less than 10 mm had a mean (SD) freeze time of 0.12 s (0.13); 10- to 20-mm lesions 0.16 s (0.15) and more than 20-mm lesions 0.26 s (0.11)	**Morbidity** Lesion response rate was significantly higher (91%, 267/295) in the MAL–PDT group, than the placebo-PDT group (30%, 18/61) and the cryotherapy group (68%, 278/407), $p < 0.001$ for both. Response rates were higher in the thin lesions than the moderately thick lesions with MAL–PDT; in the cryotherapy group, response rates were higher for thicker lesions **QoL and return to normal activity** A significantly higher proportion of MAL–PDT patients graded overall cosmetic outcome as excellent than with cryotherapy patients (83% vs 51% as assessed by investigator, $p < 0.001$; 76% vs 56% as assessed by the patient, $p = 0.013$). Hypopigmentation was present in 5% MAL–PDT treated sites vs 29% cryotherapy sites. Hyperpigmentation, scar formation or tissue defects were present in less than 6% of total lesion sites. MAL–PDT patient satisfaction was rated better than previous treatment in 61%, equal in 24% and worse in 15%. Placebo-PDT patient satisfaction was rated better than previous treatment (cryotherapy, surgery or 5-FU) in 21%, equal in 14% and worse in 64% **AEs** No systemic AEs were reported. The most common AEs were local reactions (74%). 73% patients experienced at least 1 local AE after the 1st PDT session and 66% after the 2nd PDT session; 35% after cryotherapy; 30% after the 1st and 27% after the 2nd placebo PDT. Most of the AEs in the MAL–PDT group were mild (48%) or moderate (40%) intensity. Other reported AEs common with MAL–PDT were: burning sensation, stinging, painful skin (46%), erythema (23.9%), oedema (8.5%), skin peeling (5.1%), blisters (3.4%), itching (5.1%) and crusting (2.3%). Median duration was 1 wk or less (all events). 1 MAL–PDT patient discontinued due to the burning sensation	**Authors' conclusions** PDT with MAL–PDT is an excellent treatment option, particularly for patients with widespread damage or AK lesions in cosmetically sensitive areas **Brief study appraisal** Generally a well-conducted and reported study; although the conclusions appear likely to be reliable, it should be noted that cryotherapy was delivered using 'locally accepted regimens' allowing clinical variation between the nine centres

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Study details	Population details	Treatment details	Results	Interpretation
Authors Gupta (2004)[35] **Data source** Abstract **Country** Canada **Language** English **Study design** RCT **No. of participants** Total: 50 Intervention: 25 Comparator: 25 **No. of recruiting centres** One **Follow-up period and frequency** FU at wk 4, 8, 12 and 26	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Participants with 5–20 lesions of moderate to severe AKs were eligible **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT vs 5-FU **Intervention** ALA–PDT: Incubation with ALA for 45–60 min before illumination with a Blue Light PDT Illuminator (400–450 nm). Treatment repeated at wk 8 if there was less than a 75% reduction in AKs. No further details reported **Comparator** 5-FU: Application of 5-FU to the face or scalp twice daily for 2–4 wk as tolerated	**Morbidity** Not assessed **QoL and return to normal activity** Not assessed **AEs** At 1 wk FU ALA–PDT patients showed few signs of irritation (erythema, scaling and crusting); 5-FU patients exhibited moderate to severe erythema	**Authors' conclusions** If short-duration ALA–PDT is shown to be as effective as 5% 5-FU at wk 12 and 26 then it may be a suitable treatment alternative for subjects with multiple moderate to severe AKs **Brief study appraisal** As there were few details available in the abstract, the efficacy of the treatments was not described and the study is not yet complete, the reliability of the author's conclusion is unclear. (Attempts were made to contact the study author.)

Study details	Population details	Treatment details	Results	Interpretation
Authors Hauschild *et al.* (2008),[60] Trial AK03 Linked publications[166] **Data source** Full published paper **Country** Germany **Language** English **Study design** RCT **No. of participants** Total: 103 (587 lesions) Intervention: 69 Comparator: 34 **No. of recruiting centres** 29 (unclear whether this was for each trial) **Follow-up period and frequency** FU after 12 wk	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Caucasian males and females (at least 18 yr old) with skin types I–IV were eligible for inclusion. AK lesions had to be mild to moderate (Cockrell definition) with a maximum diameter of 1.8 cm and interlesional distance of at least 1 cm. The following were excluded: women of child-bearing potential, non-responders to previous PDT, patients with particular dermatological conditions, porphyria, dementia or clinically relevant immunosuppression, topical treatment that may affect response 4 wk before and during the study (various criteria), treatment with cytostatics or radiation 3 mth prior to/during study, and intolerance to ingredients of ALA **Patient characteristics** % Male: 82 Mean Age: ALA 70.4; Placebo 71.4 Age Range: 51–89 yr Skin Type: I 9%; II 83%; III 1% **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT patch vs placebo PDT patch **Intervention** ALA–PDT: 3–6 patches (4 cm^2) containing 8 mg of 5-ALA was applied to lesions without preparation. One patch per lesion. After 4 h, illumination with red light (37 J/cm^2, 630 ± 3nm) with an LED source. Patients were instructed to protect lesions from light for 48 h after therapy **Comparator** Placebo-PDT: As for ALA–PDT but with placebo on the patches	**Morbidity** CCCR (lesions) was 82% (316/384) for ALA–PDT vs 19% (34/179) for placebo, $p < 0.0001$. Corresponding clearance rates on a patient basis were 62% (41/66) vs 6% (2/33), $p < 0.0001$ **QoL and return to normal activity** There was no difference between PDT or placebo in the cosmetic assessment of 'cleared lesions' (patient assessment $p = 0.35$; investigator assessment 0.54). Pigmentation status classed as 'normal' in the ALA–PDT groups were 91% vs 12%. There was no statistical difference from those treated with placebo-PDT ($p = 0.95$). 95% of ALA–PDT patients were very satisfied or satisfied with the overall cosmetic outcome vs 44% with placebo-PDT. Patient satisfaction with overall outcome was greater with PDT ($p < 0.0001$) **AEs** One AE was described as relating to therapy (transient discoloration of the skin with ALA) Transient skin discoloration in one patient was related to ALA treatment. ALA patients had more overall local reactions when treatment was applied (mostly itching, 42% vs 13%; the 13% placebo figure appears to be pooled from the 2 trials)	**Authors' conclusions** ALA–PDT is an easy to handle one-step procedure for therapy of isolated mild to moderate AK lesions. Compared with current PDT procedures, pre-treatment (e.g. curettage) is not needed and handling is considerably facilitated. ALA–PDT leads to efficacy rates superior to placebo **Brief study appraisal** This study appeared to be generally well conducted; however, it was unclear how many centres were used and the reporting of results was sometimes unclear

CCCR, Complete clinical clearance rate.

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Study details	Population details	Treatment details	Results	Interpretation
Authors Hauschild *et al.* (2008),[60] Trial AK04 Linked publications[166] **Data source** Full published paper **Country** Germany **Language** English **Study design** RCT **No. of participants** Total: 349 (1950 lesions) Intervention: 148 Comparator: 149 (cryosurgery) 2nd Comparator: 49 (placebo) **No. of recruiting centres** 29 (unclear whether this was for each trial) **Follow-up period and frequency** FU after 12 wk	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Caucasian males and females (at least 18 yr old) with skin types I–IV were eligible for inclusion. AK lesions had to be mild to moderate (Cockrell definition) with a maximum diameter of 1.8 cm and interlesional distance of at least 1 cm. The following were excluded: women of child-bearing potential, non-responders to previous PDT, patients with particular dermatological conditions, porphyria, dementia or clinically relevant immunosuppression, topical treatment that may affect response 4 wk before and during the study (various criteria), treatment with cytostatics or radiation 3 mth prior to/during study and intolerance to ingredients of placebo or known reactions to cryotherapy **Patient characteristics** % Male: 72 Mean age: PDT 70, cryosurgery 71, placebo 72 Age range: 41–94 yr Skin type: I 18%, II 66%, III 15%, IV 1% **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT patch vs cryosurgery vs Placebo PDT patch **Intervention** ALA–PDT patch: 4–8 patches (4 cm^2) containing 8 mg of 5-ALA were applied to lesions without preparation, one patch per lesion. After 4 hr, illumination with red light (37 J/cm^2, 630 ± 3 nm) with Omnilux (11 centres). Patients were instructed to protect lesions from light for 48 hr after therapy **Comparator cryosurgery**: A standardised protocol was used. Open spraying procedure with liquid nitrogen in 1 cycle was used (with size C nozzles) and freeze time (of 5–10 s) started after ice ball formation **2nd comparator** Placebo PDT patch: As for ALA–PDT but with placebo on the patches	**Morbidity** The complete clinical clearance rates (lesions) were 89% (664/750) for ALA–PDT, 77% (530/692) for cryosurgery and 29% (75/259) for placebo. PDT was significantly better than placebo PDT ($p < 0.001$) and cryosurgery ($p = 0.007$). Clearance rates (patients) were ALA–PDT 67% (86/129), cryosurgery 52% (66/126) and placebo 12% (5/43). PDT was significantly better than placebo and cryosurgery ($p < 0.001$ for both) **QoL and return to normal activity** Patients' and investigators' assessment of cosmetic outcome of cleared lesions was significantly better for ALA–PDT than cryosurgery ($p < 0.001$). 95% of ALA–PDT patients were very satisfied or satisfied with the overall cosmetic outcome vs 82% with cryosurgery. It appears to be reported that ALA patients were significantly more satisfied than placebo and cryosurgery ($p < 0.0001$). Pigmentation status classed as 'normal' in the ALA–PDT groups was 88%. Hypopigmentation was seen in 33% of lesions with cryosurgery. Hyperpigmentation was seen in 9% PDT patients vs 4% placebo. Pigmentation status was significantly different between ALA–PDT and cryosurgery ($p < 0.001$) but the difference between ALA–PDT and placebo was not significant ($p = 0.87$) **AEs** Three per cent in the ALA and cryosurgery arms and 2% placebo reported an AE related to therapy. 99% of ALA patients experienced an adverse reaction at some stage of treatment (placebo data was pooled with trial AK03)	**Authors' conclusions** ALA–PDT is an easy to handle one-step procedure for therapy of isolated mild to moderate AK lesions. Compared with current PDT procedures, pre-treatment is not needed and handling is considerably facilitated. A single PDT treatment results in efficacy rates being statistically significantly superior to placebo and cryosurgery **Brief study appraisal** The study appears to be generally well conducted but reporting of some of the methodology and results was unclear

Study details	Population details	Treatment details	Results	Interpretation
Authors Hauschild *et al.* (2008)[55] **Data source** Full published paper **Country** Germany **Language** English **Study design** RCT **No. of participants** Total: 149: 146 patients completed study, of which 140 (520 lesions) were in the per protocol population Intervention: 34 (128 lesions) 0.5-hr incubation Comparator: 38 (138 lesions) 1-hr incubation 2nd Comparator: 34 (124 lesions) 2-hr incubation 3rd Comparator: 34 (130 lesions) 4-hr incubation **No. of recruiting centres** 12 **Follow-up period and frequency** 4 and 8 wk after treatment	**Treatment intention** Curative **Type(s) of lesion and histology** AK (mild to moderate) **Main eligibility criteria** Caucasian males or females aged at least 18 yr with histologically confirmed mild to moderate AK. Lesions were required to have maximum diameter of 1.8 cm and interlesional distance of at least 1 cm. Patients with dermatological conditions likely to impact on results were excluded. Further eligibility criteria were reported **Patient characteristics** % Male: 74 Age range: 39–91 yr across groups Mean age: 72 yr, 72 yr, 70 yr, 70 yr, respectively, for the four treatment groups Most lesions were located on the scalp or forehead in all groups, severity was fairly evenly split between mild and moderate. Mean lesion diameter was similar across groups at around 8–9 cm **Concomitant treatment** Any other topical treatment able to affect AK not permitted 4 wk prior to and during study. No urea and salicylic acid-containing preparations permitted 2 wk prior and during study	**Trial treatments** Patch containing ALA (PD P 506 A) applied to lesions for 0.5, 1, 2 or 4 hr followed by illumination with red light **Intervention** PDT patch + 0.5-hr incubation: Between three and four lesions per patient were treated using a PDT patch (one patch per lesion) containing 8 mg of ALA. Patch is lightproof therefore provides occlusive protection. After patch was removed, lesion illuminated with red light (dose 37 J/cm^2, wavelength around 630 nm). Further PDT parameters were not reported **Comparator** PDT patch + 1-hr incubation: see above **2nd comparator** PDT patch + 2-hr incubation: see above **3rd comparator** PDT patch + 4-hr incubation: see above	**Morbidity** The majority of lesions showed clearance 8 wk after PDT and the 4-hr incubation group showed the best response – estimated 86% clearance rate and this was 'statistically selected as the best treatment'. All but 1 of the 12 centres found similar results (details not reported). In some patients, lesions that appeared 'cleared' at wk 4 then worsened by wk 8 – this effect was most apparent in the 0.5-hr group, and was not present in the 4-hr group **QoL and return to normal activity** Not assessed **AEs** Five patients reported AE considered to be related to the study treatment: headache, moderate epistaxis and mild increase of alanine transaminase. Local reactions during application and incubation included burning, pruritis and erythema – all but one case was rated as mild or moderate. Local reactions during illumination appeared to be dose dependent and ranged from 26% in the 0.5-hr group to 66% in the 4-hr group. Most frequent reactions were pain, burning and pruritis. One patient's treatment was interrupted due to severe pain. Almost all patients had local reactions after treatment, with erythema, scabbing, desquamation, burning and pruritis being common. Patients with clearance experienced local reactions to a greater extent than patients without clearance	**Authors' conclusions** PD P 506 A-PDT patches are suitable for the treatment of up to eight AK lesions of mild to moderate intensity on the head and face, and 4-hr application results in excellent outcomes. Further Phase III trials are required to confirm these outcomes **Brief study appraisal** This study was relatively poorly reported making it difficult to assess the reliability of the methodology or results. The use of multiple centres in a small trial raises the possibility of centre-effects on treatment and outcomes. Patients were only followed up for 8 wk. No statistical test results were reported; therefore it is difficult to be confident in the conclusions of efficacy

Study details	Population details	Treatment details	Results	Interpretation
Authors Jeffes *et al.* (1998)[41] **Data source** Abstract **Country** USA **Language** English **Study design** RCT **No. of participants** Total: 36 Intervention: 36 Comparator: 36 **No. of recruiting centres** Not stated multicentre **Follow-up period and frequency** 8 and 16 wk	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Patients with four AKs on the face and scalp **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT vs PDT with placebo (within-participant comparison) **Intervention** ALA–PDT: Two AKs were treated with 20% ALA solution (Levulan) and after 14- to 18-hr exposed to blue (non-laser) light at doses of 2, 5 and 10 J/cm^2. Patients were re-treated at 8 wk if necessary. Further PDT parameters were not reported **Comparator** Placebo PDT: As above except placebo control was used in place of ALA solution	**Morbidity** At 8 wk, 66% of AKs treated with ALA had a CR vs 17% with placebo ($p < 0.001$). At 16 wk. CR was seen in 56/66 (85%) of ALA–PDT patients (no results reported for placebo). AKs treated with ALA–PDT at 5 or 10 J/cm^2 of light resulted in a significantly better response than the corresponding placebo group, although there was no significant difference between the groups at 2 J/cm^2 **QoL and return to normal activity** Not assessed **AEs** The authors reported that hyperpigmentation was seen in 11% of AKs treated with ALA–PDT, which was not different from the placebo group. The treatment was well tolerated and no patients withdrew due to an AE	**Authors' conclusions** The authors did not report any conclusions **Brief study appraisal** Little useful evidence could be retrieved from this abstract which provided very few methodological or result details, and involved a fairly small sample followed up for 16 wk

Study details	Population details	Treatment details	Results	Interpretation
Authors Kaufmann *et al.* (2008)[46] **Data source** Full published paper **Countries** Australia, Belgium, Germany, UK **Language** English **Study design** RCT **No. of participants** Total: 121 (1343 lesions) Intervention: 121 (691 lesions) Comparator: 121 (652 lesions) **No. of recruiting centres** 24 **Follow-up period and frequency** FU at wk 12 and 24. Additional telephone calls were made at wk 1 and 13 when patients were re-treated	**Treatment intention** Curative **Type(s) of lesion and histology** Non-hyperkeratotic AK **Main eligibility criteria** Males and non-pregnant women aged 18 or over, with a clinical diagnosis of non-hyperkeratotic AK, of mild or moderate thickness, on locations other than the face or scalp, were eligible for inclusion. Patients had to have at least four comparable symmetrical AKs, of similar severity and total number on both sides of the body. Further eligibility criteria were reported **Patient characteristics** % Male: 65 Age range: 38–89 yr Mean age: 68.9 yr Cancer stage: Grade I, 687; grade II, 656 Patients had (a mean of) six lesions per side. Further patient characteristics were reported **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs cryotherapy (within-participant comparison) **Intervention** MAL–PDT: After scraping of lesions, a 1-mm layer of 160-mg/g MAL cream was applied to each lesion (including 5 mm of surrounding tissue) for 3 hr (under occlusion). After saline cleansing, a standard LED lamp illuminated lesions with narrow band red light (average 630 nm, dose 37 J/cm^2, mean time 8 min 36 s). Lesions with a non-CR were re-treated after 12 wk **Comparator** Cryotherapy: Double freeze–thaw cryotherapy using liquid nitrogen spray applied with a 1- to 2-mm frozen rim outside the lesion outline. Timing of freeze–thaw application was as per usual practice of each centre (mean time 20 s ± 14 s)	**Morbidity** At wk 24 the mean reduction in lesion count from baseline was 78% for MAL–PDT and 88% for cryotherapy (per-protocol population) ($p = 0.002$), 95% CI of the bilateral difference (MAL–PDT/cryotherapy) was between –16.6% and 3.9%. ITT (last observation carried forward) analysis confirmed this (75% reduction with MAL–PDT vs 87% with cryotherapy, $p < 0.001$). 76% (455) of lesions were cured with MAL–PDT vs 88% (490) with cryotherapy. The difference was similar for mild- and moderate-thickness lesions **QoL and return to normal activity** Investigator-assessed cosmetic outcome was significantly better for MAL–PDT than cryotherapy ($p < 0.001$). In the MAL–PDT group, 79% of lesions had an excellent cosmetic outcome, 19% good, 3% fair and 0% poor (compared with 56% excellent, 36% good, 8% fair and 0.9% poor with cryotherapy). After 24 wk, 50% of patients preferred MAL–PDT in terms of cosmetic outcome compared with 22% for cryotherapy ($p < 0.001$). 28% had no preference (ITT analysis). Patients preferred MAL–PDT to cryotherapy for all questions in the patient questionnaire (between 12% and 58% of difference). The differences were marked apart from effectiveness of treatment (39% favoured MAL–PDT vs 26% cryotherapy, not significant). Patients preferred MAL–PDT in terms of comfort (60% vs 10%, $p < 0.001$), procedure (49% vs 28%, $p = 0.05$) and healing (64% vs 6%, $p < 0.001$). Overall patient satisfaction favoured MAL–PDT (49% vs 20%, $p < 0.001$). If re-treatment was required 59% would prefer MAL–PDT over cryotherapy (25%, $p < 0.001$) **AEs** There were 63% patients with 99 AEs with cryotherapy vs 45% patients with 67 AEs with MAL–PDT. Most were dermatological and related to treatment. The most commonly reported AE for MAL–PDT was photosensitivity reaction (43% of patients with 63 AEs) and cold exposure injury for cryotherapy (62% patients with 95 AEs). Most were of mild intensity. Two patients in the cryotherapy group reported severe cold exposure injury	**Authors' conclusions** MAL–PDT showed inferior efficacy for treatment of non-face/scalp AK compared with cryotherapy. However, both treatments showed high efficacy, and MAL–PDT conveyed the advantages of better cosmesis and higher patient preference **Brief study appraisal** The study was quite well conducted, but it was open in design and therefore there was potential for investigator/patient bias. The possibility of institutional differences and/or protocol deviation (24 centres in four countries) affecting the reliability of results was illustrated by the wide variation of freeze–thaw timings used for cryotherapy

Study details	Population details	Treatment details	Results	Interpretation
Authors Kurwa *et al.* (1999)[47] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 17 Intervention: 17 Comparator: 17 **No. of recruiting centres** Not stated **Follow-up period and frequency** 1 wk, 4 wk and 6 mth	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** It appeared that patients with a long history of AKs affecting the forearms and hands were eligible for inclusion **Patient characteristics** % Male: 47 Age range: 53–79 yr **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT vs 5-FU (within-participant comparison) **Intervention** ALA–PDT: Thick surface scale was removed if present then 20% 5-ALA was applied topically and covered in a light-impermeable dressing for 4 hr. PDT was administered with a halogen lamp (580–740 nm, 150 J/cm^2, mean fluence rate 80 mW/cm^2) **Comparator** 5-FU cream (5%) was applied topically twice a day to one hand for 3 wk by thorough massage	**Morbidity** The mean lesional area before treatment for PDT was 1322 mm^2 and 6 mth after treatment was 291 mm^2 (a reduction of 73%, 95% CI 61% to 84%). For 5-FU, mean lesional area was 1390 mm^2 before treatment and 297 mm^2 after (a reduction of 70%, 95% CI 61% to 80%). There was no statistically significant difference in reduction of lesional area between PDT and 5-FU at 6 mth ($p = 0.72$). No patients were completely cleared of AKs with either treatment **QoL and return to normal activity** Not assessed **AEs** All patients experienced mild to moderate pain at PDT sites. In wk 1, PDT sites were significantly more painful than 5-FU sites, but this difference was absent in wk 2 and reversed in wk 4. There was no significant difference between treatments overall over the 4-wk period. Daily symptom diaries were completed by 11 patients. In wk 1, PDT sites were significantly more erythematous than 5-FU sites but this difference was absent in wk 2 and reversed in wk 3 and 4. There was no significant difference between treatments overall over the 4-wk period. There was no blistering, ulceration, scarring or photosensitivity reaction after either treatment method. One patient experienced contact sensitivity to 5-FU	**Authors' conclusions** One treatment with PDT using topical 5-ALA appears to be as effective and well tolerated as 3 wk of twice-daily topical 5-FU, a cheap and widely available alternative **Appraisal** This study appeared to be too small to detect significant treatment effects. The methods and results were not clearly reported and measures to reduce bias (e.g. randomisation, blinding and allocation concealment) were not reported at all so the reliability of the conclusions is questionable

Study details	Population details	Treatment details	Results	Interpretation
Authors Legat *et al.* (2006)[36] **Data source** Abstract **Country** Austria **Language** English **Study design** RCT **No. of participants** Total: 22 (mean number AKs 47, range 17–89) Intervention: 22 (no. of AK not reported) Comparator: 22 (no. of AK not reported) 2nd Comparator: six (no. of AK not reported) **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 4, 12 and 24 wk	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Not stated **Patient characteristics** % Male: 100 Age range: 59–84 yr Median age: 75 yr Patients had multiple AKs **Concomitant treatment** Not stated	**Trial treatments** PDT with fractionated illumination vs PDT with unfractionated illumination. Within-participant comparison, but six patients had PDT with fractionated illumination vs alternative fractionated illumination, due to severe pain after 1st fractionated dose **Intervention** PDT with unfractionated illumination: Following application of MAL cream for 3 hr, red light illumination (peak emission 635 nm) of a single dose of 37 J/cm^2 was applied **Comparator** PDT with fractionated illumination: As for PDT with unfractionated illumination except PDT was given in two doses of 18.5 J/cm^2 divided by a dark interval of 15 min **2nd comparator** PDT with alternative fractionated illumination: As for PDT with unfractionated illumination except with three doses of 12.3 J/cm^2, with two dark intervals of 5 min	**Morbidity** The mean number of AK at wk 4, 12 and 24 was reduced by 65, 60 and 48% with unfractionated PDT and 56, 53, and 50% with fractionated PDT respectively (difference not significant, $n = 14$). Similar results seen for alternative fractionated PDT group **QoL and return to normal activity** Not assessed **AEs** PDT induced pain (VAS score) was 6.7 (SE 0.5) for unfractionated PDT and 6.0 (0.5) for fractionated PDT ($n = 14$, $p = 0.02$). There was no significant difference in pain between fractionated and alternative fractionated patients [8.0 (0.7) vs 8.2 (0.3) respectively]	**Authors' conclusions** PDT with fractionated and unfractionated illumination were similarly effective in reducing AKs. However, pain sensation during PDT was significantly less intense with standard fractionated than unfractionated illumination **Brief study appraisal** Few methodological details were provided in the abstract and the results of this small study may not be generalisable

Study details	Population details	Treatment details	Results	Interpretation
Authors Moloney *et al.* (2007)[37] **Data source** Abstract **Country** Not stated **Language** English **Study design** RCT **No. of participants** Total: 16 Intervention: 16 Comparator: 16 **No. of recruiting centres** Not stated **Follow-up period and frequency** 1 mth	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Not stated **Patient characteristics** % Male: 100 Age range: 59–87 yr All patients had AKs on the scalp **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs ALA–PDT **Intervention** MAL–PDT: MAL cream was applied for 3 hr. Further PDT parameters were not reported **Comparator** ALA–PDT: 20% ALA cream was applied for 5 hr. Further PDT parameters were not reported	**Morbidity** AK counts reduced by 5.6 ± 3.2 (MAL) vs 6.2 ± 1.9 (ALA) ($p = 0.588$) ($n = 15$) **QoL and return to normal activity** Not assessed **AEs** All patients ($n = 15$) experienced pain, which was of greater intensity on the ALA treated side at all time points: 3 min, $p = 0.151$; 6 min, $p = 0.085$; 12 min, $p = 0.012$; 16 min, $p = 0.029$. There was also longer duration of discomfort post treatment with ALA ($p = 0.044$)	**Authors' conclusions** Both ALA and MAL–PDT result in significant reduction in scalp AKs. There is no significant difference in efficacy. However, ALA is more painful than MAL–PDT in the treatment of extensive scalp AKs **Brief study appraisal** The abstract provided few methodological details and involved a small sample, followed up for only 1 mth, so the reliability of the conclusions is unclear

Study details	Population details	Treatment details	Results	Interpretation
Authors Morton *et al.* (2006)[48] Linked publications[167,168] **Data source** Full published paper **Countries** Ireland, UK **Language** English **Study design** RCT **No. of participants** Total: 119 (1501 lesions) Intervention: 119 (758 lesions) Comparator: 119 (743 lesions) **No. of recruiting centres** 25 **Follow-up period and frequency** FU at wk 12 and 24. Additional telephone FU was performed at wk 1 and 13	**Treatment intention** Curative **Type(s) of lesion and histology** Non-hyperkeratotic AK **Main eligibility criteria** Males and females over 18 yr (16 yr in Scotland) with clinical diagnosis of (at least three) non-hyperkeratotic AK on the face and/or scalp (of similar severity and number on both sides) were eligible for inclusion. Patients that received topical treatment within the previous 3 mth, regular UV therapy, patients with thick or pigmented lesions or porphyria were excluded **Patient characteristics** % Male: 91 Age range: 54–93 yr Mean age: 75 yr Mean no. of lesions per side: six Median lesion diameter: 7 mm Further patient characteristics were reported **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs cryotherapy (within-participant comparison) **Intervention** MAL–PDT: After scraping of lesions, a 1-mm layer of MAL 160 mg/g cream was applied (including 5 mm of surrounding tissue) for 3 hr (under occlusion). Following saline cleansing, lesions were illuminated with narrowband light (approximately 630 nm, dose 37 J/cm^2) using a standard LED light source. Mean illumination time was 8 min 41 s. Lesions with a non-CR were re-treated at 12 wk **Comparator** Double freeze–thaw cryotherapy: Liquid nitrogen spray applied to achieve a 1- to 2-mm frozen rim around the marked outline of the lesion. Mean freezing time was 16 s (± 7 s)	**Morbidity** At wk 12 lesion reduction with MAL–PDT was 87% vs 76% ($p < 0.001$). Reduction in lesion count at wk 24 was 89% with MAL–PDT vs 86% with cryotherapy ($p = 0.2$, $n = 108$). At wk 12 CR was 83% with MAL–PDT vs 72% with cryotherapy. At wk 24 it was 86% (650/758) with MAL–PDT vs 83% (613/743) with cryotherapy. 21% of lesions with CR at wk 24 had needed re-treatment with cryotherapy at wk 12 vs 10% with MAL–PDT, results were independent of initial severity grade or location (ITT population) **QoL and return to normal activity** Overall participant preference (i.e. cosmetic outcome, efficacy, and skin discomfort) was 49% for MAL–PDT vs 21% for cryotherapy ($p < 0.001$, ITT analysis). Results reported for per-protocol population were 45% vs 10%, $p < 0.001$. Investigator preference for cosmetic outcome was 43% for MAL–PDT vs 12% for cryotherapy, $p < 0.001$, and for overall preference was 52% vs 16%, $p < 0.001$. Most subjects were 'satisfied' to 'very satisfied' with MAL–PDT (compared with cryotherapy and previous other AK treatments) for 7/11 questions of a satisfaction questionnaire. More than 90% were satisfied with MAL–PDT in terms of effectiveness of treatment, scarring, skin colour and appearance at 1- and 3-mth FU. Cryotherapy was preferred for time taken over treatment (92%) compared to 78% for MAL–PDT. 65% would prefer to be re-treated with MAL–PDT vs 32% with cryotherapy ($n = 108$) **AEs** Skin discomfort VAS scores (mean) were 5.2 with MAL–PDT vs 4.9 with cryotherapy ($p = 0.24$) after 1st treatment. For re-treated lesions, mean VAS scores were 3.7 vs 4.4. Patients preferred cryotherapy in terms of skin discomfort after 1st treatment (45% vs 33%, no preference 22%, $p = 0.07$), but there was no difference for re-treated lesions. Skin-related AEs were reported by 62% MAL–PDT patients vs 72% for cryotherapy. There was one discontinuation with MAL–PDT due to a local reaction. Most skin-related AEs were mild to moderate and transient	**Authors' conclusions** When treated with both MAL–PDT and cryotherapy, patients significantly prefer MAL–PDT treatment for AK. MAL–PDT is an attractive treatment option for AK, with comparable efficacy and superior cosmetic outcomes compared with double freeze–thaw cryotherapy **Brief study appraisal** This study was generally well conducted and reported; however, it was an open-label trial, which can lead to bias in favour of a particular treatment. The possibility of institutional differences and/or protocol deviation (25 centres in two countries) affecting the reliability of results was illustrated by the variation of freezing times used for cryotherapy

UV, ultraviolet.

Study details	Population details	Treatment details	Results	Interpretation
Authors Pariser *et al.* (2003)[49] **Data source** Full published paper **Country** USA **Language** English **Study design** RCT **No. of participants** Total: 80 (502 lesions) Intervention 42 (260 lesion) Comparator: 38 (242 lesions) **No. of recruiting centres** Five **Follow-up period and frequency** FU was at 3 mth. AEs were assessed during, immediately after PDT, at wk 2 and 3 mth after the 2nd PDT treatment	**Treatment intention** Curative **Type(s) of lesion and histology** Mild and moderate AK **Main eligibility criteria** Males and females over 18 yr with 4–10 previously untreated mild to moderate non-pigmented AK on the face and scalp (at least 3 mm diameter) were eligible for inclusion. Further eligibility criteria were reported **Patient characteristics** % Male: 88 Age range: 31–84 yr Mean age: MAL–PDT 64; placebo PDT 67 The majority of lesions were mild and located on the face. Most patients were Fitzpatrick skin type I or II **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs PDT with placebo cream **Intervention** MAL–PDT: Scales and crusts were removed using a curette MAL cream (160 mg/g) was applied (1-mm thickness and 5 mm around lesion) for mean 3 hr under occlusion. Cream was washed off using a 0.9% saline solution, then a non-coherent red light was applied: 570–670 nm, dose 75 J/cm^2, mean intensity 155 mW/cm^2 (range 50–200 mW/cm^2). Treatment was repeated after 1 wk **Comparator** PDT with placebo cream: As for MAL–PDT but with placebo cream	**Morbidity** For the MAL–PDT group, patient response was 32/39 (82%) vs 8/38(21%) in placebo, treatment difference –61% ($p = 0.001$) For the MAL–PDT group lesion response rate was 209/236 (89%) vs 92/241 (38%) for placebo. Response rate was similar for mild and moderate lesions in the MAL group (90% and 84%, respectively); placebo response was higher in the mild lesions (44% and 25%) **QoL and return to normal activity** Investigator assessed cosmetic outcome in the MAL–PDT group was 'excellent' or 'good' in 31/32 (97%) patients and when assessed by patients this was 29/32 (91%). The outcome was not rated 'poor' by either investigator or patient. 73% of 32 patients preferred MAL–PDT to previous treatments (5-FU, cryotherapy, surgery) **AEs** 38 (90%) MAL–PDT patients had an AE vs 22 (58%) in placebo. One MAL–PDT patient discontinued due to AE. Common local AEs were: burning sensation of the skin (27 MAL patients vs 4); erythema (22 vs 8); crusting (16 vs 6); pain on the skin (10 vs 0); blisters (8 vs 2); skin oedema (6 vs 1); stinging skin (6 vs 1) and skin ulceration (5 vs 0). More details in paper	**Authors' conclusions** PDT using topical MAL was a safe and effective treatment for AK with excellent cosmetic outcome. It is a promising treatment that could benefit from further study **Brief study appraisal** This study appeared to be generally well conducted

Study details	Population details	Treatment details	Results	Interpretation
Authors Pariser *et al.* (2008)[56] Linked publications[169] **Data source** Full published paper **Country** USA **Language** English **Study design** RCT **No. of participants** Total: 100 (723 lesions) (four patients were treated as 'training' population) Intervention: 49 (363 lesions) Comparator: 47 (360 lesions) **No. of recruiting centres** Eight **Follow-up period and frequency** FU 3 mth after last treatment	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Previously untreated males and non-pregnant/ non-lactating females with adequate contraception during and 1 mth after treatment that were at least 18 yr old with 4–10 non-pigmented, non-hyperkeratotic grade I or II lesions on the face and scalp (at least 3-mm diameter) were eligible for inclusion. Exclusion criteria were extensive but included: immunosuppression, porphyria, allergy to MAL or similar, allergy to nut products or protein antigens, regular UV therapy or treatment of face and scalp with local therapy in previous 30 d, topical therapy in previous 3 mth **Patient characteristics** % Male: 82 Mean age: MAL–PDT 66.1; Placebo PDT 66.7 Age range: 43–89 yr Skin type: I 23%; II 50%; III/IV 27% Grade of lesions: Grade I 73%; grade II 27% The majority of lesions were thin (grade I) and located on the face. About 50% of patients had between 8 and 10 lesions in total **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs Placebo PDT **Intervention** MAL–PDT: Preparation of lesions by removal of scales and crusts by dermal curette, then application of 1-mm-thick MAL cream to lesion and surrounding 5 mm skin. Occlusive dressing applied for at least 3 hr (permitted range 2.5–4 hr) and avoidance of exposure to sunlight, bright indoor light and extreme cold. Area then illuminated (average duration, 8 min) with red LED (total dose 37 J/cm^2, 5–8 cm from skin). This procedure was repeated after 1 wk **Comparator** Placebo PDT: As for MAL–PDT but with placebo cream	**Morbidity** Lesion CR rate was 86% for MAL–PDT vs 52% for placebo, OR 6.9 (95% CI 4.7 to 10.3, $p < 0.0001$). Patient CR rate was 59% (29/49) for MAL–PDT vs 15% (7/47) for placebo, OR 13.2 (95% CI 4.1 to 43.1, $p < 0.0001$). 3 mth after treatment 31% (15/49) MAL–PDT patients had 42 new lesions vs 26% (12/47) placebo-PDT patients with 34 new lesions. Four MAL–PDT patients had at least five new lesions vs two placebo. In the MAL–PDT group 67% of new lesions were on the face vs 50% placebo ($p = 0.16$), no difference between location of new lesions ($p = 0.16$) **QoL and return to normal activity** Not assessed **AEs** Any AE/any local AE was reported by 98% (52/53) in the MAL–PDT group. 45% (22/47) reported any AE in placebo group, 45% (21/47) reported any local AE. In the MAL group 32% were mild (vs 38%), 49% were moderate (vs 6%) and 17% were severe (vs 0%). Commonly reported local AEs for the MAL–PDT ($n = 53$) (vs placebo, $n = 47$) patients were: erythema (77 vs 15%), skin burning sensation (72 vs 11%), pain of skin (60 vs 21%), pruritis (23 vs 11%), skin oedema (28 vs 2%), scab (26 vs 0%), skin discomfort (23 vs 2%), blister (15 vs 0%) and skin exfoliation (11 vs 4%)	**Authors' conclusions** Given that MAL–PDT has proved excellent cosmetic outcomes, superior to conventional therapy, this suggests a role for MAL–PDT using a red LED light source in patients with multiple (up to eight) AK lesions **Brief study appraisal** This study appeared to be generally well conducted and explored centre-effects on the results, although further details of the PDT light treatment would have been useful

d, day(s).

Study details	Population details	Treatment details	Results	Interpretation
Authors Puizina-Ivic *et al.* (2008)[57] **Data source** Full published paper **Country** Croatia **Language** English **Study design** RCT **No. of participants** Total: 36 Intervention: Fractionated illumination: 16 Comparator: Single illumination: 20 **No. of recruiting centres** One **Follow-up period and frequency** 24 wk	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Previous histologically confirmed diagnosis of AK **Patient characteristics** Not stated	**Trial treatments** ALA–PDT with 16-hr incubation and two light fractions vs ALA–PDT with 5-hr incubation and a single illumination **Intervention** ALA–PDT with 16-hr incubation and two light fractions: Thick crusts were 1st removed with ointments (and wet dressings). After cleaning the area with a saline solution, the 20% ALA cream was applied to a thickness of approximately 1 mm, covering the treated area, and 1 cm of the surrounding skin. The area was covered by occlusive dressing. Aluminium foil was placed on top in order to protect skin from ambient light. There was then a 16-hr incubation period before red light (635 nm) was applied. The total of 100 J/cm^2 was delivered in 2 doses of 50 J/cm^2 with a fluence intensity of 30 mW/cm^2. There was a 2-hr break between illuminations. Spraying of water and cooling with fan was carried out to minimise pain sensations. After the treatments sunblock ointments were recommended for the next few days in addition to sun protection measures. Biopsies were performed 24 wk after illumination in patients with fluorescence detected after 4 hr **Comparator** PDT with 5-hr incubation with ALA cream and single light fraction: Preparation for illumination was as for the intervention group. There was then a 5-hr incubation period before red light (635 nm) was applied. 100 J/cm^2 was delivered in 1 dose, with a fluence intensity of 30 mW/cm^2. Spraying of water and cooling with fans, and sun protection measures were as for the intervention group. Biopsies were performed 24 wk after illumination in patients whom fluorescence after 3-hr incubation with ALA was detected	**Morbidity** At 24 wk, residual tumour was found in 15 of 20 (75%) biopsied patients in the single illumination, shorter-incubation group. Treatment was repeated. At 24 wk, there was persistence of tumour in 2 of 16 (13%) biopsied patients in the fractionated, longer-incubation group **QoL and return to normal activity** Not assessed **AEs** Not assessed	**Authors' conclusions** PDT delivered as fractionated illumination with 16 hr of incubation separated by a 2-hr dark interval significantly improves therapeutic outcome in tumour eradication **Brief study appraisal** This trial had only a small number of patients. Procedures of randomisation and blinding of outcome assessors were unclear. No patient details were provided. Although the group receiving fractionated illumination had better outcomes, the relative contribution of the longer incubation time and the fractionated delivery are unclear. It is also unclear if there were any AEs

Study details	Population details	Treatment details	Results	Interpretation
Authors Sotiriou *et al.* (2009)[61] **Data source** Full published paper **Country** Greece **Language** English **Study design** RCT **No. of participants** Total 30 (256 lesions) Intervention 30 (133 lesions) Comparator 30 (123 lesions) **No. of recruiting centres** Not stated **Follow-up period and frequency** Followed up at 1 and 6 mth after treatment; if given a 2nd treatment then cycle final FU was at 6 mth after last treatment	**Treatment intention** Curative **Type(s) of cancer and histology** Non-hyperkeratotic AK **Main eligibility criteria** Clinical diagnosis of non-hyperkeratotic grade I (mild) and grade II (moderate) AK on dorsa of hands and forearms. Each patient required to have at least three lesions of comparable severity on each side of body (total of six lesions minimum). Exclusion criteria were any other dermatological diseases or conditions in treatment area or within 3 cm, topical treatments for AK within previous 2 mth, and any invasive tumours in the treatment area **Patient characteristics** % Male: 83 Mean age: 64 yr Age range: 49–79 yr Severity of lesions: Grade I: 54% (PDT), 54% (Imiquimod); grade II: 46% (PDT), 46% (Imiquimod) **Concomitant treatment** None	**Trial treatments** ALA–PDT vs Imiquimod 5% intraindividual right/left comparison **Intervention** ALA–PDT: lesions prepared by removing crusts and curettage, where lesions were not prepared these were all grade I. 20% 5-ALA cream applied to lesions and 5-mm surrounding skin and left for 4 hr. Illumination immediately following removal of dressing using non-coherent red light source, light dose 75 J/cm^2, and fluence rate of 75 mW/cm^2. Patients given two PDT sessions on same day, 1st session targeting the hand and lower forearm, 2nd treating upper two-thirds of the forearm. Two complete PDT treatments were delivered to all areas 15 d apart. Pain management during treatment included use of a fan and/or cooling sprays **Comparator** Imiquimod: treatment based on approved dosage regime for the head. Patients applied 500 mg of imiquimod 5% cream daily for 3 d/wk prior to sleep, cream left on skin for at least 8 hr. This treatment continued for 4 wk (course 1). Following a 4-wk post-treatment period for observation, any patients with lesions remaining repeated the process for a further 4 wk (course 2)	**Morbidity** 1 mth: PDT CR rates were significantly better overall and for grade I and grade II lesions. CR for PDT 70% (87/124) and 18% (21/115) for imiquimod ($p < 0.05$). Grade I lesion CR was 75% for PDT (50/67) and 34% (21/61) for imiquimod ($p < 0.05$). Grade II CR for PDT was 65% (37/57), no grade II lesions achieved CR with imiquimod (0/54). 6 mth: The CR was 65% (81/124) for PDT and 56% (64/115) for imiquimod, but the difference was not statistically significant ($p > 0.05$). There was also no significant difference for grade I lesions, 72% (48/67, PDT) vs 72% (44/61, imiquimod). CR were significantly higher for grade II lesions in the PDT treatment areas (58%, 33/57) than with imiquimod (37%, 20/54, $p < 0.05$) **QoL and return to normal activity** Cosmetic outcome was assessed by the investigators 6 mth after treatment according to scarring, atrophy, erythema and pigment change. Outcomes were graded as excellent, good, fair or poor. No significant differences between the groups were observed; excellent outcomes were 85% in PDT and 75% for imiquimod. A patient-completed questionnaire at 6 mth assessed treatment preferences. The PDT procedure was preferred by 69% of patients, 55% favoured PDT in terms of efficacy and 70% would prefer PDT for future treatments **AEs** No unexpected safety issues were recorded. PDT reactions during treatment: stinging (83%), burning (100%), pain (100%), moderate erythema (100%), oedema (67%), blistering (27%). Reactions were well tolerated, no further treatment was required and all resolved within 7–15 d. Imiquimod reactions were most commonly application site related: itching (21%), burning (11%), pain (4%). Local skin reactions in the treatment area were mostly mild to moderate and well tolerated, and more intense during course 1 than course 2: erythema (93%), crusting (11%), scaling (11%), erosions/ulcerations (7%), oedema (7%)	**Authors' conclusions** ALA–PDT and imiquimod 5% cream are comparable treatments for upper extremity AK. ALA–PDT should be considered as a 1st-line therapy for both grade I and grade II AK of the extremities **Brief study appraisal** Although this trial used an intraindividual randomisation design for treatment, it failed to report on aspects of methods (including randomisation) and did not use an ITT analysis Outcome assessors were not blinded and only investigator-assessed cosmetic outcomes were reported. The results suggest there may be little difference between PDT and imiquimod for grade I lesions, but PDT may be better for grade II These results can be considered moderately reliable, but uncertainties do exist about the choice of statistical techniques used, the inconsistent reporting of some results, and the sample size (as the authors assumed that lesions within patients were independent)

Study details	Population details	Treatment details	Results	Interpretation
Authors Smith *et al.* (2003)[50] **Data source** Full published paper **Country** USA **Language** English **Study design** RCT **No. of participants** Total: 36 Intervention 12 (ALA with blue light) Comparator: 12 (ALA with laser light) 2nd Comparator: 12 (5-FU) **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at end of treatment, 2 wk and 4 wk	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** It appeared that Caucasian patients with a minimum of four non-hyperkeratotic AK of the face or scalp were eligible for inclusion **Patient characteristics** % Male: 81 Mean age: ALA with blue light, 58.9; ALA with laser light 61.0; 5-FU 64.3 Mean no. of lesions: 6–7 per patient **Concomitant treatment** Patients with more dramatic cutaneous reactivity (6/11 5-FU and 1/12 PDT-laser patients) were treated with dilute acetic acid soaks and topical low potency corticosteroid (2–3 times daily)	**Trial treatments** Broad area ALA–PDT with blue light vs broad area ALA–PDT with laser light vs 5-FU **Intervention** ALA–PDT (blue light): Following topical application of ALA for 1 hr to a broad area, illumination with blue-light PDT for 1000 s. Two treatments 30 d apart were applied **Comparator** ALA–PDT (with laser): Following broad area topical ALA application for 1 hr, pulsed dye laser was administered (595 nm, 75 J/cm^2 with 10-ms pulse duration using a 10-mm spot size, 10% overlap of each laser impact and two passes across treatment area). Patients received two treatments 30 d apart **2nd comparator** 5-FU: 5% fluorouracil cream applied once or twice daily for 4 wk	**Morbidity** 75% or more lesions were cleared in 9/12 PDT-blue light patients vs 5/12 PDT-laser vs 9/11 5-FU. 100% of lesions were cleared in 6/12 PDT-blue light patients vs 1/12 PDT-laser vs 6/11 5-FU. The cumulative clearance rate (or individual AK lesion rate) was 80% (PDT-blue light), 50% (PDT-laser) and 79% (5-FU) **QoL and return to normal activity** All three treatments showed improvement in global response, tactile roughness and mottled hyperpigmentation; the 5-FU and PDT-blue light groups tended towards more benefit for tactile roughness, whereas the 5-FU and PDT-laser groups favoured pigmentation. PDT-blue light was the only group in which the signs of photoageing completely resolved based on the global response score (two patients). None of the treatments worsened signs of photoageing **AEs** Four PDT-blue light and 3 PDT-laser patients reported mild or moderate stinging directly after therapy but not at subsequent FU. Erythema was the most pronounced AE; 5-FU patients had the greatest average increase and showed residual erythema at 4 wk. Crusting and erosions were only seen with 5-FU. There was one discontinuation in the 5-FU group due to a severe confluent erythematous reaction	**Authors' conclusions** Broad area PDT treatment with ALA plus activation with blue light appears to be as effective as 5-FU in the treatment of AK. ALA plus laser light is somewhat less effective than the above therapies **Brief study appraisal** This was a small study with poorly reported methodology. Additional treatment was given to patients that had severe reactions, which may have been a confounding factor. The reliability of the results is therefore uncertain

Study details	Population details	Treatment details	Results	Interpretation
Authors Szeimies *et al.* (2007)[38] Linked publications[170–173] **Data source** Abstract **Country** Not stated **Language** English **Study design** RCT **No. of participants** Total: 25 (238 lesions) Intervention: Not stated Comparator: Not stated **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 2 wk and 3 mth	**Treatment intention** Curative **Type(s) of lesion and histology AK** **Main eligibility criteria** Not stated **Patient characteristics** % Male: 68 Mean age: 73 yr **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT with VPL vs MAL–PDT with LED light (within-participant comparison) **Intervention** PDT-VPL: MAL cream was applied to target area for 3 hr. One side received VPL at 80 J/cm^2 (double pulsed at 40 J/cm^2) with a pulse train of 15 impulses, each of 5-ms duration, using a 610–950 nm filtered hand piece. The opposite side received LED light (37 J/cm^2 for 12 min) **Comparator** PDT-LED: See above	**Morbidity** Infiltration and keratoses score: No significant difference between LED 0.86 (0.71) and VPL 1.05 (0.74), $p = 0.292$ **QoL and return to normal activity** No significant differences in patient satisfaction between treatments ($p = 0.425$) **AEs** Pain assessment (VAS) immediately after PDT showed significantly lower pain levels for the VPL side (4.3 vs 6.4)	**Authors' conclusions** The use of VPL is an efficient and useful alternative in the photodynamic treatment of AK, where otherwise pain development can be a limiting factor for the performance of PDT **Brief study appraisal** Minimal reporting of both methods and results means little can be deduced from this conference abstract

VPL, variable pulsed light.

Study details	Population details	Treatment details	Results	Interpretation
Authors Szeimies *et al.* (2002)[51] Linked publications[174,175] **Data source** Full published paper **Countries** Austria, Germany, Italy, Switzerland, the Netherlands **Language** English **Study design** RCT **No. of participants** Total: 202 (732 lesions) Intervention: 102 (384 lesions) Comparator: 100 (348 lesions) **No. of recruiting centres** 13 **Follow-up period and frequency** At 2 wk and 3 mth	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Patients > 18 yr old, with up to 10 AK lesions suitable for cryotherapy and no treatment within the last 4 wk when eligible. Diagnosis was based on clinical assessment (and histology where needed). Patients receiving regular UV therapy and patients with pigmented lesions or porphyria were excluded **Patient characteristics** % Male: 61 Age range: 42–89 yr Mean age: 71 yr (PDT), 72 yr (cryotherapy) 58% of patients had 1–3 lesions, 33% had 4–7 lesions, and 9% had 8–10 lesions. Lesions were mostly of thin (40%) or moderate (52%) grade, and most were located on the face (63%) or scalp (28%) **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs Cryotherapy **Intervention** MAL–PDT: Loose crusts were removed using a curette and the surface gently roughened. MAL cream (160 mg/g) was applied as a 1-mm-thick layer and to 5 mm of surrounding normal tissue. The area was covered with an occlusive dressing for 3 hr, after which the cream was washed off with a saline solution, followed by illumination with non-coherent red light (570–670 nm) with a total light dose of 75 J/cm^2 and a light intensity of 70–200 mW/cm^2. The mean illumination time was 11 min. Up to 10 lesions were treated at the same session. The procedure was repeated after 1 wk in lesions not on the face or scalp (8% of patients) **Comparator** Cryotherapy: preparation with superficial curettage, followed by cryotherapy with liquid nitrogen spray to achieve a 1- to 2-mm frozen rim outside the marked lesion outline. The mean total freezing time was 24 s. The freezing procedure was performed in two cycles during the single treatment session	**Morbidity** The overall CR rate was 69% (252/367) for PDT vs 75% (250/332) for cryotherapy. Higher response rates were observed in grade 1 (thin) lesions than in thicker lesions. Grade 1 facial lesions showed the best response regardless of intervention arm **QoL and return to normal activity** Cosmetic outcome was significantly better in PDT group ($p = 0.035$), where 96% of investigators and 98% of patients graded outcome as excellent or good (vs 81% and 91%, respectively, for cryotherapy group). In the PDT group, of the 43 previously treated patients (various treatments such as cryotherapy and 5-FU) 32 rated PDT as better, 10 as equal, and one worse than the previous treatment **AEs** Local AEs were reported by 44 (43%) of PDT patients vs 26 (26%) of cryotherapy patients. The commonest were burning sensation (PDT 32% vs cryotherapy 9%), skin pain (10% vs 13%) and crusting (5% vs 6%). Three patients stopped treatment due to local reactions – one PDT (burning) and two cryotherapy (pain)	**Authors' conclusions** PDT for treating AK has a similar response rate to cryotherapy, but with superior cosmetic results and high patient satisfaction **Brief study appraisal** In relation to CR, the authors' conclusions appeared only to relate to thin facial lesions, with uncertainty surrounding other results (which frequently lacked *p*-values). Cosmetic outcome and satisfaction results were based on smaller patient numbers. The study was not blinded which coupled with the real possibility of institutional differences and protocol deviation (13 centres in five countries) casts further doubt on the reliability of the results

Study details	Population details	Treatment details	Results	Interpretation
Authors Szeimies *et al.* (2009)[58] Linked publications[169] **Data source** Full published paper **Countries** Germany, USA **Language** English **Study design** RCT **No. of participants** Total: 131 Intervention: 57 (plus 16 not randomised – included only in AE analysis) Comparator: 58 **No. of recruiting centres** 10 **Follow-up period and frequency** FU 3 mth after last treatment	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Males and non-pregnant, non-lactating women aged over 18 yr with 4–10 previously untreated, non-pigmented, non-hyperkeratotic grade I or II lesions on the face and scalp (at least 3-mm diameter) were eligible for inclusion. Exclusion criteria were extensive and included: immunosuppression, porphyria, allergy to MAL or similar, hypersensitivity to nut products or other protein antigens, regular UV treatment of face or scalp in previous 30 d, topical therapy in previous 3 mth **Patient characteristics** % Male: 79 Mean age: MAL–PDT 69.5; Placebo PDT 67.0 Age range: 41–90 yr skin type: I 19%; II 44%; III/IV 27%; IV 10% lesions: grade I (thin) 41%; grade II (moderate) 59% The majority of lesions were located on the face or scalp, patients had a median of seven lesions each and the median maximum diameter was 9 mm **Concomitant treatment** 22 patients (14 MAL, 8 placebo) received oral analgesic treatment or fentanyl patches	**Trial treatments** MAL–PDT vs Placebo PDT **Intervention** MAL–PDT: After debridement of lesions, 1-mm-thick MAL cream (160 mg/g) was applied to each lesion and 5-mm surrounding skin for 3 hr (permitted range 2.5–4 hr) under occlusion. Lesions were cleaned with a saline solution, then illuminated with non-coherent LED red light (average duration 9 min, mean dose 37 J/cm^2, mean intensity 74 mW/cm^2, range 56–83 mW/cm^2) with the light source kept at 5–8 cm from skin. Breaks in illumination were allowed provided that treatment was completed within 4 h of occlusion. This process was repeated after 1 wk **Comparator** Placebo PDT: As for MAL–PDT but with placebo cream	**Morbidity** Lesion response rate was 83% (348/418) with MAL vs 29% (119/414) for placebo, OR 13.8 (9.5 to 19.9, $p < 0.001$). Patient CR rate with MAL was 68% (39/57) vs 7% (4/59) for placebo, OR 39.5 (10.5 to 149.2, $p < 0.001$). At 3 mth after treatment, development of new lesions was 18% (10/56) in MAL patients vs 34% (20/58) for placebo, $p = 0.04$. 73% were on the scalp in the MAL group vs 59%. Response rates were higher for small lesions (3–10 mm) on the face but better for large lesions (> 20 mm) on the scalp **QoL and return to normal activity** Not assessed **AEs** 85% (62/73) MAL patients reported AEs vs 60% (35/58) and most were associated with treatment site (312/368 and 56/89, respectively). The most commonly reported local AEs with MAL were pain of the skin 55% (40/73) vs 22% (13/58), erythema 52% (38/73) vs 5% (3/58), and skin burning sensation 36% (26/73) vs 12% (21/58). In the placebo group all but six local AEs were mild; most MAL AEs were mild to moderate. Nineteen MAL patients had severe local AEs considered treatment related: pain of the skin 13, erythema six, skin burning sensation five, skin exfoliation four, scab one, skin swelling one and face swelling one. There were also six non-local AEs: dizziness and increased perspiration, eyelid oedema (three reports) and headache (one report). Two MAL patients discontinued due to severe skin pain	**Authors' conclusions** Topical MAL–PDT using an LED is an effective treatment for multiple AKs **Brief study appraisal** Generally a well-conducted trial that considered centre effects on the results; however, a subgroup analysis of patients that received additional painkillers may have been useful

Study details	Population details	Treatment details	Results	Interpretation
Authors Tarstedt *et al.* (2005)[52] **Data source** Full published paper **Country** Sweden **Language** English **Study design** RCT **No. of participants** Total: 211 (413 lesions) Intervention: 105 (198 lesions) Comparator: 106 (215 lesions) **No. of recruiting centres** 21 **Follow-up period and frequency** At 3 mth	**Treatment intention** Curative **Type(s) of lesion and histology** AK (grade I or II) **Main eligibility criteria** Patients aged at least 18 yr with up to 10 clinically diagnosed AK lesions on the face and/or scalp, which were mild (grade I) or moderate (grade II) and non-pigmented, were eligible **Patient characteristics** % Male: 39 Mean age: 69 yr single-session group, 68 yr 2-session group Around one-half of the patients had received prior treatment for AK. Mean lesion diameter was around 10 mm. The majority of patients (76–83% in both groups) had 1 or 2 lesions, and 90% of lesions were on the face, with the rest being on the scalp. Further characteristics were reported **Concomitant treatment** Local anaesthetic if needed during treatment	**Trial treatments** MAL–PDT single session vs MAL–PDT 2 sessions (1 wk apart) **Intervention** MAL–PDT single session: Any lesion crust was removed using a curette or scalpel (without anaesthetic) and a 1-mm-thick layer of MAL (Metvix, 160 mg/g) was applied to each lesion and 5 mm of surrounding tissue and covered with an occlusive dressing for mean of 3 hr. The dressing was removed and the cream washed off with 0.9% saline solution immediately before illumination, for mean of 8 min, with red LED light (peak wavelength 634 ± 3 nm, light dose 37 J/cm^2, irradiance 50 mW/cm^2 at 50 mm from skin). Re-treatment if there was a non-CR after 3 mth **Comparator** MAL–PDT two sessions: See above, but two treatment sessions, 1 wk apart	**Morbidity** Analyses based on 400 lesions (198 single session; 202 double session MAL–PDT). The lesion CR rates were similar (81% single treatment vs 87% 2 treatments). A further 22 lesions showed a CR after re-treatment (increasing the CR for the single treatment group to 92%). Single and two-treatment schedules had similar CRs for thin lesions (93% vs 89%), but not for moderately thick lesions (70% vs 84%), although again this improved after re-treatment (88%) **QoL and return to normal activity** Cosmetic outcome was rated as excellent for each of four parameters in > 75% of lesions in each group. 66% of single treatment patients, who had previously been treated with cryotherapy, preferred PDT to cryotherapy vs 58% in the two-treatment group **AEs** AEs were reported in 42 single-treatment patients and in 53 two-treatment patients. Most local AEs were of mild to moderate intensity and of relatively short duration. Burning of skin occurred in 15% of single treatment patients vs 19% of the treatment group, whereas pain occurred in 9% and 18% of patients, respectively. One patient randomised to two sessions discontinued due to moderate erythema (which resolved completely)	**Authors' conclusions** Single MAL–PDT treatment is as effective as a two-treatment schedule for thin AK lesions. Repeated treatment is recommended for thicker or non-responding lesions **Brief study appraisal** Although this study appears to have been quite well conducted, it was unclear whether the outcome assessors were blinded to treatment allocation. 21 centres recruited the 211 patients (around five participants per centre on average) increasing the possibility that protocol deviation and institutional differences would affect results. *p*-values were not reported

Study details	Population details	Treatment details	Results	Interpretation
Authors Touma *et al.* (2003)[39] **Data source** Abstract **Country** USA **Language** English **Study design** RCT **No. of participants** Total: 18 Intervention: Not stated Comparator: Not stated 2nd Comparator: Not stated **No. of recruiting centres** Not stated **Follow-up period and frequency** Day 1, then at 1 wk, and 1 and 5 mth	**Treatment intention** Curative **Type(s) of lesion and histology** Non-hypertrophic AK **Main eligibility criteria** Patients with at least four non-hypertrophic AK and diffuse photodamage **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT, 1-hr incubation vs 2-hr incubation vs 3-hr incubation **Intervention** 1-hr incubation: Pre-treatment with 40% urea cream (penetration enhancer) and xylocaine HCL 3% (pain control) followed by 20% ALA–PDT with 417-nm blue light. Further PDT parameters were not reported **Comparator** 2 hr incubation: See above **2nd comparator** 3-hr incubation: See above	**Morbidity** Results not broken down by treatment group, but it was reported that there was no effect of ALA incubation time or urea cream on any of the measured outcomes. At 1 mth, 90% of AKs had cleared (analysis on 17 patients) **QoL and return to normal activity** Patient satisfaction with cosmetic results was reported as moderately high, and all patients commented on improved skin texture **AEs** Phototoxic reactions were well tolerated	**Authors' conclusions** Short incubation (1–3 hr) broad area ALA–PDT appears as effective in eradicating AKs as the long incubation application, with tolerable phototoxicity **Brief study appraisal** Little information on methods and very limited results presented for this very small study. The conclusions appear inappropriate if they were based on the study results, as short incubation appears to be defined as 1–3 hr, yet no group received long incubation treatment

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Study details	Population details	Treatment details	Results	Interpretation
Authors Wennberg *et al.* (2008)[59] Linked publications[176–178] **Data source** Full published paper **Country** Not stated, 'Europe' **Language** English **Study design** RCT **No. of participants** Total: 81 (889 lesions, 90% AK) Intervention: 476 lesions Comparator: 413 lesions **No. of recruiting centres** 11 **Follow-up period and frequency** 3, 9, 15, 21 and 27 mth after initial treatment	**Treatment intention** Curative. This trial aimed to treat existing lesions and also prevent recurrence. Only response rates and cosmetic outcomes have been reported here **Type(s) of lesion and histology** AK (some BCC and SCC in situ included but data not reported) **Main eligibility criteria** Organ transplant recipients who had received immunosuppressive therapy for more than 3 yr and had between two and 10 lesions in two symmetrical 50-cm^2 contralateral areas on the face, scalp, neck, trunk or extremities. All patients were required to have received at least one previous treatment for the lesions. Exclusion criteria were reported **Patient characteristics** % Male: 68 Age range: 30–78 yr Median age: 57 yr Most patients had Fitzpatrick skin types I–III, organ transplantation occurred between 3 and 34 yr previously (median 16 yr) with the majority more than 10 yr prior to treatment. Selected treatment areas were mostly on the face, scalp or extremities. AKs were mostly grade I or II and almost all were ≤ 10 mm in diameter **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs investigator's choice of treatment (within-participant comparison) **Intervention** MAL–PDT: 2 treatments were given, 1 wk apart (baseline and 1 wk after randomisation). Additional single treatments were given at 3, 9 and 15 mth for a total of five treatments. Any visible lesions at 21 and 27 mth were treated at the investigators' discretion. Lesions were prepared using a small curette to debride the area. MAL 160 mg/g cream applied in 1-mm layer to 50-cm^2 treatment area and covered for 3 hr with an occlusive dressing. Excess cream was removed with saline and the area illuminated with non-coherent red light from a lamp (630 nm, light dose 37 J/cm^2). Patients' eyes were protected during treatment. Fans and cold water spraying were used for all patients to minimise pain **Comparator** Control area was treated at the investigator's discretion utilising any suitable therapy in accordance with normal clinical practice EXCEPT 5-FU cream or imiquimod cream. Treatment was carried out at baseline and 3, 9 and 15 mth later. Any visible lesions at 21 or 27 mth were treated according to the investigator's preference. Control treatments utilised: cryotherapy (83%) curettage and cautery (4%) laser therapy (2%) surgery (1%)	**Morbidity** This trial aimed to treat existing lesions and also prevent recurrence. Only response rates and cosmetic outcomes have been reported here. Lesion CR rate at 3 mth: MAL–PDT 77% and control 74% (no *p*-value reported). Lesion response rate at 15 mth: MAL–PDT 88% and control 89% Recurrence rates for lesions that were present at baseline and rated as CR by 3 mth were similar in both groups (PDT 24% and 20% control) with no significant difference **QoL and return to normal activity** Cosmetic outcomes were rated by the investigator on a 3-point scale. Overall MAL–PDT resulted in more favourable outcomes than the control treatments for hypopigmentation ($p < 0.001$). At 15 mth, more hypopigmentation was reported in the control group and obvious hypopigmentation was 0% (MAL–PDT) vs 25% (control). No significant difference was found between groups for scar formation **AEs** Local AEs associated with MAL–PDT were reported by 75% of patients although most were transient and resolved within 1 wk (erythema, pain and crusting). 6% of patients discontinued MAL–PDT due to pain; pain was judged as severe in 17 out of 420 treatment sessions but most reported were of moderate pain. 48% of patients reported AEs in the control area including pain, erythema, crusting or blistering of mild to moderate intensity	**Authors' conclusions** Treating field cancerisation in organ transplant recipients with topical MAL–PDT is efficacious and generally well tolerated (further conclusions relating to prevention of AK reported) **Brief study appraisal** This study was primarily intended to evaluate prophylactic PDT in immunosuppressed patients and this should be borne in mind. Few details were provided about concealment of allocation, and blinding was not used. The control treatment was not predefined and intercentre differences are likely to have impacted on the results (of which few figures were provided). As a comparative study, the results should be considered with caution and may not be reliable

Study details	Population details	Treatment details	Results	Interpretation
Authors Wiegell *et al.* (2008)[53] **Data source** Full published paper **Country** Denmark **Language** English **Study design** RCT **No. of participants** Total: 30 (29 treated) Intervention: 30 (29 treated) Comparator: 30 (29 treated) **No. of recruiting centres** One **Follow-up period and frequency** FU at 1–3 d (AEs) and 3 mth (CR)	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Patients with AKs symmetrically distributed on the face or scalp. Pregnant or lactating women were excluded **Patient characteristics** % Male: 79 Age range: 63–90 yr Mean age: 78 yr Most lesions were grade I, with around a third grade II and very small number were grade III **Concomitant treatment** Sunscreen for exposed areas not covered by treatment	**Trial treatments** MAL–PDT with daylight vs MAL–PDT with red LED (within-participant comparison) **Intervention** PDT with daylight: Before treatment, lesions were counted, graded, mapped, and photographed. AK lesions of face or scalp were marked into two symmetrical treatment areas (~80 cm^2 each) and scales and hyperkeratoses were removed using a curette. Around 1 g of MAL cream was applied to each area and covered with a dressing and light-impermeable lead rubber. Following 30 min indoors, the daylight area had the dressing removed and patients spent 2.5 hr outside in daylight (mean effective total dose 43 J/cm^2, mean effective red light dose 1.9 J/cm^2, patients treated in period between July and September), before returning to have MAL cream from both treatment areas removed. The area randomised to red LED light was treated with a light dose of 37 J/cm^2 (effective red light dose 1.2 J/cm^2, peak irradiance at 632 nm) after covering the daylight treatment area with light-impermeable rubber **Comparator** PDT with red LED: See above	**Morbidity** At 3 mth the absolute decrease in the mean number of lesions compared to baseline was 8.0 (71%) in the LED areas vs 8.4 (79%) in the daylight areas ($p = 0.13$ for percentage, $p = 0.50$ for mean number) **QoL and return to normal activity** Eighteen patients (62%) preferred the daylight treatment, four (14%) LED treatment, and six (21%) had no preference **AEs** Analyses based on 24 patients: The daylight areas were significantly less painful on a 10-point VAS scale than the LED areas (mean maximal pain score, 2.0 for daylight vs 6.7 for LED, $p < 0.0001$). In the LED light group, 15 patients needed cold water spray to make pain tolerable, and one-half of these patients needed one or two breaks during illumination. In two patients this was not enough, so treatments were stopped after one-third of illumination time. Pain scores 6 hr after LED treatment were not significantly different (mean maximal score of 1 for daylight vs 1.3 for LED, $p = 0.14$). Both areas developed erythema and crusting after treatment. These AEs were most severe in the daylight area in 10 patients (42%), in the LED area in five patients (21%) and there was no difference between the areas in nine patients (38%)	**Authors' conclusions** Continuous activation PDT using daylight exposure was as effective as, and better tolerated than, conventional PDT **Brief study appraisal** This was a generally well conducted but small study and the results appear likely to be reliable. It should be noted though that six patients had previously received PDT in the treated areas (although more than 1 yr before the study), and that the LED illumination time was not clearly stated

Study details	Population details	Treatment details	Results	Interpretation
Authors Wiegell *et al.* (2008)[40] **Data source** Abstract **Country** Denmark **Language** English **Study design** RCT **No. of participants** Total: 29 Intervention: 29 Comparator: 29 **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 3 mth	**Treatment intention** Curative **Type(s) of lesion and histology** AK **Main eligibility criteria** Patients with AK of the face and scalp **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** PDT with 8% MAL vs PDT with 16% MAL (within-participant comparison) **Intervention** PDT 8% MAL: Patients were given both treatments, randomised to two symmetric areas, one area was given 8% MAL cream and the other 16% MAL cream. Patients were sent home and instructed to spend as much time as possible outside, in daylight. Patients spent an average of 210 min outdoors (range 62–372 min). Light exposure was measured using an electronic dosimeter watch **Comparator** PDT 16% MAL: See above	**Morbidity** At 3 mth, there was no significant difference in CR rate (77% in 16% area vs 80% in 8% area), $p = 0.37$ **QoL and return to normal activity** Not assessed **AEs** Erythema and crusting occurred in both treatments (and were similar to inflammation seen after conventional PDT). Pain diaries were used but not reported by intervention arm	**Authors' conclusions** PDT using daylight activation will make AK treatment more time and cost-effective, and more convenient for the patient **Brief study appraisal** The authors compared overall pain scores, and AEs in a small sample, with those seen in conventional PDT, but using a comparator treatment of conventional PDT in this study would have been much more informative. This abstract also featured minimal reporting of methods and results

Appendix 14

Bowen's disease data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors de Haas *et al.* (2007)[69] **Data source** Full published paper **Country** The Netherlands **Language** English **Study design** RCT **No. of participants** Total: 40 (50 Bowen's disease patches) Intervention: 25 lesions (participant no. not stated) Comparator: 25 lesions (participant no. not stated) **No. of recruiting centres** One **Follow-up period and frequency** 4 wk, then at 3 mth intervals up to 28 mth	**Type(s) of lesion and histology** Bowen's disease **Main eligibility criteria** Not stated **Patient characteristics** % Male: 43 Age range: 49–91 yr Mean age: 74 yr Mean lesion diameter: 14.5 mm (range 5–40 mm) Locations: Trunk 12, lower leg 11, hand 8, ear 7, upper leg 4, cheek and/or nose 3, eyelid 2, arm 1, frontal and/or temporal area 1, scalp 1 The sample included seven organ recipients **Concomitant treatment** Lidocaine, 2% without adrenaline was used if patients required it	**Trial treatments** ALA–PDT using a single illumination vs ALA–PDT with a twofold illumination **Intervention** Single Illumination: Surface scale or crusts were removed. 20% ALA, locally produced, was applied topically and left in place for 4 hr with a margin of 1 cm. A diode laser and light emitting diode provided illumination at a wavelength of 630 nm, 4 hr after ALA application at a dose of 75 J/cm^2 Further PDT parameters were not reported **Comparator** Twofold illumination: As for single illumination except patches were light treated 4 and 6 hr after ALA application at doses of 20 and 80 J/cm^2, respectively, separated by a 2-hr dark interval. Each illumination was delivered at 50 mW/cm^2	**Morbidity** In the single illumination group, CR was seen in 22 patches (80%) at 12 mth. In the twofold-illumination group CR was seen in 22 patches (88%) (NS). Patients reported a 3-wk maximum healing time, which was not different between treatments **QoL and return to normal activity** Not assessed **AEs** All patients in both groups experienced some discomfort during treatment but all finished therapy. No SAEs were seen in either group. In the single-illumination group none of the patients complained of pain during treatment. In the twofold-illumination group five patients complained about pain in the treatment of six patches. Lidocaine without adrenaline was used in four patches	**Authors' conclusions** ALA–PDT may offer the best treatment option for Bowen's disease. This study shows the potential of light fractionation for enhancing the response of the disease to ALA–PDT and illustrates the need for a larger, suitably powered trial to determine if the effect is statistically significant **Brief study appraisal** This was a small trial with unclear methods of randomisation and blinding. Treatment methods were reported but not all outcomes were detailed. This study shows the potential of PDT and its enhancement through light fractionation but would need confirmation, as the authors state, in an adequately powered trial

Study details	Population details	Treatment details	Results	Interpretation
Authors Lui *et al.* (2004)[68] **Data source** Full published paper **Countries** Canada, USA **Language** English **Study design** RCT **No. of participants** Total: Not stated by diagnosis (34 lesions) Intervention: Not stated by diagnosis (27 lesions) Comparator: Not stated by diagnosis (one lesion) 2nd Comparator: Not stated by diagnosis (six lesions) **No. of recruiting centres** Four **Follow-up period and frequency** 6 wk, and 3, 6, 12, 18 and 24 mth	**Type(s) of lesion and histology** Superficial BCC, 277 lesions (66%); nBCC, 93 lesions (22%); Bowen's disease, 34 lesions (8%); BCC unspecified 17 lesions (4%) **Main eligibility criteria** Patients with at least two biopsy-proven superficial or nBCC or Bowen's lesions **Patient characteristics** Not stated for Bowen's group **Concomitant treatment** Oral analgesics for pain	**Trial treatments** PDT at 60 J/cm^2 vs PDT at 120 J/cm^2 vs PDT at 180 J/cm^2 **Intervention** PDT at 60 J/cm^2: 10 min intravenous infusion of 1.4 mg/m^2 verteporfin followed 1–3 hr later by exposure to 60 J/cm^2 of red light (688 ± 10 nm) from a non-thermal LED panel. The exposed area had a margin of 3–4 mm around the lesion. The irradiance delivered was 200 ± 40 mW/cm^2. Tumours re-treated at 3 mth if necessary (with dose increased to 18 mg/m^2) **Comparator** PDT at 120 J/cm^2: See above **2nd comparator** PDT at 180 J/cm^2: See above	**Morbidity** At 6 mth, the histopathological response (i.e. no residual tumour) was 85% at 60 J/cm^2, 100% at 120 J/cm^2, and 50% at 180 J/cm^2 **QoL and return to normal activity** Assessed but not reported for Bowen's group **AEs** Assessed but not reported for Bowen's group	**Authors' conclusions** A single course of verteporfin PDT showed treatment benefit for patients with multiple non-melanoma skin cancers **Brief study appraisal** There was a lack of information on issues such as blinding and allocation concealment, and the authors did not present many results and population details by diagnosis. It is therefore difficult to make any reliable conclusions about the efficacy of verteporfin in patients with Bowen's disease, particularly as they formed a small proportion of the overall number of lesions

Study details	Population details	Treatment details	Results	Interpretation
Authors Morton *et al.* (2000)[70] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 19 (70 lesions) randomised 16 (61 lesions) followed up Intervention: 32 lesions (no of patients not specified) Comparator: 29 lesions (no of patients not specified) **No. of recruiting centres** Not stated **Follow-up period and frequency** After clearance, all patients were reviewed at monthly intervals, up to 12 mth	**Type(s) of lesion and histology** Bowen's disease **Main eligibility criteria** Biopsy-proven disease with individual lesions of ≤21 mm in diameter. No lesion had been previously treated **Patient characteristics** Age range: 50–87 yr Mean age: 73 yr No. of lesions per patient varied between one and six (median three) **Concomitant treatment** Local anaesthetic (1% plain lidocaine by intradermal injection) was offered during PDT treatment	**Trial treatments** ALA–PDT with red light vs ALA–PDT with green light **Intervention** Red light: Surface crusts were removed and the surface was gently abraded. Topical ALA in an oil-in-water emulsion was applied to the lesions 4 h pre-illumination. Approximately 50 mg/cm^2 of cream was applied to cover the entire field of illumination, including a clinically disease-free margin of at least 4 mm. The cream was kept in place under an occlusive dressing A 'Paterson' lamp with 300W xenon short arc plasma discharge was adjusted using appropriate filters to 630 ± 15 nm for red light. At a fluence rate of 86 mW/cm^2 lesions received 125 J/cm^2 of red light A repeat treatment was given after 2 mth if necessary **Comparator** As for red light except a wavelength of 540 ± 15 nm was used to deliver 62.5 J/cm^2 of light	**Morbidity** In the red light group 24 lesions cleared following one treatment and a further six after a repeat treatment giving an initial response rate of 94%. Eighteen lesions treated using green light cleared after one treatment with a further three clearing on repeat giving an initial response of 72%. Difference in response was statistically significant ($p = 0.002$). A high recurrence rate was observed in the green light group with seven recurrences in comparison with two lesions relapsing after PDT with red light. OR for recurrence = 0.13 (95% CI 0.04 to 0.48) **QoL and return to normal activity** No clinically obvious scars were evident at 1 yr in either group **AEs** No ulceration or infection complicating therapy and no photosensitivity reactions were documented after PDT treatment in either group. No significant difference in pain was seen between the treatment groups. No red light patients needed anaesthesia whereas two lesions (one patient) treated in the green light group needed anaesthesia Twelve patients received both types of light. Four stated that green light was the most painful, six that red light was the most painful, while two patients could not distinguish between the light used	**Authors' conclusions** Green light is less effective than red light in the treatment of Bowen's disease by ALA–PDT **Brief study appraisal** A small study, with unclear methods of randomisation, allocation concealment and blinding of outcome assessors

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Study details	Population details	Treatment details	Results	Interpretation
Authors Morton *et al.* (1996)[71] Linked publications[179] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 19 (40 lesions) Intervention: 20 lesions, participant no. not stated Comparator: 20 lesions, participant no. not stated **No. of recruiting centres** Not stated **Follow-up period and frequency** 2 d and 10 d for AEs. 2-monthly intervals for clinical response. Following clearance, 2-monthly intervals for 12 mth for recurrence and late AEs	**Main eligibility criteria** Histological confirmation of Bowen's with individual lesions ≤ 21 mm in diameter. No lesion had been previously treated **Patient characteristics** % Male: 16 Age range: 62–88 yr Mean age: 76 yr Location and no. of lesions: legs 33, face five, hand two **Concomitant treatment** Patients were offered local anaesthetic (1% plain lidocaine by intradermal injection) during treatment	**Trial treatments** PDT with ALA vs Cryotherapy **Intervention** PDT: Surface crusts were removed and the surface gently abraded prior to application with topical 5-ALA in an oil-in-water emulsion 20%. Approximately 50 mg/cm^2 of cream was applied to cover the entire irradiation field including the clinically disease-free margin. The cream was kept in place under an occlusive dressing Four hours later lesions were illuminated with a prototype lamp. The lamp incorporated a 300W xenon short arc plasma discharge producing a continuous wave broadband flat spectral output across the entire visible spectrum. Using filters, the spectral output of the lamp was adjusted to a 30-nm bandwidth, about 630 nm. To broaden the treatment field and to produce uniform irradiation of the lesions, a 25-mm collimating lens was attached to the 5-mm fibre bundle. Allowing at least a 10% margin around lesions in the field of irradiation permitted the treatment of lesions ≤ 21 mm in diameter, at a fluence rate of 70 mW/cm^2 and a treatment time of 30 min, lesions received 125 J/cm^2. Following therapy, 3-mm punch biopsies were performed in lesions where there was doubt over clinical clearance or recurrence. Repeat treatments were administered if lesions persisted **Comparator** Cryotherapy: Liquid nitrogen was applied to lesions via a hand-held Cry-Ac spray. After initial ice field formation, the freeze was maintained for 20 s. A single freeze–thaw cycle technique was used with a 2–3 mm rim of clinically healthy tissue included in the treatment field. Following therapy, 3-mm punch biopsies were performed in lesions where there was doubt over clinical clearance or recurrence. Repeat treatments were administered if lesions persisted	**Morbidity** Clearance after one treatment: PDT, 15 of 20 lesions; cryotherapy, 10 of 20 lesions Clearance after two treatments: PDT, five remaining lesions; cryotherapy, six lesions The remaining four lesions in the cryotherapy group required a third treatment. There was no significant difference between the two treatments in clearance rates. However, by chance lesions treated by PDT were overall larger than those in the cryotherapy group. In a linear regression model taking size of lesion into account, the probability that a lesion of any size is completely cleared at the 1st treatment was significantly greater with PDT than with cryotherapy ($p < 0.01$). Recurrence Rate during 12-mth following clinical clearance: PDT zero; cryotherapy two (6 mth and 8 mth). CR rate was, therefore, 100% for PDT and 90% for cryotherapy **QoL and return to normal activity** Visible scarring 12 mth following clearance (no. of lesions): PDT zero, cryotherapy four **AEs** Pain during treatment (no. of lesions): PDT, six mild and five moderate; cryotherapy, 12 mild and seven moderate ($p = 0.01$). Free from pain 10 d following treatment (no. of lesions): PDT 15; cryotherapy 10 All six patients who received both treatments, due to having multiple lesions, reported PDT as less painful. Blistering (no. of lesions): PDT zero; cryotherapy seven. Ulceration (no. of lesions): PDT zero; cryotherapy five. Secondary infection (no. of lesions): PDT zero; cryotherapy two. No photosensitivity reactions occurred after PDT	**Authors' conclusions** PDT is at least as effective as cryotherapy in the treatment of Bowen's disease and was associated in this study with fewer AEs and a lower recurrence rate **Brief study appraisal** This was a small trial using a prototype lamp as a light source. Results were reported by lesion rather than by patient. By chance lesions were significantly larger in the PDT group but this was taken into account when assessing clearance rates. The results of the trial are promising but would require confirmation in larger trials

Study details	Population details	Treatment details	Results	Interpretation
Authors Morton *et al.* (2006)[73] Linked publications[180–184] **Data source** Full published paper **Countries** Not stated, 11 European countries **Language** English **Study design** RCT **No. of participants** Total: 229 randomised, 225 treated (275 lesions) Intervention: 96 (124 lesions) Comparator: 17 (24 lesions) 2nd Comparator: 82 (91 lesions) 3rd Comparator: 30 (36 lesions) **No. of recruiting centres** 40 **Follow-up period and frequency** 3, 12 and 24 mth after last treatment	**Type(s) of lesion and histology** Bowen's disease **Main eligibility criteria** Inclusion criteria: Patients 18 yr or older with histologically confirmed diagnosis of SCC in situ from a biopsy specimen taken within the last 5 mth and with no evidence of any change in appearance suggestive of lesion progression Lesions that had been treated within the previous 3 mth or that were strongly pigmented, less than 6 mm or more than 40 mm in diameter or located on the genitalia were excluded **Patient characteristics** For the treated patients: % Male: 39 Age range: 39–99 yr Mean age: 73 yr Location of lesion (no. of lesions): face (scalp) 68, neck, trunk 34, extremities 173 **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT vs Placebo PDT vs Cryotherapy vs 5-FU **Intervention** MAL–PDT: Lesions were prepared by gentle surface debridement with a curette. 160 mg/g of topical MAL cream was applied to the lesions. It remained on the skin for 3 hr then was washed off with 0.9% saline solution before illumination with non-coherent red light. Wavelength was 570–670 nm, light dose was 75 J/cm^2. Mean illumination time was 10 min 37 s. Treatment was repeated once after 1 wk for a complete treatment cycle. Lesions with a PR at 12 wk were re-treated **Comparator** Placebo cream: As for MAL–PDT. Lesions with a PR at 12 wk were re-treated **2nd comparator** Cryotherapy: A handheld liquid nitrogen spray was used in a single freeze–thaw cycle. After an initial ice field formation with a 2-mm rim of clinically healthy tissue, the ice field was maintained for a minimum of 20 s. Mean total freezing time was 25 s Lesions with a PR at 12 wk were re-treated **3rd comparator** 5-FU: Topical 5% 5-FU cream was applied for 4 wk, once daily during the 1st week, and twice daily thereafter. Mean number of applications was 42 and 45 in the 1st and 2nd treatments, respectively. Lesions with a PR at 12 wk were re-treated	**Morbidity** CR rate at 3 mth: PDT, 103/111 (93%); Placebo, 4/19 (21%); Cryotherapy, 73/85 (86%), and 5-FU 24/29, (83%). 12-mth recurrence rate: PDT, 15%; Placebo, not stated; Cryotherapy, 24% and 5-FU, 21%. Estimated sustained CR rate at 12 mth: PDT, 80%; Placebo, not stated; cryotherapy, 67%; 5-FU, 69%. There was a statistically significant difference between MAL–PDT and combined standard therapy (OR = 1.73; 95% CI 1.03 to 2.93). MAL–PDT was significantly different from cryotherapy (OR = 1.77 to 1.01, 3.12). Estimated sustained CR rate at 24 mth: PDT, 68%; placebo, 11%; cryotherapy, 60%; 5-FU, 59% **QoL and return to normal activity** Good or excellent cosmetic outcome at 3 mth: PDT, 77/82 (94%); cryotherapy, 43/65 (66%); 5-FU, 16/21 (76%). This was maintained at 12 mth **AEs** SAEs: PDT, 6%, cryotherapy, 12%. SAEs (including four deaths) were reported. PDT, four patients; placebo cream, two patients; cryotherapy, three patients	**Authors' conclusions** MAL–PDT is an effective treatment option for Bowen's disease with excellent cosmetic outcome **Brief study appraisal** The authors' conclusions appear appropriate, although mitigating factors include the fact that 11% of treated lesions were excluded from the per-protocol population, the lack of reporting on methods of randomisation and allocation concealment, and the possibility of institutional differences and protocol deviation (40 centres in 11 countries) affecting results

Study details	Population details	Treatment details	Results	Interpretation
Authors Puizina-Ivic *et al.* (2008)[57] **Data source** Full published paper **Country** Croatia **Language** English **Study design** RCT **No. of participants** Total: 15 Intervention: Nine Comparator: Six **No. of recruiting centres** One **Follow-up period and frequency** 24 wk	**Treatment intention** Curative **Type(s) of lesion and histology** Bowen's disease **Main eligibility criteria** Previous histologically confirmed diagnosis of Bowen's disease **Patient characteristics** Not stated	**Trial treatments** ALA–PDT with 16-hr incubation and two light fractions vs ALA–PDT with 5-hr incubation and a single illumination **Intervention** ALA–PDT with 16-hr incubation and two light fractions: Thick crusts were 1st removed with ointments (and wet dressings). After cleaning the area with a saline solution, the 20% ALA cream was applied to a thickness of approximately 1 mm, covering the treated area and 1 cm of the surrounding skin. The area was covered by occlusive dressing. Aluminium foil was placed on top in order to protect skin from ambient light. There was then a 16-hr incubation period before red light (635 nm) was applied. The total of 100 J/cm^2 was delivered in two doses of 50 J/cm^2 with a fluence intensity of 30 mW/cm^2. There was a 2-hr break between illuminations. Spraying of water and cooling with fan was done to minimise pain sensations. After the treatments sunblock ointments were recommended for the next few days in addition to sun protection measures. Biopsies were performed 24 wk after illumination in patients with fluorescence detected after 4 hr **Comparator** PDT with 5 hr incubation with ALA cream and single light fraction: Preparation for illumination was as for the intervention group. There was then a 5-hr incubation period before red light (635 nm) was applied. 100 J/cm^2 was delivered in one dose, with a fluence intensity of 30 mW/cm^2. Spraying of water and cooling with fans, and sun protection measures were as for the intervention group. Biopsies were performed 24 wk after illumination in patients whom fluorescence after 3-hr incubation with ALA was detected	**Morbidity** At 24 wk, residual tumour was found in four of six (67%) biopsied patients in the single-illumination, shorter-incubation group. Treatment was repeated. At 24 wk, there was persistence of tumour in two of nine (22%) biopsied patients in the fractionated, longer incubation group **QoL and return to normal activity** Not assessed **AEs** Not assessed	**Authors' conclusions** PDT delivered as fractionated illumination with 16 hr of incubation separated by a 2-hr dark interval significantly improves therapeutic outcome in tumour eradication **Brief study appraisal** This trial had only a small number of patients with Bowen's disease. Procedures of randomisation and blinding of outcome assessors were unclear. No patient details were provided. Although the group receiving fractionated illumination had better outcomes, the relative contribution of the longer incubation time and the fractionated delivery are unclear. It is also unclear if there were any AEs

Study details	Population details	Treatment details	Results	Interpretation
Authors Salim *et al.* (2003)[72] Linked Publications[185] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 40 Intervention: 20 (33 lesions) Comparator: 20 (33 lesions) **No. of recruiting centres** Two **Follow-up period and frequency** 12 mth	**Type(s) of lesion and histology** Bowen's disease **Main eligibility criteria** Patients with 1–3 lesions of previously untreated, histologically proven Bowen's disease measuring 0.5–4 cm **Patient characteristics** % Male: 20 Age range: 65–88 yr Mean age: 76 yr Lesion site: Legs 58, arms 4, face 4 Patients had between one and three lesions and were of skin types I–III **Concomitant treatment** Local anaesthetic (1% plain lidocaine by intradermal injection) was offered to patients experiencing pain during PDT treatment	**Trial treatments** PDT vs 5-FU **Intervention** 20% ALA in an oil-in-water emulsion was applied to lesions including a 5-mm margin of clinically normal skin 4-hr before PDT. Illumination was with a 300-W xenon lamp at a dose of 100 J/cm squared with a density of 50–90 mW/cm squared narrowband red light (630 ± 15 nm). The time of illumination was dependent on lesion size and ranged from 12 to 40 min. All patients were reviewed at 6 wk and PDT was repeated if required. Further PDT parameters were not reported **Comparator** 5-FU (Efudix) was applied thinly to the lesions initially once daily during wk 1 and then twice daily (wk 2–4). All patients were reviewed at 6wk and 5-FU was repeated if required	**Morbidity** 29 of 33 lesions (88%) showed initial complete clinical clearance with PDT with a PR in the four remaining lesions. 22 of 33 lesions (67%) had complete clinical clearance after 5-FU and six had PR. Five lesions were withdrawn prior to completion of a single cycle of 5-FU. After adjustment for the influence of lesion size on response, the difference in clearance rates was NS. At 12 mth FU there were two recurrences in the PDT group (at 6 and 7 mth). There were six recurrences in the 5-FU group (at 5, 7, 8, 11 and 2 at 12 mth). Overall clearance (at 12 mth) in the PDT group was 27 of 33 lesions (82%) vs 16 of 33 lesions in the 5-FU group (48%). OR = 4.78 (95% CI 1.56 to 14.62, $p = 0.006$) **QoL and return to normal activity** Not assessed **AEs** Three patients with five lesions from the 5-FU group developed widespread dermatitic reactions over the treated limbs and were withdrawn from the study. Another patient with two lesions from the 5-FU group had widespread dermatitic reactions but elected to continue the treatment. In the 5-FU group, three lesions ulcerated and two developed painful erosions on completion of the treatment cycle. The ulcerated lesions healed leaving prominent scarring. There were no reactions in the PDT group and no clinically obvious scar formation at 12 mth at any PDT treatment site. 10 of 15 patients in the 5-FU group and 14 of 19 in the PDT group reported pain during the treatment cycle. During PDT pain was rated 'mild' by six patients, 'moderate' by six and 'severe' by two. Pain settled following illumination in 4 patients and persisted to 24 hr in four. Mild discomfort was reported by the remaining six patients lasting 7–42 d (mean 14). In the 5-FU group pain was rated 'mild' by six patients, 'moderate' by two and 'severe' by two. Discomfort persisted in the 5-FU group for 7–42 d (mean 21). In assessment of intensity and duration of pain, more pain was found in the 5-FU group ($p = 0.01$). Comparison of total pain over time revealed no statistically significant difference in the median pain scores between the two groups	**Authors' conclusions** Topical ALA–PDT is more effective than topical 5-FU in the treatment of Bowen's disease with fewer AEs. ALA should be considered one of the 1st-line therapeutic options for Bowen's disease **Brief study appraisal** Methods of randomisation, allocation concealment and blinding of outcome assessors were not described. This study, although small, highlights the potential of PDT for Bowen's disease but results should be confirmed in further trials

Appendix 15

Basal cell carcinoma data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Bassett-Seguin *et al.* (2008)[79] Linked publications[186–190] **Data source** Full published paper **Country** Not stated **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 120 randomised, 118 treated (219 lesions) Intervention: 60, 58 treated and analysed (103 lesions) Comparator: 58, 57 treated and analysed (98 lesions) **No. of recruiting centres** 13 across seven European countries **Follow-up period and frequency** 3 mth, then at 1, 2, 3, 4 and 5 yr	**Treatment intention** Curative **Type(s) of cancer and histology** Primary superficial BCC **Main eligibility criteria** Patients aged 18 yr or older with up to 10 previously untreated primary superficial BCC lesions suitable for cryotherapy. Diagnosis confirmed using punch biopsy. Lesions had to have diameter > 6 mm but < 15 mm on face/scalp, < 20 mm on neck/extremities, or < 30 mm on trunk. Further eligibility criteria were reported **Patient characteristics** Not stated **Concomitant treatment** Concomitant treatment with immunosuppressive medication was prohibited	**Trial treatments** MAL–PDT vs Cryotherapy **Intervention** MAL–PDT: A single treatment was initially given. Lesions were prepared by surface debridement. MAL cream, 160 mg/g, was applied in a layer of 1 mm to the lesion and 5 mm of surrounding tissue for 3 hr. The cream was washed off using a saline solution and the treated area was then illuminated with non-coherent red light (wavelength 570–670 nm) using a light dose of 75 J/cm. In patients with incomplete CR at 3-mth treatment was repeated (two consecutive MAL–PDT sessions 7 d apart) **Comparator** Cryotherapy: Cryotherapy was applied in two freeze–thaw cycles using liquid nitrogen spray applied to the lesion and a 3-mm surrounding area of healthy tissue. Procedure was repeated after a thaw period of two to three times the freeze duration. In patients with an incomplete response at 3-mth treatment was repeated (double freeze–thaw cryotherapy)	**Morbidity** 3 mth (115 patients): Lesions with inCR after 3 mth were 32% in the PDT group and 30% in the cryotherapy group. CR rates did not differ between the groups (PDT: 97% vs cryotherapy: 95%, $p = 0.49$) 12 mth (105 patients): Fewer lesions recurred with MAL–PDT than with cryotherapy (8% vs 16%) More patients had an 'excellent/good' cosmetic outcome with MAL–PDT than with cryotherapy at 3 and 12 mth 36 mth (107 patients): Proportion of lesions in CR was 66% for MAL–PDT and 67% for cryotherapy (NS). 74% estimated CR rate in both groups according to per-protocol population. The lesion recurrence rates in lesions with CR 3 mth after the last treatment were 23% for MAL–PDT and 20% for cryotherapy The overall cosmetic outcome was rated by physicians as 'excellent' or 'good' for 89% of the MAL–PDT patients and 63% of the cryotherapy patients 5 yr: CR rates did not differ between the groups (PDT: 75% vs cryotherapy: 74%, $p = 0.90$). Cumulative recurrence rate after 5 yr was PDT: 22% and cryotherapy: 20%, $p = 0.86$ **QoL and return to normal activity** Cosmetic outcome was better with PDT at both 3 mth and 5 yr 3 mth: 30% of PDT patients had an 'excellent' outcome compared with 4% for cryotherapy ($p = 0.0005$) 5 yr: 60% of PDT patients had an 'excellent' outcome compared with 16% for cryotherapy ($p = 0.00078$) All cosmetic outcomes rated by investigators using a 4-point scale **AEs** AEs were reported by 73% (44/60) PDT patients and 79% (46/58) cryotherapy patients. Most AEs were local and transient, no patients discontinued as a result of treatment-related AEs Pain: 37% PDT, 33% cryotherapy Crusting: 35% PDT, 47% cryotherapy Erythema: 30% PDT, 21% cryotherapy Mild: 80% PDT 73% cryotherapy Moderate: 13% PDT, 25% cryotherapy Severe: 5% PDT, 1% cryotherapy	**Authors' conclusions** This study demonstrated that lesion recurrence rate with MAL–PDT treatment was comparable to double freeze thaw cryotherapy for treatment of superficial BCC and provided a better cosmetic outcome **Brief study appraisal** Overall this trial was well conducted clearly reported. The lack of a power calculation means it is unclear if there was no difference between the treatments, or if the study was underpowered to detect such a difference. This trial did include a long term FU of 5 yr as well as examination of safety, efficacy and cosmetic outcomes

Study details	Population details	Treatment details	Results	Interpretation
Authors Berroeta *et al.* (2007)[87] Linked publications[191] **Data source** Full published paper (letter) **Country** UK **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 31 (40 lesions) Intervention: 18 (21 lesions) Comparator: 13 (19 lesions) **No. of recruiting centres** One **Follow-up period and frequency** FU to assess response at 3, 6 and 12 mth. FU to assess pain at 3, 6, 24 and 48 hr and also at 1 wk	**Treatment intention** Curative **Type(s) of cancer and histology** Nodular BCC **Main eligibility criteria** Non-pregnant adults (18 or over) with well-defined BCCs ≤ 2cm on anatomically non-critical sites were eligible Patients with recurrent BCCs, or BCCs at high-risk sites or patients with immunodeficiency or photosensitivity were excluded % Male: 100 **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT (following superficial curettage) vs Excision surgery **Intervention** Initial 4-mm punch biopsy to assess tumour depth, followed by superficial curettage (without anaesthetic) and PDT with 630-nm laser after 20% ALA applied for 6 hr (under occlusion). Irradiance was 12 mW/cm^2 and total dose 125 J/cm^2. PDT repeated at 3 mth if residual BCC was clinically evident **Comparator** Excision with surgical margins as recommended by the British Association of Dermatologists. Scalpel surgery was performed under infiltrative lidocaine anaesthesia but surgical re-excisions were not conducted	**Morbidity** For the PDT group 13/21 lesions (62%) were clear at 1 yr compared to 15/19 lesions (79%) in the surgery group, $p = 0.24$ There were five persistent BCCs in the PDT group but none in the surgery group (ns) **QoL and return to normal activity** There was no difference in mean scar severity (on a 1–4 scale) between the groups when judged independently by 10 non-medical men (1.9 for PDT vs 2.1 for surgery, $p = 0.42$) or 10 non-medical women (2.2 for PDT vs 2.5 for surgery, $p = 0.23$) **AEs** Median pain scores for the 1st BCC treated (scored out of 10) both during treatment, and immediately after treatment, were five for the PDT group, and 0 for surgery group ($p = 0.001$, and $p = 0.004$, respectively). Both groups had a score of zero at later assessments	**Authors' conclusions** There was no suggestion that PDT was, in general, better than surgery. PDT appears more painful than surgery for low-risk nBCCs. Surgery remains the 1st treatment choice for nBCCs **Brief study appraisal** This small pilot study was generally of high quality in its methods and reporting. The absence of anaesthetic for the PDT group before curettage may explain the differences in pain scores

Study details	Population details	Treatment details	Results	Interpretation
Authors de Haas *et al.* (2006)[83] **Data source** Full published paper **Country** The Netherlands **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 154 (505 lesions) Intervention: 55 (262 lesions) Comparator: 100 (243 lesions) **No. of recruiting centres** One **Follow-up period and frequency** FU four times a year in 1st year, then twice yearly. Patients tending to develop more lesions were seen more frequently. Minimum FU period was 1 yr, maximum FU period was 5 yr	**Treatment intention** Curative **Type(s) of cancer and histology** Primary superficial BCC **Main eligibility criteria** Not stated **Patient characteristics** Age range: 31–83 yr Mean age: 57 yr All participants were Caucasians **Concomitant treatment** Paracetamol, lidocaine (without adrenaline) or bupivacaine if required	**Trial treatments** Fractionated illumination PDT vs single-illumination PDT **Intervention** Fractionated illumination PDT: Crusts and scaling were gently removed using a disposable curette before ALA application. Illumination using doses of 20 and 80 J/cm^2 (at 50 mW/cm^2) delivered 4 and 6 hr after administration of 20% ALA ointment (containing 2% lidocaine) with a 1-cm margin. One of three different light sources were used on each lesion (a 630-nm diode laser, coupled into a 600-μm optical fibre and using a combination of lenses for uniform fluence rate; a light-emitting diode 633 nm with a bandwidth of 20 nm; or a 2nd broadband source with an output of between 590 and 650 nm), with a margin of at least 5 mm. A light-protective bandage (including aluminium foil) was used to provide the 2-hr dark interval between fractions. Participants were instructed to stay out of the cold **Comparator** PDT with placebo cream: Patients received two cycles (1 wk apart) of placebo cream PDT. There was surface debridement and slight lesion debulking prior to PDT. BCC with partial clinical response at 3 mth were re-treated. Further parameters were not reported	**Morbidity** CR of lesions was significantly greater using fractionated illumination compared with single illumination (at 1 yr, 97% vs 89%, $p = 0.002$). The results were very similar when analysis was undertaken on a subgroup of histologically proven BCCs. 10/262 (4%) lesions failed to respond, or recurred, in the fractionated-illumination group compared with 32/243 (13%) in the single-illumination group ($p = 0.0002$). There were no significant differences in response rates, within each illumination group, for the different light sources used **QoL and return to normal activity** Assessed but not reported **AEs** 5/100 (5%) patients required pain relief in the single illumination group compared to 15/55 (27%) patients in the fractionated illumination group	**Authors' conclusions** There is a significant increase in the CR rate of PDT using two-light fraction illumination scheme compared with a single-illumination scheme **Brief study appraisal** Although treatment methods were very well described, study design details on issues such as randomisation, blinding, and dropouts (were 154 or 155 patients treated?) were not provided, making it difficult to assess the reliability of the results

Study details	Population details	Treatment details	Results	Interpretation
Authors Foley *et al.* (2003)[77] **Data source** Abstract **Country** Australia **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 66 Intervention: 33 Comparator: 33 **No. of recruiting centres** Not stated **Follow-up period and frequency** Not clear, but appeared to be at least 6 mth	**Treatment intention** Curative patients with histologically confirmed nBCC **Type(s) of cancer and histology** nBCC **Main eligibility criteria** Patients with histologically confirmed nBCC **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** PDT (methyl aminolevulinate) vs PDT (placebo cream) **Intervention** Lesions 1st prepared by debridement/debulking. PDT with 160 mg/g of methyl aminolevulinate cream and 3 hr of red light (570–670 nm) with a total light dose of 75 J/cm^2. Treatment repeated after 7 d. Lesions with PR at 3 mth were re-treated. Further PDT parameters were not reported **Comparator** As for active PDT group, but using placebo cream	**Morbidity** At 6 mth, histological evaluation there were no signs of malignancy in 73% of the active PDT group vs 21% in the placebo PDT group ($p < 0.001$) **QoL and return to normal activity** Cosmetic outcome rated as excellent or good in 95% of the active PDT patients **AEs** There were no treatment-related serious or systemic AEs. Burning, stinging, pain, and erythema were transient, and graded as mild or moderate	**Authors' conclusions** PDT is a good alternative to existing therapies, particularly in areas where an excellent cosmetic outcome is crucial **Brief study appraisal** Limited reporting of methods and results makes meaningful interpretation difficult. No details were reported on who assessed cosmetic outcomes, and whether outcome assessors were blinded. Outcomes not always reported for both groups, or broken down by group

nBCC, nodular basal cell carcinoma.

Study details	Population details	Treatment details	Results	Interpretation
Authors Kuijpers *et al.* (2006)[84] **Data source** Full published paper **Country** The Netherlands **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 43 BCCs in 39 patients Intervention: 22 BCCs Comparator: 21 BCCs **No. of recruiting centres** One **Follow-up period and frequency** 8 wk	**Treatment intention** Curative **Type(s) of cancer and histology** Nodular primary BCC **Main eligibility criteria** Patients with nodular primary BCC located anywhere on skin except periocular area and hairy scalp, with a clinical diameter smaller than 20 mm. Pigmented BCCs and patients with more than five BCCs were excluded, as were patients with porphyria, contraindications to surgery, or hypersensitivity to daylight or to either of the creams **Patient characteristics** % Male: 62 Age range: 39–87 yr Mean age: 68 yr Most tumours were less than 10 mm in diameter **Concomitant treatment** Topical emollient for pain	**Trial treatments** PDT with 5-aminolevulinate (ALA–PDT) vs PDT with methyl aminolevulinate (MAL–PDT) **Intervention** ALA–PDT: All tumour tissue above skin level was removed by curettage (with ethyl chloride spray anaesthetic). The visible tumour, plus 5-mm margin, was covered in a layer of 20% ALA cream (around 2 mm thick) and polyurethane and opaque dressings were applied. After 3 hr the area was cleaned and illuminated with light of 600–730 nm (from metal halogen source) with an intensity of 100 mW/cm^2 giving a total dose of 75 J/cm^2. After illumination the area was covered with a light protective dressing for 1 d Procedure repeated after 7 d (but without debulking) **Comparator** MAL–PDT: Same methods as for PDT with 5-aminolevulinate group, except 16% methyl aminolevulinate cream was used instead of 20% ALA	**Morbidity** There was no statistically significant difference in incomplete clearance rates [6/22 (27%) ALA vs 6/21 (29%) MAL, $p = 0.92$] **QoL and return to normal activity** Not assessed **AEs** Average intensity of pain did not differ significantly between groups (1st treatment: VAS = 4.4 for ALA vs 2.8 for MAL, $p = 0.09$, 2nd treatment: VAS = 4.8 for ALA vs 3.9 for MAL, $p = 0.4$), nor did character of pain. Most pain was described as being burning or stinging	**Authors' conclusions** The study found no difference in short-term efficacy between ALA–PDT and MAL–PDT, so both can be equally recommended as photosensitisers **Brief study appraisal** This pilot study blinded both patients and outcome assessors. However, there was no mention of a power calculation and the sample size was very small; a larger study would have been more informative, particularly on differences in pain scores

Study details	Population details	Treatment details	Results	Interpretation
Authors Lui *et al.* (2004)[68] **Data source** Full published paper **Countries** Canada, USA **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: Not stated by diagnosis (387 lesions classified as BCC) Intervention: Superficial BCC 120 lesions; nBCC 47 lesions; BCC (not specified) zero Comparator: Superficial BCC 77 lesions; nBCC 30 lesions; BCC (not specified) nine 2nd Comparator: Superficial BCC 80 lesions; nBCC 16 lesions, BCC (not specified) eight **No. of recruiting centres** Four **Follow-up period and frequency** FU at 6 wk, and 3, 6, 12, 18 and 24 mth (optional beyond 6 mth)	**Treatment intention** Curative **Type(s) of cancer and histology** Superficial BCC, 277 lesions (66%); nBCC, 93 lesions (22%); Bowen's disease, 34 lesions (8%); BCC unspecified 17 lesions (4%) **Main eligibility criteria** Patients with at least two biopsy-proven superficial or nBCC or Bowen's lesions **Patient characteristics** Not stated for BCC only (study also included SCC) but overall: Average tumours treated per patient = eight Age range: 22–79 yr Mean age: 55 yr Most patients had Fitzpatrick skin type II or III **Concomitant treatment** Oral analgesic drugs for pain	**Trial treatments** PDT at 60 J/cm^2 vs PDT at 120 J/cm^2 vs PDT at 180 J/cm^2 **Intervention** PDT at 60 J/cm^2: 10 min intravenous infusion of 1.4 mg/m^2 verteporfin, followed 1–3 hr later by exposure to 60 J/cm^2 of red light (688 ± 10 nm) from a non-thermal LED panel. The exposed area included a margin of 3–4 mm around the lesion. The irradiance delivered was 200 ± 40 mW/cm^2. Tumours re-treated at 3 mth if necessary (with dose increased to 18 mg/m^2) **Comparator** PDT at 120 J/cm^2: See above **2nd comparator** PDT at 180 J/cm^2: See above	**Morbidity** At 6 mth, the histopathological response (i.e. no residual tumour) was: nBCC: 76% at 60 J/cm^2, 82% at 120 J/cm^2, and 100% at 180 J/cm^2; superficial BCC: 63%, 80%, and 97%; BCC not specified: 0%, 56% and 75% There was a trend indicating a better response with a higher light dose ($p = 0.06$) **QoL and return to normal activity** Reported by light dose rather than tumour type **AEs** Reported by light dose, rather than by tumour type	**Authors' conclusions** A single course of verteporfin PDT showed treatment benefit for patients with multiple non-melanoma skin cancers **Brief study appraisal** No clinically relevant comparator treatment was used, there was a lack of information on issues such as blinding and allocation concealment, and the authors did not present many results and population details by diagnosis. It is therefore difficult to make any reliable conclusions about the efficacy of verteporfin in patients with BCC

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Authors Mosterd *et al.* (2008)[86] **Data source** Full published paper **Country** The Netherlands **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 149 (173 lesions randomised, 171 treated) Intervention: 85 lesions Comparator: 88 lesions **No. of recruiting centres** One **Follow-up period and frequency** 1–2 wk for surgery, then 3, 6, 12 and 18 mth; 2, 3, 4 and 5 yr	**Treatment intention** Curative **Type(s) of cancer and histology** nBCC **Main eligibility criteria** Previously untreated primary nBCC with maximum diameter of 20 mm in patients of 18 yr or older. Pregnancy, life expectancy of less than 5 yr and use of photosensitive drugs were exclusion criteria. Tumours were excluded if recurrent, pigmented or located on hairy or concave areas. Further details were reported **Patient characteristics** % Male: 50 Mean age: 65 yr Most tumours were located on the forehead/temple, back or nose area. Maximum mean tumour diameter 9.1 mm **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT vs Surgical excision **Intervention** ALA–PDT: Partial tumour debulking performed under local anaesthetic 3 wk prior to PDT treatment. 20% ALA cream applied to lesion including 5-mm surrounding area and covered with occlusive dressing for 4 hr. Lesion then illuminated using a broadband metal-halogen light source for 15 min with intensity of 100 mWcm^2 and dose of 75 J/cm^2. Area was then covered and re-illuminated after 60 min. This produced a fractionated treatment on the same day with a total light dose of 150 J/cm^2. Any incomplete responses or recurrent tumours were re-treated surgically **Comparator** Surgical Excision: Local anaesthetic using lidocaine (1%) with adrenaline followed by excision of the tumour and a 3-mm surrounding margin. Closure was by sutures or transposition/transplantation depending on lesion location. Sections of the lateral and deep margins were histologically examined; if residual tumour was found then this was regarded as a treatment failure and re-excisions were performed until margins were free from tumour	**Morbidity** 3 mth: 78/83 (94%) CR in PDT and 86/88 (98%) in SE patients, $p = 0.27$ Failure rates: Cumulative incidence of failure probability at 3 yr was 2.3% for SE and 30.3% for PDT ($p < 0.001$) **QoL and return to normal activity** Not assessed **AEs** No serious complications were observed	**Authors' conclusions** Treatment of nBCC with SE is significantly more effective than treatment with ALA–PDT after debulking. PDT should not therefore be used as a standard treatment for nBCC **Brief study appraisal** This was a well-conducted and generally well-reported study, which draws appropriate conclusions and can be considered to be reliable. As the authors suggest further studies are required to explore possible variations in PDT treatment

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Authors Rhodes *et al.* (2007)[85] Linked publications[192–197] **Data source** Full published paper **Countries** Not stated 'European hospitals' **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 103 randomised (101 treated) Intervention: 53 (60 lesions) Comparator: 50 (58 lesions) **No. of recruiting centres** 13 **Follow-up period and frequency** 3 mth, then at 1, 2, 3, 4 and 5 yr	**Treatment intention** Curative **Type(s) of cancer and histology** Primary nBCC **Main eligibility criteria** Histologically confirmed nBCC, previously untreated in patients ≥ 18 yr. Patients with more than 10 lesions, porphyria, or Gorlin syndrome were excluded. Further exclusion criteria were reported **Patient characteristics** % Male: 60 Age range: 38–95 yr Mean age: 69 yr (PDT group), 67 yr (surgery group) Around 90% of patients had only one lesion, and around three-quarters of lesions were between 5 and 14 mm in diameter. The majority of patients were classified as Fitzpatrick skin type II or III, and lesions were mostly on the face/scalp/trunk and neck	**Trial treatments** MAL–PDT vs excision surgery **Intervention** Surface scale removed using scalpel or curette (without anaesthesia). Then one or two PDT cycles with methyl aminolevulinate (160 mg/g), each comprising of two sessions (1 wk apart). Cream was applied 1 mm thick and to 5 mm of surrounding tissue, then covered with an occlusive dressing for 3 hr. Cream then washed off with 0.9% saline solution immediately before illumination with non-coherent red light (570–670 nm, total fluence 75 J/cm^2, fluence rate of 50 to 200 mW/cm^2), mean light density of 127 mW/cm^2 from a standard light source If not CR by 3mth, 2nd treatment cycle administered. 76% of lesions treated with one cycle only **Comparator** Simple elliptical excision surgery with at least 5-mm margins. Local anaesthesia	**Mortality** Four patients in each group died during FU (all considered to be unrelated to treatment) **Morbidity** At 3 mth: 48 lesions (91%, 50 patients) in the PDT group, and 51 lesions (98%, 47 patients) in the surgery group, showed CR, mean diff = 4.8%, ns. At 1 yr: 44/53 PDT lesions (83%) had CR vs 50/52 (96%) surgery lesions ($p = 0.15$). Recurrence was 4% in PDT group vs 0% in surgery group. At 2 yr: 32/53 (60%) PDT lesions had CR vs 44/52 (85%) surgery lesions. By this stage, 11 (21%) of PDT lesions were lost to FU vs six (11%) surgery lesions. Recurrence was 9% in PDT group vs 2% in surgery group. At 36 mth: CR 79% in PDT group vs 96% in surgery group. Recurrence was 10% in PDT group vs 2% in surgery group. At 5 yr: CR was 76% in the PDT group and 96% in the surgery group (per-protocol population, $p = 0.01$). There was recurrence in 14% of lesions in PDT group and 4% in the surgery group ($p = 0.09$). Only one lesion (in the surgery group) recurred within the 3- to 5-yr FU period. In the PDT group, there was no evidence that the recurrence rate was higher in larger lesions **QoL and return to normal activity** Cosmetic outcome was rated by investigator as being: At 3mth, excellent or good in 36/44 patients (82%) having PDT vs 15/45 patients (33%) having surgery ($p < 0.001$). At 1 yr, excellent or good in 33 of 42 (79%) PDT patients vs 17 of 45 (38%) surgery patients ($p < 0.001$). At 2 yr, excellent or good in 24/29 (83%) PDT patients vs 16 of 39 (41%) surgery patients ($p < 0.001$). At 36 mth, excellent or good in 83% of PDT patients vs 37% surgery patients. At 5yr, excellent or good in 27 of 31 (87%) PDT patients vs 19 of 35 (54%) surgery patients, $p = 0.007$). Patients also rated global cosmetic outcome on a 4-point scale at 3, 12 and 24 mth. No significant difference at 3 mth, at 12 mth excellent or good in 41/42 (98%) for PDT patients vs 36/43 (84%) for surgery, $p = 0.03$. At 24 mth, PDT patients reported 28/29 (97%) vs 27/36 (75%) for surgery, $p = 0.04$ **AEs** More PDT patients reported AEs [27/52 (52%) vs 14/49(29%), $p = 0.03$]. Most AEs were transient local reactions such as burning sensations, skin pain, or erythema. One PDT patient had to stop treatment due to a severe burning sensation; three surgery patients had skin infections	**Authors' conclusions** Long-term FU indicates superior efficacy of surgery to PDT. However, PDT is also an effective treatment and exhibits a more favourable cosmetic outcome **Brief study appraisal** This generally well-conducted trial, which had a long FU period, was reported in two papers and four abstracts. The results are likely to be reliable, although the 3-mth CR results did vary slightly between reports

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Authors Schleier *et al.* (2007)[81] **Data source** Full published paper **Country** Germany **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 24 (112 lesions) Intervention: 13 Comparator: 11 **No. of recruiting centres** One **Follow-up period and frequency** 2, 4 and 12 wk and 6 mth after primary treatment	**Treatment intention** Curative **Type(s) of cancer and histology** Superficial BCC **Main eligibility criteria** Histologically verified BCC of the skin, histologically proven superficial BCC with no deep infiltration (< 2 mm), no morpheic and pigmented BCC and good patient compliance. Exclusion criteria were: Unclear histology, clinically nBCC, expected poor compliance of the patient, untreated diabetes mellitus and pregnancy **Patient characteristics** % Male: 54 Age range: 42–96 yr Mean age 74 yr The vast majority of the tumours were located in the head and neck area. The average diameter of the lesions was 7 mm (range 3–12 mm). Three patients with GGS were included in the study **Concomitant treatment** Not stated	**Trial treatments** ALA-based PDT vs mALA-based PDT **Intervention** ALA and mALA gels were prepared less than 1 hr before treatment by dissolving in a cold (approx 4°C) thermo gel (Lutrol F-127) up to a concentration of 10% of ALA (mALA)/ml (w/v). The gel was applied 3 mm beyond the visible margin of the tumour and was approximately 5 mm thick. The area was covered with plaster and protected from light. 3 hr later, residues were removed and tumour areas circled with a blue skin marker. The lesion was then illuminated with a diode laser equipped with a microlens fibre. The power density was 0.1 W/cm^2 and the energy density was 120 J/cm^2. A diameter of the irradiated area of approximately 10 mm was selected and distance laser-diffuser-skin corresponded to 15 mm. The procedure was performed with or without local anaesthesia according to the pain management needs of the patient. In cases where treatment was only partially successful, the therapy was repeated after the final examination (12th wk). Further PDT parameters were not reported **Comparator** See 'Intervention' for details	**Morbidity** ALA group: 44 of 72 BCC (61%) showed a CR 12 wk after the 1st treatment vs mALA group: 23 of 40 BCC (58%) NS There was no statistically significant difference in partial successes (reduction of the diameter of the BCC of at least 50% of the initial tumour size) between the groups. Three tumours (4%) in the ALA group and one BCC (3%) did not respond to treatment and showed no reduction in tumour size. These patients were given surgical treatment. Eight BCCs in the ALA group and five in the mALA group developed a recurrence during the 6-mth period. After a second PDT, seven lesions in the ALA group and seven in the mALA group were treated successfully **QoL and return to normal activity** Not assessed **AEs** During illumination, eight ALA patients and five mALA patients experienced moderately painful sensations in the treated are (1–4 on the pain scale). Two patients in the mALA group had stabbing pain sensations (level 6–7 on the pain scale) during the laser application and had to be treated with local anaesthetic. Five patients in ALA group and two in mALA group felt moderate pain sensations up to the 3rd day post illumination (1–3 on the pain scale)	**Authors' conclusions** The therapeutic outcome of this pilot study showed no difference between PDT with ALA and mALA. This preliminary result will require confirmation in further research **Brief study appraisal** This was a pilot study in preparation for a larger clinical trial. As such, it is likely to have been underpowered to detect statistically significant differences for at least some of the outcomes investigated. Treatment methods were well described but study methods, such as methods of randomisation, concealment of allocation and blinding, were not reported in detail

GGS, Gorlin–Goltz syndrome.

Study details	Population details	Treatment details	Results	Interpretation
Authors Soler *et al.* (2000)[82] **Data source** Full published paper **Country** Norway **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 83 (245 lesions) Intervention: 41 (111 lesions) Comparator: 42 (134 lesions) **No. of recruiting centres** One **Follow-up period and frequency** FU at 1 wk, and 3 and 6 mth. Some participants also followed up after 1 and 2 yr	**Treatment intention** Curative **Type(s) of cancer and histology** Superficial BCC **Main eligibility criteria** Patients with histologically/cytologically confirmed superficial BCC with thickness < 1 mm, and diameter < 3 cm. Patients with fewer than six lesions **Patient characteristics** % Male: 47 Mean age: 62 yr All Caucasian **Concomitant treatment** Not stated	**Trial treatments** PDT-laser vs PDT-broadband lamp **Intervention** PDT-laser: Pre-treatment with dressing soaked with 99% dimethylsulphoxide for 15 min followed by 20% ALA cream and covering with occlusive dressing for 3h. Cream was washed off before exposure to light of 630 nm from a copper vapour laser pumping a dye laser. Irradiance of 120–150 mW/cm^2, and a light dose of 100–150 J/cm^2 (median dose 100 J/cm^2) **Comparator** PDT-broadband lamp: As for PDT-laser except light source was a 150W halogen bulb broadband lamp, giving filtered light of between 570 and 740nm. Irradiance was 100–180 mW/cm^2 and total light dose ranged from 150–200 J/cm^2 with median light dose of 200 J/cm^2. Total irradiance including infra-red was 135–240 mW/cm^2	**Morbidity** Overall, there were no statistically significant differences ($p = 0.49$) in response rates (complete, partial, or none) between the groups [CR was 95/111 lesions (86%) for laser vs 110/134 (82%) for lamp]. Patients with CR were followed up beyond the protocol 6-mth period. Data were presented, but not statistically analysed – recurrence after 2 yrs occurred in four lesions for the laser group, and five lesions for the lamp group **QoL and return to normal activity** Overall there were no statistically significant differences in cosmetic results ($p = 0.075$). Results were scored as being excellent or good in 80 lesions (84%) in the laser group vs 102 lesions (92%) in the lamp group **AEs** During the 1st wk after treatment 68% of the laser group and 74% of the lamp group patients reported some degree of discomfort (e.g. stinging, itching, pain). There were no statistically significant differences between the groups for AEs either during or after treatment. No SAEs were reported during 6-mth FU period	**Authors' conclusions** Topical ALA–PDT with a broadband halogen light source gives cure rates and cosmetic outcome similar to those obtained with a laser source **Brief study appraisal** Although this was quite a well-conducted study, there were still issues which question the reliability of its results: the authors acknowledged that the optimum wavelength for ALA–PDT is 635 nm, but 630 nm was used for the laser group, for reasons of practicality; light doses varied between patients within a treatment group; and the M/F ratio differed substantially between the treatment groups

Study details	Population details	Treatment details	Results	Interpretation
Authors Szeimies *et al.* (2008)[80] **Data source** Full published paper **Countries** Australia, Germany, Switzerland, UK **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 196 (182 analysed) Intervention: 100 Comparator: 96 **No. of recruiting centres** 27: 10 in UK, 10 in Germany, two in Switzerland, five in Australia **Follow-up period and frequency** 3, 6 and 12 mth	**Treatment intention** Curative **Type(s) of cancer and histology** Superficial BCC **Main eligibility criteria** Patients over 18 yr with histologically confirmed primary sBCC suitable for simple excision surgery. Patients with more than five lesions, lesions in the mid-face area, lesions smaller than 8 mm or larger than 20 mm were excluded (other criteria reported) **Patient characteristics** % Male: 67 Age range: 31–92 yr Mean age: 64 yr All patients were Caucasian, and the mean no. of lesions per patient was 1.4 (range 1–5). Most lesions were located on the trunk or neck **Concomitant treatment** concurrent treatment on the lesion areas was not permitted	**Trial treatments** MAL–PDT vs Surgery **Intervention** MAL–PDT: Patients received two treatment sessions, 7 d apart. Lesions were prepared prior to each session if deemed necessary by removing crusts and roughening the surface. 160 mg/g of MAL cream was applied 1 mm thick to the lesion and surround 5–10 mm of skin and covered with an occlusive dressing for 3 hr. Cream was washed off using saline solution and the area exposed to red light from a large-field LED source for between 7 and 10 min, total light dose 37 J/cm^2. Mini-desk fans were provided to cool the irradiation sites during light exposure **Comparator** Surgery: One simple elliptical excision surgery was performed according to the investigators routine practice with an estimated 3-mm margin from estimated edge of the lesion	**Morbidity** (all per protocol analyses) 3-mth complete lesion response: 118/128 (92%) for PDT vs 117/118 (99%) in surgery 12-mth lesion recurrence: 11/118 (9%) for PDT vs 0.117 (0%) for surgery **QoL and return to normal activity** Cosmetic outcome assessed by patient and investigator, in both cases PDT treatment was judged to be superior 12-mth investigator rated assessment: 77/83 (93%) for PDT and 44/86 (51%) for surgery were considered as a 'success', $p < 0.001$ **AEs** Treatment-related AE were higher in the PDT (37%) than surgery (15%) group. Most related AEs were of mild to moderate severity and were most commonly photosensitivity (31%) reaction for PDT and wound infection (5%) for surgery patients 11% of PDT patients with related AEs required treatment while 57% of surgery patients with related AEs needed treatment No SAEs were recorded that were considered to be related to either treatment	**Authors' conclusions** MAL–PDT has high levels of efficacy and excellent cosmetic outcomes when treating sBCC and should be considered as an alternative to surgery **Brief study appraisal** This was a well-reported and conducted trial; however, longer-term FU would provide useful outcome data on the recurrence rates. It was not clear if the study was adequately powered to show equivalence of treatments. Given that included patients were restricted to those eligible for surgery, as the authors have highlighted it seems plausible that PDT may be more effective than shown here

Study details	Population details	Treatment details	Results	Interpretation
Authors Tope *et al.* (2004)[78] **Data source** Abstract **Country** USA **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 65 (80 lesions) Intervention: 33 patients (41 lesions) Comparator: 32 patients (39 lesions) **No. of recruiting centres** Not stated but described as being multicentre **Follow-up period and frequency** Not clear, but appeared to be at least 6 mth	**Treatment intention** Curative **Type(s) of cancer and histology** nBCC **Main eligibility criteria** Not stated **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** MAL–PDT (methyl aminolevulinate) vs PDT (placebo cream) **Intervention** MAL–PDT: Patients received two cycles (1 wk apart) of methyl aminolevulinate PDT. There was surface debridement and slight lesion debulking prior to PDT. BCC with partial clinical response at 3 mth were re-treated. Further PDT parameters were not reported **Comparator** As for MAL–PDT using placebo cream	**Morbidity** Complete clinical response was 80% (33/41 lesions) for active PDT vs 51% (20/39 lesions) for placebo PDT. Complete histological response was 78% (32/41 lesions) vs 33% (13/39 lesions), both appeared to be at $p < 0.001$ **QoL and return to normal activity** For sites showing complete clinical response, investigator-assessed cosmetic outcome was excellent or good in 93% of active PDT vs 90% of placebo PDT Patient satisfaction with PDT compared with previous treatment was better in 60% of MAL–PDT patients, and 52% in placebo PDT patients **AEs** There were no systemic AEs in either group. Local AEs: 91% in the active group vs 75% in the placebo group. Mild to moderate erythema, burning, stinging, and pain found in both groups. Pain occurred for a median of 2 d in active PDT group vs 3–6 d in placebo PDT group. All SAEs in both groups were not related to treatment	**Authors' conclusions** PDT was clinically and histologically superior to placebo PDT in treating nBCC **Brief study appraisal** Very little information was available in this abstract. It was not always clear whether results were for lesions or individual patients

Study details	Population details	Treatment details	Results	Interpretation
Authors Wang *et al.* (2001)[88] **Data source** Full published paper **Country** Sweden **Language** English **Study design** RCT (between-participant comparison) **No. of participants** Total: 88 Intervention: 47 Comparator: 41 **No. of recruiting centres** One **Follow-up period and frequency** FU at 1, 4, 8 and 12 wk, and at 1 yr	**Treatment intention** Curative **Type(s) of cancer and histology** Non-morphoeic BCCs (superficial and nodular) **Main eligibility criteria** Patients aged 20–90, with histopathologically verified BCCs suitable for both PDT and cryosurgery, were eligible. Exclusion criteria (e.g. pregnancy) were also reported **Patient characteristics** % Male: 50 Age range: 42–88 yr There were 39 patients with superficial BCCs and 49 with nBCCs. 54% were on the trunk, 28% on head and neck, 11% on legs, and 7% on arms **Concomitant treatment** Local anaesthetic available during procedures. Use of analgesic drugs was permitted for pain relief during the week following procedures	**Trial treatments** ALA–PDT vs Cryotherapy **Intervention** Lesions were 1st prepared (removal of stratum corneum material using scalpel/96% alcohol/ isotonic saline). 20% ALA was then applied to lesion with 1-cm margin, and covered with a thin occlusive dressing. 6 hr after ALA, 635-nm light through a 600-μm optical fibre (with a clear-cut polished end) from a Nd:YAG laser was applied. The single light dose was 60 J/cm^2, and the mean fluence rate 80 mW/cm^2. Larger lesions had to be illuminated with more than one light source. Patients with pain during light exposure received water spray at 15–20°C. Additional treatment given if there was evidence of residual tumour growth at the 4, 8 or 12 wk examinations **Comparator** Treatment with a liquid nitrogen unit using a spray technique. Two freeze–thaw cycles were given, and the area frozen for 25–30 s each time, with a thawing period of 2–4 min in between. Additional treatment given if there was evidence of residual tumour growth at the 4-, 8- or 12-wk examinations	**Mortality** One patient died in each group after the 3-mth FU. Both deaths were unrelated to BCC and its treatment **Morbidity** More participants in the PDT group had to be re-treated (13/44, 30%) compared with the cryosurgery group (1/39, 3%). The recurrence rate at 1 yr was higher in the PDT group (11/44, 25% vs 6/39, 15%), though not statistically significant (and the PDT group had fewer clinically obvious recurrences). After 1 wk, the PDT group had a significantly shorter healing time in terms of leakage and oedema ($p < 0.001$), but not erythema. There was also a significant difference in leakage at 1 mth, favouring the PDT group **QoL and return to normal activity** The cosmetic outcome was significantly better at 1 yr in the PDT group for hypopigmentation, scar formation, tissue defects (all $p < 0.001$), and hyperpigmentation ($p < 0.05$) **AEs** There was no statistically significant difference in mean pain VAS scores during treatment (PDT 43 vs cryosurgery 32). One PDT patient required local anaesthetic. One cryosurgery patient developed a bacterial infection at the treatment site. During the 1st week post treatment eight PDT patients and two cryosurgery patients used analgesic medication ($p < 0.05$)	**Authors' conclusions** ALA–PDT is comparable with cryosurgery as a treatment modality for BCCs. Retreatments are more common with PDT, but this can easily be performed due to shorter healing times, less scarring, and better cosmetic outcome, which follows ALA–PDT **Brief study appraisal** This study was generally quite well conducted and the results are likely to be reliable. However, more information on losses to FU and any sample size calculation used, would have been useful

Appendix 16

Barrett's oesophagus data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Ackroyd *et al.* (2000)[95] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 36 Intervention: 18 Comparator: 18 **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 1, 6, 12 and 24 mth	**Treatment intention** Curative **Type(s) of cancer and histology** BO – LGD **Main eligibility criteria** Patients with LGD in circumferential BO of at least 3 cm in length, who were receiving omeprazole were eligible. However, histological re-examination after biopsy had to confirm the diagnosis **Patient characteristics** % Male: 83 Age range: 30–71 yr Median age: 56 yr Range of pre-treatment lengths of Barrett's: 3–15 cm **Concomitant treatment** Patients were given analgesic and antiemetic drugs as required following treatment. Patients were also supplied with antacids to take as needed. Throughout the treatment and FU period patients were maintained on 20 mg omeprazole daily	**Trial treatments** ALA–PDT vs Placebo-PDT **Intervention** Patients drank 30 mg/kg ALA (dissolved in 50 ml of orange juice) followed 4 hr later by laser endoscopy (under intravenous sedation and analgesia) when the extent of Barrett's area was recorded. A copper vapour laser delivered by a fibre with a diffuser tip was used to deliver green light (514 nm) at a power density of 120 mW/cm^2 for 500 s per 3-cm length. All patients had two separate treatments (distal, then proximal, total treatment time 1000 s, energy density 60 J/cm^2) so that 6 cm of oesophagus was treated (upper 6 cm of Barrett's mucosa). This represented complete treatment of Barrett's epithelium in one-half of the patients. Patients remained in hospital until dark, and were advised to avoid bright light for 24 hr **Comparator** As for above, except orange juice alone was used as placebo	**Mortality** Not assessed **Morbidity** In the PDT group 16/18 (89%) showed macroscopic evidence of regression at FU endoscopy, compared with 2/18 (11%) in the placebo group; the corresponding median reduction in areas were 30% for PDT vs 0% for placebo (both $p < 0.001$). All regression cases displayed normal squamous mucosa when biopsied. There was a reduction in prevalence of dysplasia in favour of the PDT group (0/18 vs 12/18, $p < 0.001$). Although it was unclear as to which FU point these results relate to, the authors did state that the effects of treatment were maintained for up to 24 mth **AEs** All PDT patients experienced chest pain during treatment that persisted for 3–5 d, and was aggravated by swallowing or coughing. One patient developed a mild skin rash on exposure to sunlight (resolved within 48 hr). No patients complained of dysphagia. No results appeared to have been reported for the placebo group **Resource use** Not assessed	**Authors' conclusions** ALA–PDT can provide safe and effective ablation of low-grade dysplastic epithelium **Brief study appraisal** This small study was generally well conducted, and the results appear reliable. However, it should be noted that no results appear to have been reported on AEs in the placebo group, and it was unclear to which FU the main study results relate

BO, Barrett's oesophagus.

Study details	Population details	Treatment details	Results	Interpretation
Authors Ackroyd *et al.* (1996)[96] **Data source** Abstract **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 28 Intervention: Not stated Comparator: Not stated **No. of recruiting centres** Not stated **Follow-up period and frequency** Not stated	**Treatment intention** Curative (dosing study) **Type(s) of cancer and histology** Dysplastic BO **Main eligibility criteria** Not stated **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT 30 mg/kg vs ALA–PDT 50 mg/kg vs placebo **Intervention** Oral ALA at 30 or 50 mg/kg, or placebo, was followed 4 hr later by light administration. No further parameters were reported **Comparator** See 'Intervention' **2nd comparator** See 'Intervention'	**Mortality** Not assessed **Morbidity** Not assessed **AEs** In the 30-mg/kg group, one patient had mild photosensitivity, but no other AEs were seen. In the 50-mg/kg group, oesophageal discomfort, hair loss, and transient disturbance of liver function test results were observed **Resource use** Not assessed	**Authors' conclusions** ALA–PDT at 30 mg/kg should provide optimal treatment conditions in BO **Brief study appraisal** The absence of important methodological, population, and result details in this abstract of a small study, means it is difficult to assess the reliability of its results

Study details	Population details	Treatment details	Results	Interpretation
Authors Hage *et al.* (2004)[97] Linked publications[198] **Data source** Full published paper **Country** The Netherlands **Language** English **Study design** RCT **No. of participants** Total: 40 Intervention: PDT 20 + 100: 13 Comparator: PDT100: 13 2nd Comparator: APC: 14 **No. of recruiting centres** Not stated **Follow-up period and frequency** 6 wk, 6, 12, 18 and 24 mth	**Treatment intention** Curative **Type(s) of cancer and histology** Patients with BO without dysplasia or with LGD **Main eligibility criteria** Patients 18 yr or over with BO without dysplasia or with LGD on histological examination were eligible. Patients had to have a BO length of 2–5 cm and specialised intestinal metaplasia. All patients were taking PPIs for at least 6 mth before treatment. Exclusion criteria were intolerance to (repeated) endoscopy, pregnancy, acute porphyria and intercurrent diseases precluding survival during the study period **Patient characteristics** % Male: 78 Median age: 59 yr Age range: 41–72 yr Mean BO length: 3 cm (range 2–5 cm) Dysplasia: None 32; LGD eight **Concomitant treatment** If complete elimination of BO was not achieved by the designated treatment at 6 wk, the remaining BO was ablated by additional APC with a maximum of two sessions at 4-wk intervals. Patients were treated with a daily dose of at least 40 mg of omeprazole for the duration of the study. Mean dose 47.5 mg (range 40–80mg)	**Trial treatments** PDT with fractionated dose (20 + 100) ALA vs PDT with single-dose ALA vs APC **Intervention** Fractionated PDT: 60 mg/kg ALA was dissolved in 20 ml of orange juice. All patients were kept in a darkened room for 36 hr. A KTP/532 dye laser module was used to deliver light at a wavelength of 630 nm. PDT was performed with a fluence of 20 J/cm^2 at 1 hr and 100 J/cm^2 at 4 hr after ALA administration. Light delivery was performed using an inflatable balloon with an inflated diameter of 2.5 cm. Calculated total fluence rate was 100 mW/cm^2 **Comparator** Single-dose ALA–PDT: As for fractionated PDT with the exception that there was a single illumination of 100 J/cm^2 at 4 hr after ALA administration **2nd comparator** APC: an Argon Beamer 2 device, APC 300 was used with a gas flow rate of 2 l/min at a power setting of 65W. The aim was to ablate two-thirds of the oesophageal circumference of BO during the 1st session and in the following session to ablate the remainder. APC involved a maximum of two treatment sessions per patient at 4-wk intervals	**Mortality** Not assessed **Morbidity** At 6 wk, mean endoscopic BO surface reduction was 51% (range 20–100%) in the single dose PDT group, 86% (range 0–100%) in the fractionated PDT group and 93% (range 40–100%) in the APC group. This was statistically significant for the comparison between single-dose PDT and fractionated dose PDT and single-dose PDT and APC. Differences between fractionated dose PDT and APC were not significant. Rates of complete ablation were ns between the groups. 6-, 12- and 18-mth data not extracted as patients were then eligible to receive APC **AEs** 23 of 26 patients across the two PDT groups and five of 14 in the APC group experienced pain during treatment ($p < 0.01$). There were more cases of nausea and vomiting with PDT (7 vs 0 in APC, $p < 0.05$) and patients had more elevated liver enzyme results in tests (20 vs 0, $p < 0.01$). Differences in odynophagia, fever, sudden death and stricture formation were not significant **Resource use** Not assessed	**Authors' conclusions** APC alone or ALA–PDT in combination with APC can lead to complete reversal of Barrett's epithelium in at least two-thirds of patients when administered in multiple treatment sessions. The authors did not recommend use of these techniques for prophylactic ablation of BO **Brief study appraisal** This was a small trial and the low numbers of patients across the three groups may have meant there was insufficient power to detect treatment differences where they existed. A further problem is that all patients who did not respond adequately were given APC, so the long-term effect of PDT alone is unclear

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Study details	Population details	Treatment details	Results	Interpretation
Authors Kelty *et al.* (2004)[102] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 25 Intervention: Five Comparator: Five 2nd Comparator: Five 3rd Comparator: Five 4th Comparator: Five **No. of recruiting centres** One **Follow-up period and frequency** 4 wk	**Treatment intention** Curative **Type(s) of cancer and histology** Non-dysplastic BO **Main eligibility criteria** Patients already participating in a large cohort study on BO with biopsy proven Barrett's epithelium **Patient characteristics** % Male: 80 Median age: 63 yr Age range: 31–81 yr Median length of Barrett's epithelium was 4 cm (range 2–15 cm), no patients had high or LGD on biopsy **Concomitant treatment** 40 mg esomeprazole daily	**Trial treatments** ALA–PDT at various doses (30 mg/kg or 60 mg/kg) at 4- or 6-hr incubation times or with fractionated illumination **Intervention** 30 mg/kg ALA–PDT, light delivered by endoscopy after 4-hr PDT protocol: ALA dissolved in 50 ml of orange juice and taken orally. Patients kept in dimly lit room prior to treatment. At appropriate time patients underwent endoscopy with intravenous sedation, analgesia and an antiemetic drug. Balloon applicator was placed over a guidewire in the oesophagus and position confirmed endoscopically. Balloon was inflated to around 20 mmHg and light delivered by a 5-cm cylindrical diffuser fibre. Red light (635 nm, 2W diode laser) was used at fluence rate of 68 mW/cm^2 for a total dose of 85 J/cm^2. Patients recovered in a dimly lit room, discharged with oral analgesia and advice to avoid bright lights for 24 hr **Comparator** 30 mg/kg ALA–PDT, light delivered by endoscopy after 6 hr **2nd comparator** 30 mg/kg ALA–PDT repeated at 2 hr, light delivered by endoscopy after 4 hr **3rd comparator** 60 mg/kg ALA–PDT, light delivered by endoscopy after 4 hr **4th comparator** 60 mg/kg ALA–PDT, light delivered by endoscopy after 6 hr	**Mortality** Not assessed **Morbidity** At 1 mth FU all patients showed a reduction in the area of Barrett's epithelium in the treated area, median reduction for all 25 patients was 60%. Median reduction in area varied between 30% and 60% for each treatment group. The greatest reductions were seen in the fractionated and 30 mg/kg groups (all 60%), but this difference was not statistically significant **AEs** No major AEs – no perforations or strictures. Significant N&V occurred in 32% of patients who required further anti-emetic treatment. N&V was more common in patients who received the higher dose of ALA. Five patients had a documented photosensitivity reaction – all were mild cases **Resource use** Not assessed	**Authors' conclusions** Low dose ALA–PDT appears to be a safe protocol for the ablation of BO. The authors recommend that ALA should be given orally as 30 mg/kg 4- to 6-hr before activation and could be taken at home **Brief study appraisal** This was a small study that aimed to establish optimum dosage regimes. Although patients were randomised to treatment, no information on blinding or allocation concealment was provided. The sample size appears to have been too small to view the authors' conclusions as being reliable

Study details	Population details	Treatment details	Results	Interpretation
Authors Kelty *et al.* (2004)[98] Linked publications[199–201] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 72 Intervention: 35 (PDT) Comparator: 37 (APC) **No. of recruiting centres** One **Follow-up period and frequency** 1 day, 4 wk then 6, 12 and 24 mth after successful treatment or five sessions	**Treatment intention** Curative **Type(s) of cancer and histology** BO **Main eligibility criteria** Patients were invited to take part from an endoscopic screening programme (over 150 were approached). No further details reported **Patient characteristics** % Male: 81 Age range: 28–83yr Median age: 61 yr All patients had biopsy proven Barrett's epithelium (median length of 4 cm, range 2–15cm). No patients had high or LGD **Concomitant treatment** 40 mg esomeprazole daily, with oral analgesia as required	**Trial treatments** ALA–PDT vs APC **Intervention** ALA–PDT: 30 mg/kg of ALA dissolved in 50 ml of orange juice taken orally, patient kept in a dim room prior to treatment (46 hr later). Endoscopy was carried out (with intravenous sedation, analgesia and an antiemetic) and a balloon applicator was placed over a guidewire (position confirmed endoscopically) and inflated to approximately 20 mmHg. Light was delivered using a cylindrical diffuser fibre – red laser light (635 nm 3W) at a fluence rate of 68 mW/cm^2 and total light dose of 85 J/cm^2. Patients were discharged and advised to avoid bright lights for 24 hr. Follow-up at 4 wk – if residual Barrett's epithelium patient was re-treated until re-epithelisation was complete or to a maximum of five treatments **Comparator** APC: endoscopy as per PDT protocol. APC generator set with gas flow of 2 l/min and power setting of 65W. APC probe passed down biopsy channel and positioned with tip of probe 1 cm distal to the end of the scope. APC performed in a linear fashion coagulating strips of tissue approximately 2 mm wide at each pass. One-half of the affected circumference was treated at any one sitting on the rationale of reducing chances of stricture. Repeat treatment as per PDT but using APC	**Mortality** Not assessed **Morbidity** Significantly fewer treatments were performed in the APC group (median 3) than in the PDT group (median 5), $p = 0.016$. The median number of treatments required for successful ablation was two in the PDT group and three in the APC group, $p = 0.189$ Complete macroscopic reversal of the columnar segment to squamous epithelium was achieved in 50% of PDT patients and 97% of APC patients, $p < 0.0001$ **AEs** Major side effects for PDT were minimal with no strictures or perforations. Significant N&V occurred in 32% of patients who required further antiemetic treatment. Five patients reported cutaneous photosensitivity (mild erythema and pain). All APC patients reported discomfort and 91% reported transient dysphagia and odynophagia. All were resolved with oral analgesia over 3 d. No oesophageal perforations occurred, one patient developed dysphagia to solids and required four dilatations **Resource use** Not assessed	**Authors' conclusions** PDT and APC are both effective for ablating BO. APC appears more effective but larger studies should assess impact on carcinoma development **Brief study appraisal** This was a relatively robust comparative trial (despite the sample size), which would also have benefited from the use of blinded outcome assessors. However, this study, like its related dosing study[102] was of BO patients without dysplasia; such patients are often not treated at all, so the results appear to be of limited use in relation to clinical practice

Study details	Population details	Treatment details	Results	Interpretation
Authors Mackenzie *et al.* (2008)[105] Linked publications[202–204] **Data source** Full paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 27 Intervention (ALA with red light): 14 Comparator: (ALA with green light): 13 **No. of recruiting centres** One **Follow-up period and frequency** 4 wk then every 3 mth for the 1st year then every 6 mth for the 2nd year, then yearly	**Treatment intention** Curative **Type(s) of cancer and histology** BO with HGD **Main eligibility criteria** Patients with BO with HGD. Patients were not allowed to receive chemotherapy or radiotherapy within 1 mth prior to PDT. Other exclusion criteria were provided **Patient characteristics** Not stated **Concomitant treatment** All patients received PPIs. Intravenous fluids and antiemetics were given pre-operatively	**Trial treatments** ALA–PDT with red light vs ALA–PDT with green light **Intervention** *Phase 1 (eight patients)* ALA with red light: at 635 nm delivering a dose of 200 J/cm$^{2.}$ Laser treatment was applied 4 hr after oral ALA administration (30 mg/kg). Patients received up to three treatments with PDT 1 mth apart *Phase 2 (six patients)* As above but with 60 mg/kg ALA **Comparator** *Phase 1 (eight patients)* ALA with green light at 512 nm otherwise as for intervention *Phase 2 (five patients)* As above but with 60 mg/kg ALA	**Mortality** Not assessed **Morbidity** *Phase 1* 4 of 16 patients (25%) had HGD eradicated (three red light, one green light) The trial was paused following interim analysis. It then proceeded to Phase 2 *Phase 2* Six of six patients in the 60-mg red light group had successful treatment, whereas one of five was successful in the 60-mg green light group ($p = 0.01$) 60-mg ALA red light was also more successful than 30-mg ALA red light ($p = 0.03$) and than 30 mg ALA green light ($p = 0.005$) **AEs** AEs were not all reported by group. All patients receiving 60 mg PDT showed minor, self-limiting abnormalities in the results of their liver function tests **Resource use** Not assessed	**Authors' conclusions** PDT with ALA at 30 mg/kg with green or red laser is ineffective for eradication of HGD in BO. ALA at 60 mg/kg activated by 1000 J/cm red laser light has high efficacy for HGD in BO **Brief study appraisal** This trial, although small, was able to suggest a greater effectiveness with 60 mg red light. Such findings would need to be confirmed in larger trials and any AEs documented

Study details	Population details	Treatment details	Results	Interpretation
Authors Mackenzie *et al.* (2008)[104] **Data source** Abstract **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 40 recruited of a planned 66. 32 were treated Intervention: ALA–PDT: 16 Comparator: PDT with Photofrin: 16 **No. of recruiting centres** Not stated **Follow-up period and frequency** 6 wk, 4 mth and 1 yr post therapy	**Treatment intention** Not stated **Type(s) of cancer and histology** BO with HGD **Main eligibility criteria** Patients with BO with HGD confirmed by two independent pathologists were eligible for the trial. Any visible nodules of HGD were removed and patients only treated if residual HGD was still present **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** ALA–PDT vs PDT with Photofrin **Intervention** 60 mg/kg ALA activated by 1178 J/cm of red laser light **Comparator** Photofrin PDT with the standard protocol or as previously shown to be the most effective (no further details given)	**Mortality** Not assessed **Morbidity** Five patients are undergoing repeat therapy (three Photofrin, two ALA). Remission rates are 14 of 14 (100%) in the ALA–PDT group and nine of 14 (64%) in the Photofrin group ($p < 0.05$) **AEs** Strictures developed in six of 16 patients treated with Photofrin and one of 16 treated with ALA (probably not related to treatment), $p < 0.05$. Skin photosensitivity developed in seven of 16 patients treated with Photofrin, one of whom had to be briefly admitted to hospital. No instances of photosensitisation were found with ALA ($p < 0.05$). There were no other significant differences between groups regarding side effects **Resource use** Not assessed	**Authors' conclusions** The preliminary data suggest that ALA–PDT is both safer and potentially more effective than PDT with Photofrin but FU is short and not all patients in the trial have been treated as yet **Brief study appraisal** This trial was reported in abstract form only so full details of the methods are not available. The data presented are promising but would need confirmation in longer FU and with all the planned patients treated

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Study details	Population details	Treatment details	Results	Interpretation
Authors Mackenzie *et al.* (2007)[103] Linked publications[205] **Data source** Abstract **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 24 appeared to have been randomised to either red or green light and were part of a larger study of 72 patients Intervention: High-dose ALA (60 mg/kg) with high-dose red or green light (1000 J/cm) – not stated Comparator: High-dose ALA (60 mg/kg) with low-dose red light (500–700 J/cm) – not stated 2nd Comparator: Low-dose ALA (30 mg/kg) with high-dose red or green light (1000 J/cm) – not stated **No. of recruiting centres** Not stated **Follow-up period and frequency** 36 mth	**Treatment intention** Not stated **Type(s) of cancer and histology** BO with HGD **Main eligibility criteria** Not stated **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** High-dose ALA (60 mg/kg) with High-dose red or green light (1000 J/cm) vs High-dose ALA (60 mg/kg) with low-dose red light (500–700 J/cm) vs Low-dose ALA (30 mg/kg) with high-dose red or green light (1000 J/cm) **Intervention** High-dose ALA (60 mg/kg) with high-dose red or green light (1000 J/cm) **Comparator** High-dose ALA (60 mg/kg) with low-dose red light (500–700 J/cm) **2nd comparator** Low-dose ALA (30 mg/kg) with high-dose red or green light (1000 J/cm)	**Mortality** Not assessed **Morbidity** Patients in the group receiving High-dose ALA–PDT and High-dose red light had a significant decrease in cancer risk when compared with the other treatment groups at 36 mth (24% risk vs 3%). The difference in adenocarcinoma rates were significant when red light was compared with green (8% vs 45%, $p < 0.05$) **AEs** No patients suffered photosensitivity reactions or developed oesophageal strictures **Resource use** Not assessed	**Authors' conclusions** The data from this trial support the use of the optimal regimen of ALA in a RCT of ALA vs Photofrin PDT **Brief study appraisal** This small study is reported in abstract form only and no further publication is available. It is, therefore, difficult to assess the quality of the trial and the reliability of the findings

Study details	Population details	Treatment details	Results	Interpretation
Authors Overholt *et al.* (2007)[99] Linked publications[206–209] **Data source** Full published paper **Country** Not stated **Language** English **Study design** RCT **No. of participants** Total: 208 (61 in long-term phase group) Intervention: PHOPDT: 138 (48 in long-term phase group) Comparator: OM: 70 (13 in long term phase group) **No. of recruiting centres** 30 (in four unnamed countries) **Follow-up period and frequency** Every 3 mth until four consecutive biopsy results were negative for HGD, then biannually until 5 yr	**Treatment intention** Curative **Type(s) of cancer and histology** BO with HGD **Main eligibility criteria** Patients were eligible if they were diagnosed with BO with HGD proven by biopsy and be ≥ 18yr. Exclusion criteria were: cancer other than non-melanoma skin cancer within the last 5yr; prior PDT to the oesophagus, oesophageal strictures unresponsive to dilatation and further criteria detailed in full in the paper **Patient characteristics** % Male: 85 Mean age: 67 yr Further patient characteristics were reported **Concomitant treatment** 9% of patients in the PHOPDT group underwent an oesophagectomy or other endoscopic ablation (3%). 19% of the patients in the OM group had PHOPDT treatment, 10% underwent an oesophagectomy and 2.9% had another endoscopic ablation technique	**Trial treatments** PDT with PHOPDT vs OM alone **Intervention** PHOPDT: Patients in this arm received a maximum of three courses of PDT over 5 yr separated by at least 3 mth. One course of PDT consisted of a 2-mg/kg PHO injection followed by one laser light session (630 nm) applied to the oesophageal segment with HGD 40–50 hr after injection. The light dose was 130 J/cm of diffuser length with a centring balloon. A 2nd light application of 50 J/cm without the cantering balloon could be given 96–120hr after PHO injection but only for areas with insufficient mucosal response after the 1st light application. A maximum of 7 cm of BO was treated during one course of PDT. It was required that the entire length of Barrett's mucosa be treated. Patients also received 20 mg of OM twice daily. Patients had to avoid exposure of eyes and skin to direct sunlight and high intensity light for at least 30 d. They were told to wear dark sunglasses for a 30-d period when outdoors **Comparator** OM: Patients received 20 mg OM twice daily	**Mortality** Two patients in the PHOPDT and one patient in the OM group died within the 1st 2 yr from events unrelated to Barrett's disease. No deaths were related to the treatment. There were no additional patients who died over the course of the additional 3 yr of FU **Morbidity** The proportion of responders (complete ablation of HGD) was significantly higher in PHOPDT than with OM (77% vs 39%, $p < 0.0001$). Of the omeprazole alone responders there were 26% of the PHOPDT and 52% of the OM patients who terminated the trial with either HGD or cancer. Analysis of responders for both treatment groups at 10 specific time points showed a proportion of responders almost twice as large in PHOPDT compared with OM at all assessment periods (data not shown). There was a significant difference between the median time to CR in the 2 groups: PHOPDT, 113 d and OM, 551 d, $p < 0.0001$. Over the trial period 10% of PHOPDT patients had HGD compared with 31% of the OM patients By the end of the 5-year FU period, the probability of maintaining complete ablation of HGD was 48% in PHOPDT compared with 4% in OM, $p < 0.0001$. The median duration of the CR was 44.8 mth in the PHOPDT group and 3.2 mth in the OM group. A 2-yr responder in the PHOPDT group had a 90% chance of maintaining the response for 5 yr compared with 30% for a 2-yr responder in the OM group. Comparison between the 2 groups showed that patients in the PHOPDT group had a significant delay in progression to cancer compared with patients in the OM group. In the PHOPDT group, 21 (15%) patients progressed to cancer from d48 to 1793. In the OM group, 20 (29%) patients progressed to cancer from d63 to 1092. After 5yr of FU, the rate of patients who progressed to cancer in PHOPDT was significantly lower than in OM ($p = 0.027$). There was no significant difference in squamous overgrowth between groups when compared per patient or per biopsy or when the average no. of biopsies with squamous overgrowth were compared per patient. Squamous overgrowth did not obscure the most advanced neoplasia in any patient **AEs** In the initial phase of the trial, the most common AEs were photosensitivity (69%) and oesophageal strictures (36%). All photosensitivity events were resolved and 94% of patients with strictures were stricture free during the course of the initial phase. Events of severe intensity were similar for PHOPDT (16%) and OM (15%) with 65% of the PHOPDT group being related to the treatment compared with 2% in the OM group. From years 2 to 5, there were no SAEs and of those AEs reported, none was attributed to the treatments. There were no photosensitivity AEs occurring during the long term phase. Full details of all AES, both related and unrelated to treatment are available in the paper **Resource use** Not assessed	**Authors' conclusions** This trial shows that PDT with Photofrin is a clinically and statistically effective therapy in producing long-term ablation of HGD and reducing the potential impact of cancer compared with OM **Brief study appraisal** This was a RCT with procedures for blinding of outcome assessors. Outcomes were defined and appropriately assessed and AEs noted. Longer-term FU was used to trace the development of dysplasia and progression to cancer. The results of this trial appear to be reliable with the caveat being the large number of recruiting centres (and very small numbers of patients at some sites) which may have resulted in between-site differences, such as the delivery of the intervention (e.g. varying expertise in delivering PDT), which may have affected the overall results. The number recruited at individual sites ranged from one to 51 participants

OM, omeprazole; PHOPDT, Photofrin and omeprazole.

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Study details	Population details	Treatment details	Results	Interpretation
Authors Ragunath *et al.* (2005)[100] Linked publications[210] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 26 Intervention: PDT: 13 Comparator: APC: 13 **No. of recruiting centres** Not stated **Follow-up period and frequency** 4 mth and 12 mth	**Treatment intention** Curative **Type(s) of cancer and histology** BO with LGD or HGD **Main eligibility criteria** Patients with BO ≥ 3 cm and LGD or HGD with histological diagnosis confirmed on biopsy no more than 3 mth before study entry were eligible. The following were excluded: patients with oesophageal malignancy of any form, previous oesophageal resection, previous mucosal ablative therapy or endoscopic mucosal resection, patients with predominantly tongues rather than circumferential Barrett's oesophagus, patients with porphyria or patients intolerant to endoscopy. Patients pregnant, trying to get pregnant or not using contraception were also excluded **Patient characteristics** % Male: 81 Median age: 60 yr Age range: 35–86 yr Median BO length: 4 cm Dysplasia: HGD, 3(12%), 23(88%) **Concomitant treatment** After the procedures, patients received a high-dose PPI, lansoprazole 60 mg/d, during the treatment period and were then maintained on 30 mg/d. All patients also received two tablets of co-codamol, to be taken every 6 hr as pain relief for 24–48 hr after the treatment. A few patients also received 1 g of sucralfate every 6 hr for retrosternal discomfort and transient dysphagia	**Trial treatments** PDT with Photofrin vs APC **Intervention** 2 mg/kg of Photofrin was injected intravenously 48 hr before illumination with laser. PDT was performed using 630-nm red laser light with a power output of 840 mW delivering 200 J/cm through an endoscopically inserted PDT balloon. Endoscopy was performed under intravenous sedation with midazolam 5–15 mg and fentanyl 50–100 μg. Intravenous buscopan was used as an antimotility agent. A 3-cm window PDT balloon was inserted over a guidewire and inflated after positioning, adjacent to the Barrett's segment. The laser fibre was inserted into the balloon and positioned to allow uniform laser light distribution. The procedure was repeated for every additional 3 cm of the Barrett's segment. Further treatment parameters were described. All patients were admitted to the gastroenterology ward and nursed in a semi-dark room. The ward nursing staff and the patients were given instructions and an information leaflet about avoiding direct sunlight and bright indoor lights for 4–8 wk **Comparator** APC: Endoscopy was performed under intravenous sedation with midazolam 5–15 mg. After assessment of the Barrett's segment, APC was performed using the ERBE ICC 200 Argon Beamer. APC was applied until a white coagulum appeared at a power setting of 65W and argon gas flow of 1.8 l/min. Depending on the length of the Barrett's segment and patient tolerability, APC was carried out in one or more sessions with an interval of 2–4 wk between the sessions. The treatment goal was complete ablation of BO and dysplasia or a maximum of six sessions when complete ablation was not achieved. Further details were provided in the paper	**Mortality** Not assessed **Morbidity** Median length of BO eradicated at 4-mth FU: PDT 57% (3 cm); APC 65% (3 cm) Median length of BO eradicated at 12-mth FU: PDT 60% (3 cm); APC 56% (2.5 cm) Dysplasia eradication at 4 mth: PDT 77%; APC 62% ($p = 0.03$) Dysplasia eradication at 12 mth: PDT 77%; APC 67% NS Development of malignancy at 12 mth: PDT one; APC zero **AEs** Severe AEs: PDT: four of 13 (31%), photosensitivity two; oesophageal stricture two APC: three of 13 (23%), Oesophageal stricture, two; severe chest pain, odynophagia and fever requiring hospital admission, one **Resource use** A cost-effectiveness analysis was conducted from the perspective of the UK NHS. The cost of PDT per patient was calculated at £2804 and that of APC £1341. The ICERs were calculated based on differences in cost and effects between the two procedures for BO length eradication and dysplasia eradication at 4 and 12 mth. At 4 mth APC was the dominant strategy being less expensive and more effective. At 12 mth the incremental cost ratio was £266, i.e. it would cost an additional £266 for every percentage reduction in Barrett's using PDT. Full details of the cost-effectiveness analysis are provided in the paper	**Authors' conclusions** PDT and APC are equally effective in eradicating Barrett's mucosa. However, PDT is more effective in eradicating dysplasia. Long-term FU is needed to assess cancer prevention and the durability of the neosquamous epithelium. These interventions cannot be recommended as yet for routine practice **Brief study appraisal** This was a small trial that will likely have been underpowered to detect treatment differences for all outcomes. This would also have impacted on the cost effectiveness analysis, which accompanied this trial. Treatment protocols are well described but study methods such as procedures for randomisation and blinding are less well described. The authors advise a larger trial and also highlight the need for longer-term FU

Study details	Population details	Treatment details	Results	Interpretation
Authors Zoepf *et al.* (2003)[101] **Data source** Abstract **Country** Germany **Language** English **Study design** RCT **No. of participants** Total: 20 Intervention: PDT 10 Comparator: APC 10 **No. of recruiting centres** Not stated **Follow-up period and frequency** PDT: Median 27 mth, range 12–42 mth APC: Median 24 mth, range 4–46 mth	**Treatment intention** Curative **Type(s) of cancer and histology** Long-segment BO **Main eligibility criteria** Not stated **Patient characteristics** % Male: 65 Median age: 68 yr Age range: 44–77 yr PDT: 4/10 LGD, 6/10 HGD APC: 5/10 LGD, 5/10 No dysplasia **Concomitant treatment** Not stated	**Trial treatments** PDT vs APC **Intervention** PDT: 60 mg/kg bw of ALA. Cylindrical diffuser fibre in the centre of a balloon applicator and illuminated using a diode laser system with 150 J/cm^2. Number of treatment sessions was two (1–5). Further PDT parameters were not reported **Comparator** APC: APC was applied with a power of 70W. The number of treatment sessions was four (2–9)	**Mortality** Not assessed **Morbidity** Reduction of length was 90% for PDT (range 0–100%) and 90% for APC (range 50–100%) **AEs** All patients with PDT developed nausea and vomiting over a period of 4 hr after treatment. 4/10 PDT patients showed transient dysphagia. No skin phototoxity was found after PDT. There was no vomiting in the APC group but 3/10 patients developed transient dysphagia and one mediastinal emphysema and treatment had to be interrupted **Resource use** Not assessed	**Authors' conclusions** Both APC and PDT can ablate BO but for APC only half as many treatment sessions needed **Brief study appraisal** This small trial was reported in abstract only and no further full publication was located. Many of the study details and methods were unclear from the abstract and the quality of the trial was therefore difficult to assess. Treatment groups do not appear comparable in terms of dysplasia

bw, body weight.

Appendix 17

Oesophageal cancer data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Canto *et al.* (2005)[107] **Data source** Abstract **Country** Not stated **Language** English **Study design** Non-RCT **No. of participants** Total: 80 Intervention: 58 Comparator: 22 **No. of recruiting centres** Not stated, multicentre **Follow-up period and frequency** FU at 4–6 wk, every 3 mth (year 1), every 3–6 mth (year 2) then every 6–12 mth. EUS and CT scans taken every 6 mth (year 1) then every 6–12 mth. Mean FU 31.2 mth (6–96)	**Treatment intention** Curative **Type(s) of cancer and histology** T1 oesophageal cancer **Main eligibility criteria** Patients with oesophageal SCC, adenocarcinoma of the oesophagus, EGJ staged as T1 N0 M0 by EUS or CT and that refused, or were unfit for oesophagectomy, or declined radiation therapy, or declined chemoradiation therapy were eligible for inclusion **Patient characteristics** % Male: 70 Mean age: 73 yr Age range: 43–91 yr; 74 Barrett's oesophageal carcinomas, two oesophageal squamous cell cancers, four oesophagogastric junction adenocarcinomas **Concomitant treatment** Not stated	**Trial treatments** Bare fibre Ps PDT alone vs PDT plus EMR **Intervention** PDT alone: Ps infusion (2 mg/kg), then EGD plus PDT (dose 175–300 J/cm fibre, with a 1.0, 2.5, 5 or 7cm diffuser fibre without a balloon centring device) **Comparator** PDT with EMR: Lesions were staged and removed by EMR before PDT from 2001 to 2004	**Mortality** Overall and disease specific 5-yr survival was 88% and 100%, respectively **Morbidity** The CR rate was 89.7% for PDT alone vs 91.2% for PDT + EMR ($p = 0.67$). Nine patients had a 2nd course for ablation of HGD or cancer. Four patients with new HGD in residual Barrett's oesophageal cancers of 9–14 cm were treated successfully with PDT. Five (6.2%) subsquamous lesions diagnosed at FU with HGD/cancer were treated successfully with PDT (2), chemoradiation (1) or surgery (2) **QoL and return to normal activity** Not assessed **AEs** Six patients (7.5%) required hospitalisation for nausea, vomiting, dehydration, transient dysphagia, bleeding or pain); nine (11.2%) developed PDT-related strictures. There were no treatment-related deaths **Resource use** Not assessed	**Authors' conclusions** Ps-PDT without a balloon centring device, with or without EMR, is a safe and highly effective curative treatment for early cancer of the oesophagus/EGJ **Brief study appraisal** This study was available only as a short abstract, the methodology was not clearly reported and it was unclear which results were applicable to each treatment group. As a non-randomised study, the authors' conclusions may be overly strong and should be regarded with caution

CT, computerised tomography; EGD, oesophagogastroduodenoscopy; EGJ, oesophagogastric junction; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound scan; HGD, high-grade dysplasia; Ps, porfimer sodium.

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Study details	Population details	Treatment details	Results	Interpretation
Authors Grosjean *et al.* (1998)[108] **Data source** Full published paper **Country** Switzerland **Language** English **Study design** Non-RCT **No. of participants** Total: 15 (22 tumours) Intervention: 13 tumours (630 nm PDT) Comparator: Nine tumours (514 nm PDT) **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 7–10 d, then 3 mth after treatment and twice per year thereafter	**Treatment intention** Curative **Type(s) of cancer and histology** Superficial oesophageal and bronchial cancers **Main eligibility criteria** It appeared that men and women with one or several biopsy-proven superficial SCC of the bronchi or oesophagus **Patient characteristics** % Male: 80 Age range: 46–79 yr Mean Age: 59.8 yr All patients had previously received radiotherapy and/or surgery for primary invasive cancer of the head and neck **Concomitant treatment** Not stated	**Trial treatments** PDT at 630 nm with Photofrin II vs PDT at 514 nm with Photofrin II **Intervention** PDT with Photofrin (630 nm): After injection with Photofrin II (1 or 2 mg/kg) irradiation with 630 nm, 100 mW/cm^2 (total dose 100 J/cm^2) argon ion pumped-dye laser under general anaesthetic. Microlens and/or cylindrical light distributors were used in the bronchi and 180 or 240° windowed cylindrical light distributors in the oesophagus. Ten tumours had a drug–light interval of 72 hr, three tumours had a drug–light interval of 1 hr. If there was less than CR at 3-mth endoscopy, PDT was repeated. Patients were advised to avoid direct sunlight for 4–6 wk after drug administration **Comparator** PDT at 514 nm: As for PDT at 630 nm but using 514 nm and five tumours had a drug–light interval of 72 h, four tumours had a drug–light interval of 1 hr	**Mortality** Not assessed **Morbidity** CR was seen in 9/13 of the superficial tumours (69%) with 630-nm PDT vs 6/9 tumours (67%) with 514-nm PDT. In the 630-nm PDT group three tumours showed a PR (vs three in 524-nm group) and one tumour only minimally reduced in size. In the oesophagus, both wavelengths were effective in eradicating in situ and intramucosal cancer but did both cure more than half of the submucosal tumours. 2/10 tumours treated at a drug–light interval of 1 hr achieved a CR **QoL and return to normal activity** Not assessed **AEs** No major complications were observed in either treatment group. Three 630-nm PDT patients reported chest pains with associated high-grade fever for 10 d after PDT (two with pleural effusion, the 3rd with endoscopic evidence of oedema and erythema on the posterior wall of the trachea at the level of the oesophageal cancer). All three patients recovered with antimicrobial therapy **Resource use** Not assessed	**Authors' conclusions** PDT with 514-nm light has the potential to cure superficial cancer in the oesophagus and bronchi with the same probability as 630-nm PDT. In the oesophagus, green light prevents deep tissue damage, thus reducing the risk of perforation **Brief study appraisal** The numbers included in this study were small and the methods were not clearly reported – particularly in terms of comparability of the two groups. The conclusions may not therefore be reliable. Note: The majority of patients in this trial had oesophageal tumours (14/22), therefore the results have been included in the oesophageal cancer group

Study details	Population details	Treatment details	Results	Interpretation
Authors Heier *et al.* (1995)[114] **Data source** Full published paper **Country** USA **Language** English **Study design** RCT **No. of participants** Total: 42 Intervention: 22 Comparator: 20 **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 1 wk, then once per month. CT every 3 mth	**Treatment intention** Palliative **Type(s) of cancer and histology** Oesophageal cancer **Main eligibility criteria** Patients with dysphagia caused by biopsy-proven oesophageal malignancy that were not suitable for, had refused or failed surgery, radiotherapy and chemotherapy were eligible for inclusion. Prior therapy had to have ended at least 1 mth before enrolment. Exclusion criteria were: tracheal involvement by bronchoscopy and Karnofsky performance status < 30 **Patient characteristics** % Male: 62 Age range: 42–87 yr Mean age: 70 yr (PDT) 73yr Nd:YAG Mean Karnofsky status for both groups was around 73–74 Overall, 60% of tumours were squamous and 40% were adenocarcinoma. Most patients had some kind of prior therapy **Concomitant treatment** Not stated	**Trial treatments** PDT with DHE vs Nd:YAG laser **Intervention PDT:** IV DHE was given (2 mg/kg bw), then illumination with an argon pumped-dye laser. 630 ± 2 nm (300 J/cm) red light was delivered by cylinder-diffusing fibres, and tumour segments were treated sequentially in a retrograde fashion. Power density was 400 mW/cm fibre tip. Tissue dose was calculated from light dose delivered and surface area exposed, estimated from segmental luminal diameter. A 2nd dose could be given if necessary (13 patients). Patients advised to restrict sun exposure for at least 30 d post injection. If there was a recurrence of tumour obstruction another course of PDT was given if 1 mth had elapsed since DHE injection **Comparator** Nd:YAG: Standard technique was used at 90W in a retrograde fashion. Laser pulses were delivered through quartz fibres (bare or coaxial air flow). Therapy was delivered every 2–4 d until luminal patency was achieved. Most patients required two sessions	**Mortality** Mean survival was not significantly different between PDT and Nd:YAG (145 vs 128 d, $p = 0.419$) **Morbidity** At 1 mth PDT was associated with a greater increase in dietary performance ($p = 0.006$), Karnofsky performance status ($p < 0.001$) and oesophageal grade ($p = 0.002$) compared with Nd:YAG. Mean duration of response with PDT was 84 d vs 53 for Nd:YAG, $p = 0.008$. The difference in dietary levels at 1 wk and weight change between treatment groups was ns. CR was seen in two PDT patients vs one **QoL and return to normal activity** Not assessed **AEs** In the randomised trial patients complications were relatively few: fistula (one PDT patient vs two), stricture (zero vs two), skin photoreaction (four vs zero), fever (five vs one) and luminal plugging (five vs five) **Resource use** Not assessed	**Authors' conclusions** PDT can relieve oesophageal obstruction from squamous cell and adenocarcinoma and is an alternative to Nd:YAG thermal necrosis with a longer duration of response. However, PDT requires patient precautions to minimise skin photoreactions **Brief study appraisal** This was a small but well-conducted and reported study despite the apparent lack of blinding of outcome assessors. The analyses adjusted for confounding variables, and the significant benefits in favour of PDT could be considered as promising

DHE, dihaematoporphyrin ethers; ns, not significant.

Study details	Population details	Treatment details	Results	Interpretation
Authors Lecleire *et al.* (2008)[111] **Data source** Abstract **Country** Not stated **Language** English **Study design** Non-RCT **No. of participants** Total: 35 (37 lesions) Intervention: 21 (22 lesions) (primary intent PDT) Comparator: 14 (15 lesions) (PDT indicated after local failure of CRT) **No. of recruiting centres** Not stated **Follow-up period and frequency** Median FU 15 mth	**Treatment intention** Curative **Type(s) of cancer and histology** Early stage oesophageal cancer **Main eligibility criteria** Not stated **Patient characteristics** Not reported in detail, paper states no significant differences between groups. Median tumour length 2cm **Concomitant treatment** Not stated	**Trial treatments** PDT in patients treated in primary intent vs PDT in patients treated with PDT after local failure of definitive CRT **Intervention** Primary intent PDT: After IV Photofrin (2 mg/kg), illumination with a dye laser between 48h. The mean number of PDT sessions was 1.18. Control endoscopies with routine biopsies were planned 6–8 wk after PDT. No further details were reported **Comparator** PDT after failed CRT: As for primary intent PDT except mean number of PDT sessions was 1.33	**Mortality** Not assessed **Morbidity** 16/22 lesions (73%) were successfully treated in the primary intent group vs 8/15 (53%) after failed CRT, $p = 0.3$. There was no difference in recurrence rate between groups (9 vs 14%, ns) **QoL and return to normal activity** Not assessed **AEs** Severe complications were 10% in the primary intent PDT group vs 50% for failed CRT ($p = 0.015$) (two strictures requiring endoscopic dilation vs two perforations and five strictures requiring dilation respectively). Death rate directly related to PDT was 0% in primary intent patients vs 14% for failed CRT (ns) **Resource use** Not assessed	**Authors' conclusions** PDT when indicated as a salvage therapy in patients with local failure after CRT for oesophageal cancer tended to be less effective than when indicated as a 1st-line treatment. Moreover, severe complications, including death-related procedures were significantly more frequent in patients treated after prior CRT **Brief study appraisal** Few methodological and patient details were reported in this abstract of a small study so the reliability of the conclusions is unclear. The authors appear to have drawn conclusions at odds with the statistical test results *The authors' conclusions do not follow from the results reported*

CRT, chemoradiotherapy; ns, not significant.

Study details	Population details	Treatment details	Results	Interpretation
Authors Lightdale *et al.* (1995)[112] **Data source** Full published paper **Country** USA **Language** English **Study design** RCT **No. of participants** Total: 236 (218 treated) Intervention: 118 (110 treated) Comparator: 118 (108 treated) **No. of recruiting centres** 24 **Follow-up period and frequency** FU at 1 wk, then 1, 2, 3 and 6 mth	**Treatment intention** Palliative **Type(s) of cancer and histology** Oesophageal carcinoma **Main eligibility criteria** Patients with a biopsy-proven oesophageal malignancy and that were too debilitated for, refused, failed to respond to or had a recurrence following chemotherapy, radiation therapy or surgery were eligible for inclusion. Also patients with SCC or adenocarcinoma, and that were symptomatic, had malignancy-caused dysphagia to solid foods and a Karnofsky status of at least 30% were eligible. Prior therapy was required to be terminated at least 4 wk before randomisation. Bronchoscopy was required for tumours at or above the level of the carina. Patients with involvement of the tracheobronchial tree and those that had prior treatment for oesophageal carcinoma with PDT or Nd:YAG laser were excluded. Concurrent radiation and chemotherapy were not permitted **Patient characteristics** % Male: 72 Median age: PDT 68 yr; Nd:YAG 72 yr Median Karnofsky performance status: 80% Prior therapy: 45% Median tumour length: PDT 6 cm; Nd:YAG 5 cm Adenocarcinoma 51%, the rest had SCC **Concomitant treatment** Not stated	**Trial treatments** PDT vs Nd:YAG laser **Intervention** PDT: 40–50 hr after single intravenous injection with Ps (2 mg/kg bw), illumination by red light (630 nm) provided by a continuous wave argon pumped-dye laser and delivered via an optical quartz fibre with a cylindrical diffusing tip (400 mW/cm, total dose 300 J/cm). After 2–3 d patients were re-endoscoped to debride the necrotic tumour and residual tumour could be treated with a 2nd application of laser light (same dose). A maximum of three courses at 1-mth intervals was permitted **Comparator** Nd:YAG laser therapy: A laser power setting of 15–90W and pulse duration of 0.5–4.0 s was used (delivered with either contact or non-contact technique via quartz fibres). Each session ended when the endoscopist thought maximum achievable benefit or maximum patient tolerance was reached. Repeat sessions could be given if initial response was deemed insufficient (the course was deemed complete when the investigator believed dysphagia had been palliated or further therapy would be futile)	**Mortality** Not assessed **Morbidity** Dysphagia grades significantly improved from baseline at 1 wk (PDT –0.73 vs Nd:YAG –0.90) and 1 mth (PDT –0.75 vs Nd:YAG –0.68) with both treatments (ns difference between treatment groups). Objective tumour response (responders: patients with CR or PR) was 44% PDT vs 48% Nd:YAG (ns) at 1 wk and 32% PDT vs 20% Nd:YAG at 1 mth ($p < 0.05$). Data was obtained from 80% patients at 1 wk and 60% at 1 mth. Subgroup analyses showed ns differences between groups but there was a trend in favour of PDT for objective tumour response rates in the upper and lower third of the oesophagus, tumours > 10 cm and in patients that received prior therapy. There was no difference between groups for patients with squamous cell cancer and adenocarcinoma **QoL and return to normal activity** Not assessed **AEs** Significantly more PDT patients had an AE (92% vs 82%, $p < 0.05$). Sunburn (19% PDT vs 0%), nausea (8% vs 2%), fever (16% vs 5%) and pleural effusion (10% vs 2%) were significantly greater for PDT and oesophageal perforation greater for Nd:YAG (1% vs 7%) $p < 0.05$). All PDT patients were photosensitive for 1–2 mth, none severe. Treatment-related respiratory insufficiency occurred in 3% PDT (vs 1%). Severe AEs were equal overall for both treatments **Resource use** Not assessed	**Authors' conclusions** PDT with porfimer solution has overall equal efficacy to Nd:YAG laser thermal ablation for palliation of dysphagia in oesophageal cancer, and equal or better objective tumour response rate. Temporary photosensitivity is a limitation, but PDT is carried out with greater ease and is associated with fewer acute perforations than Nd:YAG laser therapy **Brief study appraisal** The methods were generally well-described though a few features were not reported. It may have been useful to gauge patient/investigator opinion of ease of treatment and importance of photosensitivity to QoL to inform the conclusions

ns, not significant.

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Study details	Population details	Treatment details	Results	Interpretation
Authors Maier *et al.* (2000)[115] **Data source** Full published paper **Country** Austria **Language** English **Study design** Non-RCT **No. of participants** Total: 52 Intervention: 23 (PDT) Comparator: 29 (PDT under HBO) **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 1 mth, then every 3 mth	**Treatment intention** Palliative **Type(s) of cancer and histology** Advanced cancer of the upper gastrointestinal tract **Main eligibility criteria** It appeared that patients with advanced cancer of the upper gastrointestinal tract who were not eligible for resection treatment due to poor performance status, functional and/or anatomic inoperability, and/or anatomic inoperability, and/or refusing surgery were eligible for inclusion **Patient characteristics** % Male: 81 Age range: 46–87 yr Mean age: 67.3 yr Most patients' cancers were judged to be stage III, dysphagia scores varied across levels 2, 3 and 4 and no significant differences at baseline were found. Tumours were SCC in 25 cases, adenocarcinoma in 25 cases. Further patient characteristics were reported **Concomitant treatment** Before PDT, 12 (seven in PDT, five in PDT/HBO) patients underwent dilatation and retrograde Nd:YAG laser disobliteration	**Trial treatments** PDT vs PDT under HBO **Intervention** PDT: Photosan-3 (2 mg/kg) was administered intravenously. After 48 hr, PDT, using a fibre with a 1-cm tip radial light-diffusing cylinder, was inserted using an endoscope. Illumination dose was 300 J/cm of fibre, 630 nm applied by a KTP-Nd:YAG laser. Treatment was under short-term intravenous anaesthesia. 2–3 d after PDT, endoscopy was repeated, and necrotic tissue removed mechanically if necessary. Treatment could be repeated after 3 mth if necessary but most patients received one session **Comparator** PDT under HBO (PDT/HBO): As for PDT but under HBO at a level of 2 ATA in a hyperbaric chamber. Oxygen was administered with the Scuba valve, transcutaneous PO_2 levels were 500–750 mmHg. Before HBO, patients had an ear, nose and throat check-up	**Mortality** Median survival after PDT was 8.7 mth vs 13.8 mth for PDT/HBO ($p = 0.021$) **Morbidity** At 3 mth, dysphagia score had decreased in both groups but there was no significant difference between treatments ($p = 0.43$). At 3 mth, mean decrease in stenosis was 5.6 mm in the PDT group vs 6.3 mm PDT/HBO, $p = 0.065$. Mean decrease in tumour length was 2 cm PDT vs 2.8 cm PDT/HBO, $p = 0.002$ **QoL and return to normal activity** A semi-solid diet was possible in all patients after PDT or PDT/HBO **AEs** No major complications related to PDT, HBO and photosensitisation, and no barotrauma of the ear or lung or sunburn was observed. Minor complications included: postinterventional odynophagia (eight PDT vs nine PDT/HBO), fever up to 39° (five vs nine) and chest pain for 1 or 2 d (five vs nine). Six oesophagotracheal fistulas were found in two cases (PDT at 5 and 17 mth) and four cases (PDT/HBO at 4, 7, 14 and 24 mth). Stenting with coated, self-expandable stents was performed in one PDT patient at 16 mth and two PDT/HBO patients at 14 and 17 mth. One patient had haemorrhage of the tumour 18 mth after PDT/HBO **Resource use** Not assessed	**Authors' conclusions** Combined PDT/HBO represents a new approach in the treatment of oesophageal and cardial cancer, which appears to have enhanced the efficacy of PDT **Brief study appraisal** This was a small pilot study that, despite not being randomised, does seem to have achieved reasonable comparison groups. The authors comment that randomisation was not possible due to the variable availability of the oxygen chamber. The conclusions are reasonable but the study would have benefited from blinded outcome assessors

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Study details	Population details	Treatment details	Results	Interpretation
Authors Maier *et al.* (2000)[116] Linked publications[211] **Data source** Full published paper **Country** Austria **Language** English **Study design** Non-RCT **No. of participants** Total: 75 Intervention: 31 Comparator: 44 **No. of recruiting centres** One **Follow-up period and frequency** FU after 1 mth, then every 3 mth	**Treatment intention** Not stated **Type(s) of cancer and histology** Advanced oesophageal carcinoma **Main eligibility criteria** Patients that were not eligible for resection treatment due to significant comorbidity were included **Patient characteristics** % Male: 80 Mean age: PDT alone, 67 yr; PDT/HBO 67.5 Age range: 46–87 yr Cancer stage: III, 59; IV, 16 Dysphagia score: level 2, 23; level 3, 37; level 4, 15. 40 SCC, 35 adenocarcinoma Further patient characteristics were reported **Concomitant treatment** Not stated	**Trial treatments** PDT vs PDT/HBO **Intervention** PDT: HpD given intravenously (2 mg/kg) and camouflage skin protection used for 2 wk, then sunblock for 10 wk. PDT given 48 hr after sensitisation with a fibre (1-cm tip, radial light diffusing cylinder) inserted through the biopsy channel of the endoscope (several placements were necessary). Light dose was 300 J/cm, 630 nm applied with a KTP-Nd:YAG laser with DYE box. Treatment given under short-term anaesthesia. Endoscopy was repeated 2–3 d after PDT and necrotic tissue removed mechanically if necessary. Prior to PDT, dilatation and retrograde Nd:YAG was necessary in 15 cases **Comparator** PDT/HBO: As for PDT except patients had ear, nose and throat check-up, then PDT given under HBO (2 atmospheres) in a walk-in hyperbaric chamber	**Mortality** Median overall survival with PDT was 7 mth (vs 12 mth in PDT/HBO group), $p = 0.0098$. 12-mth survival with PDT was 25% vs 52% with PDT/HBO **Morbidity** At 3 mth, stenosis decreased in both groups by 6 mm In the PDT group median tumour length decrease was 2 cm vs 3 cm in the PDT/HBO group, $p = 0.0002$ At 3-mth FU (or last FU in case of death) in the PDT group dysphagia score could be lowered by one level in eight cases (vs nine) and two levels in 23 cases (vs 33) (and in the PDT/HBO group it could be lowered by three levels in two cases); this significantly favoured PDT/HBO ($p = 0.0064$). No recurrent dysphagia was observed at 3-mth FU for either group **QoL and return to normal activity** At least a semi-solid diet was possible in all patients after either treatment **AEs** There were no major postinterventional complications or skin photosensitisation related to either treatment. No barotrauma was observed. Minor complications included: odynophagia (PDT group 6 vs PDT/HBO 8); fever up to 39° in the afternoon of the interventional day, one in PDT vs three in PDT/HBO); chest pain for 1 or 2 d (four in PDT vs seven in PDT/HBO). 30-day mortality was 0%. Six oesophagotracheal fistulas in two patients were found (PDT, two cases; PDT/HBO four cases) **Resource use** Hospitalisation in both groups was 3–9 d (median 4.9 d)	**Authors' conclusions** Combined PDT/HBO represents a new approach in the treatment of oesophageal and cardial cancer which appears to have enhanced the efficiency of PDT **Brief study appraisal** This study was not randomised (and so may have been subject to bias) and included a fairly small number of patients. The authors did though acknowledge that definitive conclusions could not be drawn based on these results. This publication appears to be the same study as a report of a pilot study [211], although the authors were not explicit about this

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Study details	Population details	Treatment details	Results	Interpretation
Authors Maier *et al.* (2000)[117] **Data source** Full published paper **Country** Austria **Language** English **Study design** Non-RCT **No. of participants** Total: 119 Intervention: 44 (PDT and brachyradiotherapy) Comparator: 75 (brachyradiotherapy) **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 1 mth, then every 3 mth	**Treatment intention** Palliative **Type(s) of cancer and histology** Advanced oesophageal carcinoma **Main eligibility criteria** Patients who were not eligible for resection due to tumour involvement of the adjacent tissue, poor performance status plus inoperable status as a result of comorbidity, refusal of surgical intervention, or a combination of these, were included **Patient characteristics** % Male: 81 Mean Age: Men, 67 yr; women 65 yr Age Range: 27–93 yr Cancer stage: III, 80; IV, 39. 68 SCC and 51 adenocarcinoma Further patient characteristics were reported **Concomitant treatment** Prior to therapy 21 patients required initial dilatation and tumour obliteration with Nd:YAG	**Trial treatments** PDT and brachytherapy vs brachytherapy alone **Intervention** PDT and brachytherapy: Intravenous haematoporphyrin was administered (mean 1.5 injections/patient) (2 mg/kg), after 48 hr PDT treatment using a fibre with 2-cm radial light-diffusing cylinder inserted through biopsy channel of an endoscope (dose 300 J/cm fibre, 630 nm applied by a KTP-Nd:YAG laser with DYE-box). 2–3 d after PDT, endoscopy repeated and necrotic tissue removed. Endoscopy was performed after 1 mth, then every 3 mth. PDT was not repeated within 3 mth. Iridium-192 brachyradiotherapy was given by insertion of the afterloading catheter. 5 Gy per session was given, patients received one to four sessions in total depending on endoscopic findings and dysphagia, with 3–7 d between sessions. This process was carried out under short-term intravenous anaesthesia, combined with topical anaesthesia with supported breathing. In 25 patients with Karnofsky score of > 80 (fair condition) treatment was completed by external beam irradiation using the multiple field technique to deliver mean dose of 44 Gy **Comparator Brachytherapy**: Iridium-192 brachyradiotherapy was given by insertion of the afterloading catheter. 5 Gy per session was given, patients received one to four sessions in total depending on endoscopic findings and dysphagia, with 3–7 d between sessions. This process was done under short-term intravenous anaesthesia, combined with topical anaesthesia with supported breathing. In 17 patients with Karnofsky score of > 80 (fair condition) treatment was completed by external beam irradiation using the multiple field technique to deliver mean dose of 44 Gy	**Mortality** Mean survival was 5.6 mth for brachytherapy; 7.7 mth brachytherapy and external beam irradiation; 6.3 mth PDT brachytherapy; 13 mth PDT, brachytherapy and external beam irradiation. There was a significant difference with PDT* ($p = 0.0129$) and external beam irradiation* ($p = 0.0001$). This was biased, as groups without external beam irradiation contained patients that died before entering the irradiation regimen. (Authors' comment.) *It was unclear which patient groups these results referred to **Morbidity** Dysphagia score improved in all patients by one to three levels and was significantly greater in the PDT group ($p = 0.0003$). The mean increase in opening diameter of tumour-related stenosis was significantly greater in the PDT group with or without external beam irradiation than in either of the brachytherapy conditions **QoL and return to normal activity** There were no significant differences between the two groups in terms of Karnofsky performance status scores at 3 mth, $p = 0.28$ **AEs** Major complications occurred in 9% (11/119) of patients, including oesophageal perforation after brachytherapy, severe haemorrhaging 3 d after PDT, spontaneous perforation of distal oesophagus with oesophagomediastinopleural fistula and concurrent pleural emphysema 5 mth after PDT, tracheo-oesophageal or tracheobronchial fistula. Due to strictures, dilation was necessary after PDT (four patients) and Nd:YAG (45 patients). After PDT 28 patients reported odynophagia for 2–5 d **Resource use** Not assessed	**Authors' conclusions** PDT has been shown to be an effective palliative treatment of advanced oesophageal cancer. However, proper patient selection is necessary to prevent serious complications **Brief study appraisal** A sizeable proportion of patients in each group were pre-treated with Nd:YAG, which did not appear to be accounted for in the analysis. This trial appears to have contained four separate arms, although this was poorly described. Patients in good/fair condition received a slightly different treatment protocol. These limitations make it difficult to evaluate reliability of the authors' conclusions

Study details	Population details	Treatment details	Results	Interpretation
Authors Maier *et al.* (2001)[118] Linked publications[120] **Data source** Full published paper **Country** Austria **Language** English **Study design** Non-RCT **No. of participants** Total: 49 Intervention: 22 (ALA–PDT) Comparator: 27 (Photosan-PDT) **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 1 mth, then every 3 mth	**Treatment intention** Palliative **Type(s) of cancer and histology** Advanced oesophageal cancer **Main eligibility criteria** Patients that were not eligible for resection treatment due to poor performance status, functional and/or anatomical inoperability, and/or refusing surgery were included **Patient characteristics** % Male: 78 Age range: 46–88 yr Mean age: ALA, 69 yr; Photosan 68 yr Cancer stage: III, 17; IV 32. Dysphagia score varied with most in level 2 or 3 but no significant differences Overall there were 13 SCC, 14 adenocarcinoma Further patient characteristics were reported **Concomitant treatment** Not stated	**Trial treatments** ALA- PDT vs PDT with Photosan (HpD). Both performed with additional hyperbaric oxygenation **Intervention** ALA–PDT: Diagnostic work-up was performed using barium oesophagogram, oesophagogastroscopy, bronchoscopy and CT scans. Oral administration of ALA (60 mg/kg) then skin protection by camouflage for 24 hr. 6–8 hr after ALA, PDT was carried out using a fibre with 2-cm tip radial light-diffusing cylinder, inserted through the biopsy channel of the endoscope. Light dose was 300 J/cm fibre and 630-nm light was applied by KTP-Nd: YAG laser having a DYE module. Additional hyperbaric oxygenation was applied (after an ear, nose and throat check-up) at level 2 ATA using a Scuba valve system. Treatment was performed under short-term intravenous anaesthesia. Endoscopy was performed 2–3 d after PDT and necrotic tissue removed. Endoscopy was then performed after 1 mth, then every 3 mth. Increased tumour length and dysphagia at FU indicated further PDT treatment. No treatment was repeated within 3 mth after the 1st PDT session **Comparator** Photosan-PDT: As for ALA–PDT except intravenous administration of Photosan (2 mg/kg), 48 hr before PDT	**Mortality** Median survival for ALA group was 8 mth vs 9 mth, $p = 0.44$ (Kaplan–Meier survival curve in paper) **Morbidity** At 1 mth, there was significantly more improvement in the ALA group than the Photosan group for the following outcomes: dysphagia ($p = 0.02$), tumour stenosis ($p = 0.00000$) and tumour length ($p = 0.000014$) **QoL and return to normal activity** Karnovsky Performance status improved by 23% for ALA vs 44% for Photosan, not significant ($p = 0.12$) **AEs** No barotrauma of the ear was observed. No sunburn occurred in either group. There were no major AEs. 30-day mortality was 0%. Minor complications were: postinterventional odynophagia (nine in ALA group vs 13); fever up to 39° in the afternoon of the interventional day (five vs eight); chest pain for 1 or 2 d (nine vs 13). After ALA administration all patients experienced nausea **Resource use** Hospitalisation was 4–6 d in both treatment groups	**Authors' conclusions** Despite the limitations of a non-randomised study, photosensitisation with Photosan seems to be more effective in PDT of advanced oesophageal carcinoma compared with ALA **Brief study appraisal** The conclusions that could be drawn were limited as this was a small, non-randomised study. Baseline characteristics were largely similar apart from M stage and the authors' cautious conclusions appear reliable. This study appears to have been published twice (see ref. 120) with Photosan being described as HpD. The patients, treatments and results appear to be identical, therefore only one study has been data extracted

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Study details	Population details	Treatment details	Results	Interpretation
Authors Savary *et al.* (1998)[109] **Data source** Full published paper **Country** Switzerland **Language** English **Study design** Non-RCT **No. of participants** Total: 24 (31 tumours) Intervention: Nine tumours (HpD-PDT) Comparator: Eight tumours (Photofrin II-PDT) 2nd Comparator: Two tumours (mTHPC-PDT, 0.15 mg/kg with 652 nm) 3rd Comparator: One tumour (mTHPC-PDT, 0.3 mg/kg with 514 nm) 4th Comparator: 11 tumours (mTHPC-PDT, 0.15 mg/kg with 514 nm) **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 10 d, 3 mth, then 6-mth intervals	**Treatment intention** Curative **Type(s) of cancer and histology** Early SCC of the oesophagus **Main eligibility criteria** Biopsy confirmed early SCC. Patients with porphyria were excluded **Patient characteristics** % Male: 92 Age range: 42–79 yr Mean age: 56 yr Twenty-two patients had a history of primary invasive head and neck cancer, two had no such history. Two patients had synchronous tumours, five patients developed metachronous early cancers **Concomitant treatment** None	**Trial treatments** HpD PDT vs Photofrin II PDT vs mTHPC 0.15 mg/kg (652 nm) PDT vs mTHPC 0.3 mg/kg (514 nm) PDT vs mTHPC 0.15 mg/kg (514 nm) PDT **Intervention** HpD PDT: Intravenous HpD was injected (3 mg/kg), then PDT given with an argon ion pumped-dye laser after 72 hr (630 nm, 100 J/cm^2, 80 mW/cm^2) for 21 min. Surface irradiation using 180 or 240° windowed cylindrical light distributors (15 mm diameter) was used **Comparator** Photofrin II PDT: intravenous Photofrin II was injected (1 or 2 mg/kg), then PDT given with an argon ion pumped-dye laser after 72 hr [630 nm (most patients) or 514nm, mean light dose 100 J/cm^2, 90 mW/cm^2] for 19 min. Surface irradiation using 180° or 240° windowed cylindrical light distributors (15-mm diameter) was used **2nd comparator** mTHPC 0.15 mg/kg (652 nm) PDT: Intravenous mTHPC was injected (0.15 mg/kg), then PDT given with an argon ion pumped-dye laser after 20 hr (652 nm, 6 or 8 J/cm^2, 40 mW/cm^2) for 3 min. Surface irradiation using 180 or 240° windowed cylindrical light distributors (15-mm diameter) were used **3rd comparator** mTHPC 0.3 mg/kg (514 nm) PDT: intravenous mTHPC was injected (0.3 mg/kg), then PDT given with a argon ion pumped-dye laser after 20 hr (514 nm, 30 J/cm^2, 50 mW/cm^2) for 10 min. Surface irradiation using 180 or 240 windowed cylindrical light distributors (15-mm diameter) was used **4th comparator** mTHPC 0.15 mg/kg (514 nm) PDT: intravenous mTHPC was injected (0.15 mg/kg), then PDT given with an argon ion pumped-dye laser after 20 or 96 hr (514 nm, 75 J/cm^2, 90 mW/cm^2) for 14 min. Surface irradiation using 180 or 240° windowed cylindrical light distributors (15-mm diameter) was used	**Mortality** Not assessed **Morbidity** No truly selective necrosis was seen with HpD, Photofrin II or mTHPC when irradiation was at 20 hr. With mTHPC (irradiation at 96 h) some patients had necroses that were selective. CR rates: HpD = 89%, mTHPC = 86%, Photofrin II = 75%. Failures of treatment according to sensitiser used were 1/9 (11%) in the HpD group; 2/8 (25%) Photofrin II group; 2/14 (14%) mTHPC group. Failures of treatment according to wavelength used were 2/15 (13%) for 630 or 652 nm; 3/16 (19%) for 514 nm **QoL and return to normal activity** Not assessed **AEs** All patients reported burning sensation during the injection of mTHPC. Major complications were: Stenoses (two), oesophagotracheal fistulas in PDT patients (630 or 652 nm) (two, one of which complicated by oesophageal stenosis). Three patients that did not follow prescribed precautions (not in methods) developed 2nd-degree sunburn on the face and hands (one HpD patient at 2 mth; 2 0.15 mg/kg mTHPC patients at 6 d) **Resource use** Not assessed	**Authors' conclusions** PDT eradicates early SCCs (T1a and T1b) of the oesophagus efficiently. Transmural necroses leading to fistulas can be avoided using a low-penetrating wavelength of laser light (green light at 514.5 nm instead of red light at 630 or 652 nm). Stenoses always result from circumferential irradiation of the oesophageal wall, and this can be avoided by using a 180° or 240° windowed cylindrical light distributor **Brief study appraisal** This was a relatively small trial with multiple comparator arms, the methods were not clearly reported and as the authors themselves comment – the small samples preclude any firm conclusions, so the results may not be reliable

Study details	Population details	Treatment details	Results	Interpretation
Authors Scotiniotis *et al.* (2000)[110] **Data source** Abstract **Country** USA **Language** English **Study design** Non-RCT **No. of participants** Total: 37 Intervention: 12 (PDT) Comparator: Six EMR 2nd Comparator: 19 (oesophagectomy) **No. of recruiting centres** Not stated **Follow-up period and frequency** Mean FU 15 mth (range 2–28 mth). PDT and EMR patient FU 4–6 wk after treatment, then every 3–6 mth; oesophagectomy patient FU dictated by symptoms	**Treatment intention** Curative **Type(s) of cancer and histology** Superficial oesophageal cancer **Main eligibility criteria** Superficial oesophageal cancer determined by EUS and CT including HGD, carcinoma in situ or intramucosal carcinoma **Patient characteristics** Mean age: PDT, 76; EMR, 73; oesophagectomy, 65 Thirty-six adenocarcinomas, one SCC **Concomitant treatment** Not stated	**Trial treatments** PDT vs EMR vs Oesophagectomy **Intervention** PDT: No details reported **Comparator** EMR: No details reported **2nd comparator** Oesophagectomy: No details reported	**Mortality** Not assessed **Morbidity** Eradication of lesions was achieved in 9/12 (75%) PDT, 5/6 (83%) EMR and 18/19 (95%) oesophagectomy patients **QoL and return to normal activity** Not assessed **AEs** Stricture occurred in 6/12 (50%) PDT, 0/6 EMR and 10/19 (53%) oesophagectomy patients. ≥ 3 dilatations occurred in 4/12 (33%) PDT, 0/6 EMR and 7/19 (37%) oesophagectomy patients. Other complications were reported for small numbers of patients **Resource use** Not assessed	**Authors' conclusions** In poor surgical candidates with superficial oesophageal carcinoma PDT and EMR achieved outcomes comparable to oesophagectomy in good surgical candidates. PDT and EMR are reasonable alternatives to oesophagectomy for selected patients **Brief study appraisal** This small study was available only as an abstract and few methodological details were reported. The study populations for the different interventions did not appear to be comparable at baseline with PDT/EMR patients chosen if suboptimal for surgery. In addition no statistical tests were carried out to verify the findings, the results of this study may therefore not be reliable *The authors' conclusions do not follow from the results reported*

EMR, endoscopic mucosal resection.

Study details	Population details	Treatment details	Results	Interpretation
Authors Zhang *et al.* (2003)[119] **Data source** Full published paper **Country** China **Language** Chinese **Study design** RCT **No. of participants** Total: 60 Intervention: 30 Comparator: 30 **No. of recruiting centres** One hospital (outpatients) **Follow-up period and frequency** FU at 5 and 10 yr	**Treatment intention** Palliative **Type(s) of cancer and histology** Advanced oesophageal cancer **Main eligibility criteria** Diagnosed with advanced oesophageal cancer, suitable for treatment **Patient characteristics** Age: under 70 yr Cancer length: 5–10 cm. No metastases **Concomitant treatment** Not stated	**Trial treatments** PDT with radiotherapy vs radiotherapy alone **Intervention** PDT with radiotherapy: Radiotherapy for 4 wk (40 Gy). Then intravenous haematoporphyrin derivative (5 mg/kg bw) before illumination with 630-nm red light (400–500W/cm^2 at each part of the tumour for 15 min) at 48 and 72 hr **Comparator** Radiotherapy: 40 Gy for 4 wk	**Mortality** The 5-yr survival rate was 29.9% in the PDT group compared with 16.7% ($p = 0.05$). The 10-yr survival rate was 16.7% in the PDT group vs 10.0% ($p < 0.05$) **Morbidity** Not assessed **QoL and return to normal activity** Not assessed **AEs** All PDT patients experienced pigmentation, and swelling and itchiness. All PDT patients also experienced pain when swallowing for 3–5 d (some patients had pain for > 10 d and discontinued treatment). 23 died in the PDT group: loss to FU two; uncontrolled localisation 13 including one due to blockage of oesophagus; metastases eight; other disease one; unknown cause one. 26 died in the radiotherapy group: loss to FU one; uncontrolled localisation 18, including two due to blockage of oesophagus; metastases four; other disease two; unknown cause two **Resource use** Not assessed	**Authors' conclusions** Radiotherapy combined with PDT could obviously enhance the long-term survival rate of patients with advanced oesophageal cancer **Brief study appraisal** This was a brief report and some methodological aspects were not clearly reported. The *p*-values were not reported consistently between the abstract and the text making it difficult to clarify the significant differences between groups

Study details	Population details	Treatment details	Results	Interpretation
Authors Zhang *et al.* (2007)[113] **Data source** Full published paper **Country** China **Language** English **Study design** RCT **No. of participants** Total: 140 Intervention: 42 Comparator: 98 **No. of recruiting centres** Not stated; appears to be two centres in China **Follow-up period and frequency** FU at 1 mth. Over 70% patients were followed up for 12–36 mth	**Treatment intention** Palliative **Type(s) of cancer and histology** Advanced oesophagocardiac carcinoma **Main eligibility criteria** Biopsy proven advanced oesophageal carcinoma **Patient characteristics** % Male: 79 Age range: 40–81 yr Median age: PDT 58; PDT with 5-FU 62 Cancer stage: Stage II 84; stage III 53; stage IV 3 **Concomitant treatment** Not stated	**Trial treatments** PDT vs PDT with 5-FU **Intervention** PDT: After intravenous injection of the photosensitiser PSD-007 (photocarcinorin) (3–5 mg/kg bw) and patients were kept in the dark. Irradiation was performed at 24 and 48 hr with either 630-nm copper vapour pumped-dye laser or 632.8 nm high power He-Ne laser (total dose 200–400 J/cm fibre length, median 300 J/cm). This was delivered by cylindrical diffusers under endoscope assistance. Irradiation was carried out in one to four segments (with slight overlap between each segment) depending on lesion length and diffuser. Treatment could be repeated after 1 mth unless evaluation showed effectiveness or symptoms were remitted. Patients were advised to avoid sunlight exposure for over 1 mth **Comparator** PDT with 5-FU: As for PDT but in addition, before irradiation, 200–500 mg 5-FU was locally injected into tumour tissue under endoscopic guidance. Before injection the extent of the lesions was confirmed. Most patients received four to eight injections per tumour	**Mortality** Mean survival time was 8.9 mth with PDT alone compared with 15.1 mth for PDT and 5-FU ($p < 0.01$) **Morbidity** The rate of dysphagia remission was 87% for PDT compared with 99% with PDT and 5-FU ($p < 0.05$). Differences in pharyngeal pain and weight loss were not significant. With PDT alone one patient achieved complete remission (vs five with combined therapy, $p < 0.05$), eight significant remission (vs 36) and five no remission (vs nine). With combined therapy 48 patients also achieved minor remission **QoL and return to normal activity** Not assessed **AEs** Subternal pain due to oesophageal mucosa injury and gastroesophageal reflux 1–2 d after treatment was reported by seven patients in PDT only and eight patients in combination treatment Eight patients in total accidentally exposed themselves to sunlight and developed discoloration of the skin No oesophageal stenosis or perforation reported in either group **Resource use** Not assessed	**Authors' conclusions** PDT is safe and effective for advanced oesophagocardiac cancer. Its therapeutic effect can be further improved when combined with local chemotherapy **Brief study appraisal** This study was poorly reported (e.g. method of randomisation, whether ITT analysis was used) but most importantly it appears that after over 40 patients had been treated, interim analysis was carried out and all subsequent patients were treated with combined PDT and 5-FU. These analyses were not further reported. Given this shift from an RCT to experimental without a comparator it is difficult to determine the reliability of the study results overall *The authors' conclusions do not follow from the results reported*

Appendix 18

Lung cancer data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Baas *et al.* (1994)[121] **Data source** Abstract **Country** The Netherlands **Language** English **Study design** RCT **No. of participants** Total: 39 Intervention: 15 Comparator: 12 2nd Comparator: 12 **No. of Recruiting Centres** Not stated **Follow-up period and frequency** Not stated	**Treatment intention** Palliative **Type of Lung Cancer and Histology** Non-small cell; no further details given **Main eligibility criteria** Histologically proven inoperable locoregional NSCLC, weight loss < 10% and a PS (sic) > 70% **Patient characteristics** % Male: 88 **Concomitant treatment** Not stated	**Trial treatments** ERT alone vs PDT preceding ERT vs HDR preceding ERT **Intervention** Photofrin 2 mg/kg, 200 J/cm, 630 nm given 2 wk before ERT. Other PDT parameters not stated **Comparator** ERT alone: 14 x 2.5 + 8 x 2.5 Gy to the tumour area in 4 wk **2nd comparator** HDR + ERT: As above preceded by HDR: 15 Gy at 1-cm distance along the tumour 2 wk before ERT	**Mortality** Assessed but not reported per group **Morbidity** Not assessed **AEs** Minor haemoptysis in two PDT-ERT patients. Skin photosensitivity was acceptable in patients treated with PDT (no data provided). Other AEs reported but not broken down by group	**Authors' conclusions** No conclusions specific to PDT **Brief study appraisal** This small study was an interim analysis of a RCT presented in abstract form. Although it indicated that updated results would be presented, no further information could be located. Most of the study's methodological details were not available from the abstract and the majority of the results were not broken down by treatment group

Study details	Population details	Treatment details	Results	Interpretation
Authors Diaz-Jimenez *et al.* (1999)[122] **Data source** Full published paper **Country** Spain **Language** English **Study Design** RCT **No. of participants** Total: 31 Intervention: 14 Comparator: 17 **No. of Recruiting Centres** Not stated **Follow-up period and frequency** FU at 1, 2, 3, 6 and 12 mth (and 18 mth if possible)	**Treatment intention** Palliative **Types of Lung Cancer and Histology** Non-small cell 25 SCC, three adenocarcinoma, three undifferentiated carcinoma **Main eligibility criteria** Biopsy-proven inoperable cancer with totally or partially obstructive endobronchial lesions with or without extrabronchial tumour. Patients > 18 yr, non-pregnant, infertile or postmenopausal. Karnofsky status ≥ 40%, ≥ 4 wk from last chemotherapy cycle and ≥ 3 wk from last radiation dose. Patients who had previous PDT or Nd:YAG were excluded. Further eligibility criteria were reported **Patient characteristics** % Male: 100 Age range: Not stated Mean age: 65 yr Cancer stage: Stage I, four patients; stage II, one; stage IIIA, six; stage IIIB, 10; stage IV, seven No. with recurrent tumour: three **Concomitant treatment** Not stated	**Trial treatments** PDT vs Nd:YAG laser resection **Intervention** Intravenous DHE at dose of 2 mg/kg with 630-nm argon dye laser, 40–50 hr after injection. Maximum of three doses (six photoradiations). Other parameters not reported **Comparator** Nd:YAG resection using 15- to 80-W pulses of 0.5–1.5 s. Procedure repeated every 2–4 d as necessary	**Mortality** Survival significantly longer in PDT group (265 vs 95 d, $p = 0.007$). 4/14 (PDT) and 4/17 (Nd:YAG) still alive at end of study **Morbidity** Similar response in both groups: 38.5% PDT vs 23.5% Nd:YAG at 1 mth (p = ns). PR at 1 mth in three PDT and four Nd:YAG patients. CR at 1 mth in one PDT patient. Time elapsed until treatment failure: 50 d (PDT) vs 38 d (Nd:YAG) ($p = 0.03$) **QoL and return to normal activity** Assessed but not reported **AEs** Bronchitis was the most common (four cases in PDT group, one in Nd:YAG group) Photosensitisation in four PDT patients. Five patients had no AEs, all in Nd:YAG group. One death probably related to PDT	**Authors' conclusions** PDT is a valid method of palliation in partially or totally obstructing NSCLC **Brief study appraisal** Difficult to evaluate results due to important baseline differences (presence of cough, and stage of cancer) between groups. Karnofsky performance and FU after 1 mth assessed but not reported. No details on blinding

Study details	Population details	Treatment details	Results	Interpretation
Authors Lam *et al.*, (1991)[123] **Data source** Full published paper **Country** Canada **Language** English **Study design** RCT **No. of participants** Total: 41 Intervention: 20 Comparator: 21 **No. of Recruiting Centres** Not stated **Follow-up period and frequency** FU at 1, 2, 3, 6, 12, 18 and 24 mth	**Treatment intention** Palliative **Types of Lung Cancer and Histology** Non-small cell 34 squamous cell, three adenocarcinoma, four large cell **Main eligibility criteria** Biopsy-proven stage III non-small cell bronchogenic carcinoma with obstructing or partially obstructing endobronchial lesion. Karnofsky rating ≥ 40 and ability to tolerate multiple bronchoscopies. Patients who had previous PDT or radiotherapy, or concurrent chemotherapy or Nd:YAG laser therapy were excluded, as were patients whose tumours were invasive to major blood vessels on CT scan **Patient characteristics** % Male: 76 Mean age: Around 67 yr Tumour location: 78% in main stem bronchus, 22% in lobar bronchus **Concomitant treatment** See 'Eligibility criteria'	**Trial treatments** PDT + radiotherapy vs Radiotherapy alone **Intervention** Intravenous Photofrin at 2 mg/kg followed with 40–50 hr of red (630nm) light from argon-dye laser delivered by a single-step index quartz fibre inserted into the biopsy channel of a flexible fibreoptic bronchoscope (a cylindrical diffuser tip was inserted 1–2 cm into tumour). Power density was 400 mW/cm, total light dose was 200 J/cm. Residual tumour treated by a repeat light exposure The duration of light was not stated. Radiotherapy – see below **Comparator** Radiation at 3000 cGy in 10 fractions with a 4-MeV linear accelerator over 2 wk, using a parallel pair technique. Field size defined by the 50% isodose line with 2-cm margin of normal tissue	**Mortality** 16 patients died in radiotherapy-alone group compared with 14 in PDT + radiotherapy group, in both groups eight deaths were due to metastases. Three patients in the PDT + radiotherapy group died from massive haemoptysis (67, 187 and 567 d, respectively, after treatment), compared with none in the Radiotherapy-alone group. No difference between groups in median survival times (444 d in PDT + radiotherapy vs 445 d in Radiotherapy-alone group) **Morbidity** Significantly greater reduction of haemoptysis and shortness of breath, and cough at 1 and 3 mth, in the PDT + radiotherapy group ($p < 0.05$) 14/20 PDT + radiotherapy and 2/21 radiotherapy alone achieved complete re-opening of bronchial lumen. Four patients in Radiotherapy-alone group failed to respond to treatment, none failed in PDT + radiotherapy group Median interval between treatment and local recurrence was significantly longer in PDT + radiotherapy group (233 d vs 107 d, $p = 0.005$) **QoL and return to normal activity** Assessed but not reported (Karnofsky performance) **AEs** Photosensitivity with mild erythema, which resolved without treatment, was seen in four of the PDT + radiotherapy group	**Authors' conclusions** The addition of PDT prior to radiotherapy provides significantly better and longer-lasting local control than radiotherapy alone **Brief study appraisal** No details of methods of randomisation, allocation concealment or blinding were reported for this small study (raising reliability issues). Some outcomes assessed but not reported

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Study details	Population details	Treatment details	Results	Interpretation
Authors Lam *et al.* (1987)[124] **Data source** Full published paper **Country** Canada **Language** English **Study design** RCT **No. of participants** Total: 11 Intervention: Five Comparator: Six **No. of Recruiting Centres** Not stated **Follow-up period and frequency** FU at 4 and 12 wk, then quarterly thereafter (unless progression of tumour occurs)	**Treatment intention** Palliative **Types of Lung Cancer and Histology** Non-small cell: nine squamous cell, two large cell **Main eligibility criteria** Patients with inoperable non-small cell bronchogenic carcinoma, partially or completely obstructing a central airway, who had received no prior treatment (e.g. chemotherapy or radiotherapy). Patients with evidence of metastatic disease were excluded **Patient characteristics** % Male: 82 Mean age: 66 yr All patients had tumours at more than one site **Concomitant treatment** Not stated	**Trial treatments** PDT + radiotherapy vs Radiotherapy alone **Intervention** Intravenous Photofrin II 24–48 hr prior to red light (630 nm) from a continuous argon pumped-dye laser, via single-step index quartz fibres inserted into channel of a double lumen flexible fibreoptic bronchoscope (or a single channel instrument). A cylindrical diffuser tip (0.5, 1.0 or 1.5 cm) was inserted into the tumour. Power density was 400 mW/cm and total light dose 300 J/cm. Clean-up bronchoscopy followed 2 d later, with further light at 300 J/cm (but no more Photofrin II) for any residual tumours. PDT was given 1st, with radiotherapy starting within 1 wk of PDT Tumours that could not be inserted due to small size, or hardness, received 200 J/cm^2 at power density of 200 mW/cm^2 using microlens fibre The dose of Photofrin and duration of light were not stated. For radiotherapy, see below **Comparator** All patients had 3000 cGy in 10 fractions over 2 wk using a parallel-pair technique from a 4 MeV linear accelerator. Field size defined by the 50% isodose line with 2-cm margin of normal tissue	**Mortality** One patient died in the PDT + radiotherapy group vs three in the Radiotherapy-alone group **Morbidity** Both groups had significantly improved respiratory symptoms at 4 wk (with mean scores falling from 7 to 1 in the PDT + radiotherapy group, and 7 to 4 in the Radiotherapy-alone group, $p < 0.05$). The mean score for the Radiotherapy-alone group was back up to 7 at 12 wk, but the PDT + radiotherapy group had a mean score of 2, which was significantly different from baseline ($p < 0.05$) At 4 wk, the PDT + radiotherapy group had a significant reduction in% airway obstruction (99 vs 21) and improvement in arterial oxygen (63 vs 80, both $p < 0.05$) when compared to baseline, with percentage airway obstruction still significantly improved at 12 wk (99 vs 25, $p < 0.05$). There were no significant reductions in the Radiotherapy-alone group **QoL and return to normal activity** At 4 wk, the PDT + radiotherapy patients had significant improvements ($p < 0.05$) in both Karnofsky rating (78 vs 93) and QoL (56 vs 39), compared to baseline scores. There were no significant differences in the Radiotherapy-alone group **AEs** One patient receiving PDT remained photosensitive for 8 wk	**Authors' conclusions** The addition of PDT prior to radiotherapy provides significantly better and longer-lasting palliation, than radiotherapy alone, for patients with obstructive endobronchial tumours. The combined treatment may also improve survival **Brief study appraisal** Very small sample size coupled with poorly reported methods make it difficult to draw any robust conclusions

Study details	Population details	Treatment details	Results	Interpretation
Authors Leroy *et al.* (1998)[125] Linked publications[212] **Data source** Abstract **Country** Not stated **Language** English **Study design** RCT **No. of participants** Total: 141 Intervention: Not stated Comparator: Not stated **No. of Recruiting Centres** Not stated **Follow-up period and frequency** FU at 1 wk and 1 mth	**Treatment intention** Palliative **Type of Lung Cancer and Histology** Non-small cell **Main eligibility criteria** Not stated **Patient characteristics** Not stated **Concomitant treatment** Not stated	**Trial treatments** PDT vs Nd:YAG laser **Intervention** 2 mg/kg of Photofrin followed 48 hr later by light activation Light source and duration, wavelength of light, power density, total light dose, maximum no. of sessions allowed, and postoperative advice not stated **Comparator** No details provided	**Mortality** Not assessed **Morbidity** CR + PR comparable between groups at wk 1 (PDT 65% vs Nd:YAG 61%), but significantly different at 1 mth (PDT 61% vs Nd:YAG 35%, $p < 0.05$). At 1 mth PDT also improved symptoms of dyspnoea (28% vs 13%), cough (33% vs 11%), haemoptysis (33% vs 19%), and sputum production (22% vs 14%), *p*-values not stated **QoL and return to normal activity** Not assessed **AEs** Mild-to-moderate skin photosensitivity in 21% of PDT patients. No further details	**Authors' conclusions** Photofrin is at least similar to or better than Nd:YAG thermal ablation in re-establishing the patency of the obstructed lumen and palliating symptoms at wk 1 and mth 1 following treatment **Brief study appraisal** The very limited information provided, particularly on study methods and basic results (e.g. no numbers on randomisation by treatment group) makes assessment of reliability difficult

Study details	Population details	Treatment details	Results	Interpretation
Authors Maier *et al.* (2002)[127] **Data source** Full published paper **Country** Austria **Language** English **Study design** Non-RCT **No. of participants** Total: 40 Intervention: 16 Comparator: 24 **No. of Recruiting Centres** One **Follow-up period and frequency** 1 wk and 4 wk	**Treatment intention** Palliative **Type of Lung Cancer and Histology** Non-small cell **Main eligibility criteria** Patients with malignant tracheobronchial stenosis, not eligible for resection treatment because of poor performance status, functional and/or anatomical inoperability, and/or refusing surgery **Patient characteristics** % Male: 75 Mean age: ALA, 64 yr; Photosan, 66 yr Cancer stage: Stage IIb, seven; Stage IIIa, 13; Stage IIIb, six; Stage IV, 14 Squamous cell 27, Adenocarcinoma 10, Large cell carcinoma three Stenosis mean (range): ALA, 79% (50–90%); Photosan, 50% (20–95%) 22 patients with radiological and clinical signs of poststenotic pneumonia Karnofsky status mean (range): ALA, 78 (60–90); Photosan, 70 (60–80) Further patient characteristics were reported **Concomitant treatment** At least 4 wk after combined PDT/HBO, all patients were considered for further treatment, including high-dose rate brachyradiotherapy, external beam irradiation and/or chemotherapy	**Trial treatments** PDT with 5-ALA and HBO vs PDT with Photosan and HBO **Intervention** ALA was orally administered at a dose of 60 mg/kg, 6–8 hr prior to PDT In cases of severe tumour stenosis, PDT was carried out by using a fibre with a 2-cm tip radial light-diffusing cylinder, which was inserted through the biopsy channel of the endoscope. In cases of moderate tumour stenosis a 2-cm balloon applicator system was used for homogeneous light distribution. During treatment the radial light diffusing cylinder and/or balloon applicator system was closely applied to the surface of the tumour. The light dose was 100 J/cm^2. Light at 630 nm was applied by a KTP-Nd:YAG laser with a DYE module. In both groups additional hyperbaric oxygenation at a level of 2 ATA in a walk-in hyperbaric chamber was undertaken. Oxygen was applied using a Scuba valve system. Each treatment was performed under short-term intravenous anaesthesia with endotracheal intubation and spontaneous breathing. Skin protection was managed by use of a camouflage (Covermark, Milan, Italy) for 24 hr after photosensitisation **Comparator** Photosan-3 was administered intravenously at a dosage of 2 mg/kg, 48 hr prior to PDT. See intervention for details of PDT delivery. Skin protection was by using a commercially available sun blocker for 12 wk	**Mortality** The mean survival for the ALA group was 9 mth and the Photosan group 14 mth ($p = 0.020$) **Morbidity** 4 wk FU In the ALA group, stenosis diameter dropped from a mean value of 79% to 63%. In the Photosan group the mean value dropped from 50% to 19%, $p = 0.00073$, in favour of Photosan. Dyspnoea was improved in 10/16 ALA patients and 19/24 Photosan patients. Haemoptysis subsided in 13/16 ALA patients and 20/24 Photosan patients. Radiological and clinical signs of poststenotic pneumonia subsided in 5/9 ALA patients and 9/13 Photosan patients. There was no statistically significant difference between groups on pulmonary function parameters **QoL and return to normal activity** Mean Karnofsky value changed from 78 to 79 in the ALA group, and from 70 to 78 in the Photosan group, showing a significant difference in favour of the Photosan group ($p = 0.00015$). One patient had an improvement of 10% in the ALA group, whereas 11 patients in the Photosan group improved by 10% and five improved by 20%. None of the patients in the Photosan group reported a decrease in QoL due to long-lasting need for skin protection **AEs** No sunburn occurred in either group. No major complications relating to photosensitisation, PDT or HBO were observed. Minor complications were: fever in the afternoon after PDT (12 in ALA group, 18 in Photosan group) and mild chest pain for 1 or 2 d (6 in the ALA group and 13 in the Photosan group). None of the AEs required specific treatment	**Authors' conclusions** Photosan seems to be more effective than ALA in PDT of malignant tracheobronchial stenosis. However, these results would need confirming in a randomised, blinded trial **Brief study appraisal** This small pilot study was non-randomised and the groups had differences at baseline which may have impacted on results. The survival data do not solely reflect the effectiveness of the PDT treatment, as 4 wk after PDT patients were eligible to receive a variety of other treatments. There are also doubts as to whether the ALA dosage was optimal

ATA, atmosphere absolute.

Study details	Population details	Treatment details	Results	Interpretation
Authors Moghissi *et al.* (1993)[126] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 26 Intervention: 15 Comparator: 11 **No. of Recruiting Centres** Not stated **Follow-up period and frequency** At 1, 2 and 3 mth, then at 3-monthly intervals	**Treatment intention** Palliative **Type of Lung Cancer and Histology** Non-small cell **Main eligibility criteria** Stage III inoperable NSCLC with > 50% intraluminal bronchial obstruction **Patient characteristics** % Male: 81 Age range: 43–76 yr Mean age: Intervention 60, comparator 66 (ns) **Concomitant treatment** Some patients had additional modalities of treatment after 1 mth	**Trial treatments** PDT vs Nd:YAG laser **Intervention** Intravenous Photofrin or Photofrin II at dose of 2 mg/kg followed 48–54 hr later by red light (630 nm) from a copper vapour pumped-dye laser delivered through a 600-nm quartz fibre with a terminal cylindrical diffuser. Dose of 200 J/cm at 400 mW/cm. Duration of light dose was 500 s. Further sessions provided if needed. Thorough debridement and physiotherapy after treatment. Careful counselling on photosensitivity **Comparator** Nd:YAG laser (Fibrelase 100, Pilkington) with a 400-μm diameter delivery fibre using 40–50W pulses of 3–5 s. Dose dependent on extent of tumour. Further sessions provided if needed	**Mortality** No treatment-related mortality. Longer-term mortality not assessed **Morbidity** At 1-mth, luminal diameter, as percentage of normal diameter, was significantly greater in PDT group (83%) than the Nd:YAG group (61%), $p < 0.0006$. Both FVC and FEV_1 improved significantly more with PDT 1 mth after treatment when compared to pre-treatment measurements: mean difference in FVC, 0.47 PDT vs –0.06 Nd:YAG, $p < 0.05$, mean difference in FEV_1, 0.35 PDT vs 0.01 Nd:YAG, $p < 0.05$ All patients had a PR at 1 mth **AEs** No serious post-treatment complications. Mild fever in two Nd:YAG patients. No photosensitivity in PDT patients	**Authors' conclusions** PDT is more effective than Nd:YAG in patients with extensive obstructive lung cancer **Brief study appraisal** A small study with no details of methods of randomisation, allocation concealment or blinding (raising reliability issues)

Appendix 19

Biliary tract cancer data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Dechene *et al.* (2007)[132] **Data source** Abstract **Country** Not stated **Language** English **Study design** Non-RCT **No. of participants** Total: 29 Intervention: 16 Comparator: 13 **No. of recruiting centres** Not stated **Follow-up period and frequency** Not stated	**Treatment intention** Palliative **Type(s) of Cancer and Histology** Non-resectable bile duct cancer **Main Eligibility Criteria** Advanced bile duct cancer (no further details given) **Patient characteristics** % Male: 76 Median age: 67–70 Histological confirmation was not reported **Concomitant treatment** Peri-interventional antibiotic prophylaxis	**Trial treatments** PDT with Photosan-3 vs PDT with Photofrin II **Intervention** 2 mg/kg Photosan-3 administered 48 hr before radiation. A 4-cm quartz fibre and a diode laser system (635 nm; 1, 1W, 220 J/cm). Light protection was advised for 4–6 wk. Further PDT parameters were not reported **Comparator** 2 mg/kg Photofrin II administered 48 hr before radiation. A 4-cm quartz fibre and a diode laser system (635 nm; 1, 1W, 220 J/cm). Light protection was advised for 4–6 wk. Further PDT parameters were not reported	**Mortality** Median survival in the PS-3 group was 690 d (95% CI 448 to 931) and in the PF2 group it was 494 d (95% CI 84 to 903), p = NS **Morbidity** Not assessed **QoL and return to normal activity** Not assessed **AEs** There was no substantial skin reaction observed (no data provided). 23% of patients in the PF2 group and 26% of patients in the PS3 group developed 'considerable' cholangitis **Resource use** Not assessed	**Authors' conclusions** PDT has the potential to considerably prolong survival in non-resectable bile duct cancer. The effect is not dependent on the type of haematoporphyrin photosensitiser **Brief study appraisal** This study was reported in abstract form only and did not provide details of methodology such as randomisation, blinding and allocation concealment. This is a small trial which may be underpowered to detect a difference between the photosensitisers

Study details	Population details	Treatment details	Results	Interpretation
Authors Kahaleh *et al.* (2008)[133] **Data source** Full published paper **Country** USA **Study design** Non-RCT **No. of participants** Total: 48 Intervention: 19 Comparator: 29 **No. of recruiting centres** One **Follow-up period and frequency** FU at 1 mth and every 3 mth thereafter (or earlier if there were complications)	**Treatment intention** Palliative **Type(s) of cancer and histology** Non-resectable cholangiocarcinoma **Main eligibility criteria** Unclear, PDT offered after December 2004 to all patients with non-resectable cholangiocarcinoma or resectable lesions deemed inoperable **Patient characteristics** % Male: 50 Age range: 26–94 yr Mean age: 66.6 yr Tumour extension: Bismuth I, 6%; Bismuth II, 19%; Bismuth III, 35%; Bismuth IV, 40% Further patient characteristics were reported Pathological diagnosis was confirmed in 69% of cases **Concomitant treatment** Twenty-two patients had chemotherapy and 19 had radiotherapy. All patients received periprocedure antibiotic prophylaxis	**Trial treatments** ERCP with PDT and stent vs ERCP with Stent alone **Intervention** Selective decompression of all opacified, dilated segments was attempted with bougie and balloon dilatation to assist in the placement of polyethylene stents Intravenous Photofrin at 2 mg/kg 48 hr prior to 633-nm (± 3-nm) light from a 2000-mW diode laser, delivered through a 3-m length fibre having a 2.5-cm-long cylindrical diffuser at distal end (diffuser was inserted into a 10F sheath of a plastic stent) Photoactivation performed at 633 nm* with a light dose of 180 J/cm^2, fluence of 0.25W/cm^2 and duration of 750 s. One or two segments treated at discretion of endoscopist. PDT repeated at 3-mth intervals when all stents were replaced (this was done earlier if premature occlusion or migration occurred) *Although reported as 620 nm in the paper, based on the type of laser used this appears to have been a typographic error **Comparator** Selective decompression of all opacified, dilated segments was attempted with bougie and balloon dilatation to assist in the placement of polyethylene stents (7F, 8.5F and 10F in diameter). Repeated if indicated until patient refusal or death	**Mortality** At end of study 10 patients were still alive, eight being from the PDT group There was statistically significant prolonged survival in the PDT group (mean 16.2 mth, SD 2.4) compared with the Stent-alone group (mean 7.4 mth, SD 1.6), $p < 0.003$. Mortality rates were significantly lower in the PDT group at 3 mth (0% vs 28%, $p = 0.01$), and 6mth (16% vs 52%, $p = 0.01$), but not at 12 mth (56% vs 82%, $p = 0.08$) vs Stent-alone group **Morbidity** Both groups had significantly decreased levels of serum bilirubin at 3 mth when compared to baseline levels ($p = 0.008$ for PDT and $p = 0.0001$ for stent only), although there was no significant difference between the two groups in the degree of decrease ($p = 0.78$) **QoL and return to normal activity** Not assessed **AEs** Stent-alone group: 10 patients developed cholangitis (with two patients dying as a consequence). Four patients developed pancreatitis and one had duodenal perforation. Further results reported. PDT group: three patients experienced skin phototoxicity. Seven patients developed cholangitis, two developed cholecystitis, and two haemobilia. Further results reported **Resource use** Not assessed	**Authors' conclusions** ERCP with PDT seems to increase survival in patients with unresectable cholangiocarcinoma when compared with ERCP alone, although it remains to be proved whether this is due to PDT or the number or ERCP sessions **Brief study appraisal** The aims of this study at its inception are uncertain as the study began in 2001, but PDT only became available for use in 2004. From this point on, PDT was offered to all patients, making it difficult to recruit groups with similar baseline characteristics. However, the authors acknowledged that the study design prevented definitive conclusions from being drawn

F, The 'French size' of the sheath used to introduce a stent.

Study details	Population details	Treatment details	Results	Interpretation
Authors Ortner *et al.* (2003)[134] **Data source** Full published paper **Country** Germany **Language** English **Study design** RCT **No. of participants** Total: 39 Intervention: 20 Comparator: 19 **No. of recruiting centres** Two **Follow-up period and frequency** 14 d, 3 mth, 6 mth after the intervention. Survivors then followed up at 6-mth intervals	**Treatment intention** Palliative **Type(s) of cancer and histology** NCC **Main eligibility criteria** Inclusion criteria were patients at least 18 yr of age with a proximal malignant tumour of the bile ducts (Bismuth types II–IV, TNM stages III and IV). They had a large (> 3 cm in diameter), imaging-confirmed, non-resectable tumour (assessed by two independent surgeons), positive histology and no evidence of cancer of another organ. Exclusion criteria were porphyria, previous chemotherapy or radiotherapy, previous technically successful stenting (details in paper), insertion of a metal stent, partial resection of cholangiocarcinoma, diagnostic ERCP more than 1 mth previously and a Karnofsky index of < 30%. Further detail is presented in the paper **Patient characteristics** % Male: Not stated Age range: 53–85 Median age: Intervention 64; control 68 (NS) Cancer stage: Stage III, seven; stage IVa, 19; stage IVb 13 Bismuth type: II, two; III, six; IV, 31 100% of all cases were histologically confirmed Further patient characteristics were reported **Concomitant treatment** Oral ciprofloxacin therapy, 250 mg twice daily, was started before ERCP and continued for 14 d	**Trial treatments** PDT + Double stenting vs Stenting alone **Intervention** See comparator for details of stenting. PDT patients received Photofrin at a dosage of 2 mg/kg body wt intravenously 48 hr before laser activation. Endoprostheses were removed and an endoscopic Huibregtse Cotton set catheter was introduced proximally above the strictures. Intraluminal photoactivation was performed with a laser quartz fibre with a cylindrical diffuser tip, length 40 mm, core diameter 400 μm. Photoactivation was performed at 630 nm using a light dose of 180 J/cm^2, fluence of 0.241 W/cm^2 and irradiation time of 750 s under a continuous saline perfusion. A new set of endoprostheses was inserted after completion of PDT. Further technical details of the procedure are available in the paper. Patients remained in a darkened room for 3–4 d after injection and thereafter patients were gradually adapted to light. If any FU examination showed evidence of tumour in the bile duct, PDT was repeated. Mean number of treatments was 2.4 (minimum 1, maximum 5), the mean no of illuminations per patient was 5.3 and the median treatment time was 79 min (minimum 40; maximum 180). *All patients received oxygen via a nasal catheter to optimise the PDT effect* **Comparator** Endoscopic double-stenting followed diagnostic ERCP (all patients received oral ciprofloxacin therapy 250 mg twice daily before ERCP and continued for 14 d). At least two 10F endoprostheses had to be placed above the main strictures in every patient. Endoscopic plastic endoprostheses or percutaneous plastic prostheses were used. Successful drainage after technically successful stenting (definition given in paper) was defined as a decrease in bilirubin level > 50% within 7 d after stenting. When the 1st procedure did not lead to technically successful stenting, a 2nd procedure was performed. When the 2nd procedure was not satisfactory, percutaneous stenting was performed. Patients were randomised only after technically successful stenting. Stent exchanges were performed every 3 mth. Eight patients received extra interventions (chemotherapy, four; PDT, three; immunotherapy, one) as a last resort treatment	**Mortality** Median survival in the PDT group was 493 d (95% CI 276 to 710) and 98 d in the Stenting-only group (95% CI 87 to 107) $p < 0.0001$. RR = 0.21 (95% CI 0.12 to 0.35). Two patients in the PDT group were still alive at the time of evaluation. the study was terminated early due to the superiority of PDT **Morbidity** Successful drainage was achieved in 21% of patients in both groups. After PDT serum bilirubin reached lower levels relative to baseline and stenting ($p < 0.01$). Successful drainage was obtained in 72% Mean number of stent exchanges: PDT group = 3.8, stenting alone = 3.7 **QoL and return to normal activity** The Karnofsky index improved after PDT with a median 80% score (minimum 50%, maximum 100%); mean change from baseline 3.00 but did not improve in the Stenting-alone group. The difference in change from baseline between the PDT + Stenting group and the Stenting-alone group was 11.43 (95% CI 2.92 to 19.95, $p < 0.01$). After PDT physical functioning ($p < 0.01$) and global QoL ($p < 0.001$) improved in the PDT group but not in the Stenting-alone group. The results of individual factors relating to QoL measures are listed in the paper **AEs** Burden of treatment was lower in PDT vs Stenting alone ($p < 0.001$). Photosensitivity was reported by two (10%) of PDT patients; all reactions were mild and resolved completely. Any cholangitis occurring during FU was considered an AE. There were three cases in the PDT group and seven in the Stenting-alone group. Stenosis probably related to therapy was reported by two in the PDT group and zero in the Stenting-alone group. Fatal cholangitis, sepsis possibly related to therapy: PDT group two of 18, Stenting-alone group six of 19 The following were causes of death probably not related to therapy: Pulmonary embolism: PDT group one of 18, Stenting alone three of 19 Cachexia: PDT group one of 18, Stenting one of 19 Cardiac failure: one of 18, one of 19, respectively Metastases: 12 of 18, eight of 19, respectively Chronic renal failure: one of 18, zero of 19, respectively **Resource use** Not assessed	**Authors' conclusions** PDT added to best supportive care improves survival and QoL in patients with NCC. Prolonged survival time was not associated with a high rate of AEs **Brief study appraisal** This was a well-conducted and reported trial, which was halted early due to the superiority of the PDT treatment

NCC, non-resectable cholangiocarcinoma.

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Study details	Population details	Treatment details	Results	Interpretation
Authors Witzigmann *et al.* (2006)[135] **Data source** Full published paper **Country** Germany **Language** English **Study design** Non-RCT **No. of participants** Total: 184 (191 if including seven patients not analysed due to missing FU data) Intervention: 68 Comparator: 56 2nd Comparator: 60 **No. of recruiting centres** Not stated **Follow-up period and frequency** Unclear – patients were recruited over 10 yr, which appears to be the FU period	**Treatment intention** Curative palliative **Type(s) of cancer and histology** Hilar cholangiocarcinoma **Main eligibility criteria** Not stated **Patient characteristics** % Male: 52 Age range: 22–91 yr Tumour stage: Patients from all stages, but mostly IB and IIA Tumour extent: Patients from all Bismuth types, but mostly type IV. According to both Bismuth–Corlette and UICC classifications there were more advanced tumours in the palliative treatment groups than in the resection group ($p < 0.05$). Further patient characteristics were reported The number of cases confirmed histologically was not clearly reported **Concomitant treatment** Chemotherapy, radiation therapy, chemoradiation and iridium implants were occasionally used	**Trial treatments** PDT + stenting vs Stenting alone vs Resection **Intervention** PDT + stenting: Intravenous Photofrin at 2 mg/kg with photoactivation after 1–4 d. Repeated when there was evidence of tumour progression. Further PDT parameters were not reported. See below for stenting **Comparator** Stenting: At least two 9F or 11.5F plastic endoprostheses were placed above the main strictures and exchanged every 3 mth **2nd comparator** Resection: One of right-sided hemihepatectomy, right trisegmentectomy, left hemihepatectomy, hilar resection alone or liver transplantation, with additional types of surgery when required. Neoadjuvant PDT and biliary drainage also given if required	**Mortality** PDT + stenting vs Stenting alone: 1- and 2-yr survival rates were 51% and 16% vs 23% and 10%, respectively; median survival time 12 mth vs 6.4 mth ($p < 0.01$); 63(93%) vs 51(91%) patients had died by the end of the study (the main causes were tumour progression and complications of chronic cholangitis). Resection: The 30- and 60-day death rates were 8.3% and 11.7%, respectively. Multiple organ failure from infective complications was the most common cause of death. Overall 1-, 3- and 5-yr survival rates including post op deaths were 73%, 40% and 27%, respectively, with a median survival of 23 mth. Neoadjuvant PDT before resection resulted in 1-, 3- and 5-yr survival rates of 88%, 42% and 42% compared with 66%, 28% and 19% after surgery alone (ns). There was no significant difference in median survival time between the (R1 and R2) resection group and the PDT + Stenting group **Morbidity** PDT + stenting and Stenting alone: At 3 mth, in the PDT + stenting group, there was a significant difference in mean bilirubin levels relative to baseline ($p < 0.001$). PDT + stenting group had significantly lower levels of bilirubin than the Stenting-alone group (4.1 mg/dl vs 7.3 mg/dl, $p < 0.05$). Successful drainage achieved in 75% of patients receiving PDT + stenting compared with 39% receiving stenting alone. Resection: Recurrence in 27 patients **QoL and return to normal activity** At 3 mth, median pre-treatment Karnofsky performance status increased by 2% for PDT + Stenting and decreased by 8% in Stenting-alone group ($p < 0.01$) **AEs** PDT + stenting/Stenting alone: There were no procedure-related deaths. Eight PDT patients had skin toxicity (grades I and II). Bacterial cholangitis seen in 38 PDT + Stenting patients and 32 Stenting-alone patients (ns). Resection: major complications reported in 52% of patients (37% required relaparotomy). The most common complication was bile leakage (eight patients) **Resource use** Median hospital stays were 65 d for PDT + stenting, 44 d for stenting alone, and 48 d for resection	**Authors' conclusions** Only complete tumour resection, including hepatic resection, enables long-term survival for patients with hilar cholangiocarcinoma. Palliative PDT + Stenting resulted in longer survival than stenting alone and has a similar survival time compared with incomplete R1 and R2 resection **Brief study appraisal** No firm conclusions can be drawn from the results of this study for several reasons. There was heterogeneity of treatments within the three groups (e.g. some patients in the resection group also received neoadjuvant PDT). The groups were also clinically heterogeneous (significantly different at baseline for several parameters), and there was wide variation in length of FU between groups and patients

UICC, International Union Against Cancer.

Study details	Population details	Treatment details	Results	Interpretation
Authors Zoepf *et al.* (2005)[136] **Data source** Full published paper **Country** Germany **Language** English **Study design** RCT **No. of participants** Total: 32 Intervention: 16 Comparator: 16 **No. of recruiting centres** Not stated **Follow-up period and frequency** 1, 3, 6, 9, 12 and every 3 mth. Earlier endoscopic interventions were performed when needed in case of clotting or dislocation	**Treatment intention** Palliative **Main eligibility criteria** Advanced, non-resectable BDC **Patient characteristics** % Male: 63 Median age: 68 yr (range 52–80 yr) Cancer stage: Stage II + lymph nodes, one; stage IV, 31 Initial median Karnofsky performance status: 90% (70–100) Overall 63% of cases were confirmed histologically **Concomitant treatment** All patients received prophylactic antibiotic treatment before the procedure with 1 g of Ceftriaxon, given intravenously 30 min before intervention. Ongoing antibiotic oral treatment with chinolone was given for a total of 14 d. The 1st eight PDT patients had intravenous Cefriaxon over 3 d but did not receive continuing oral antibiotic treatment	**Trial treatments** PDT + endoscopic drainage vs Endoscopic drainage alone **Intervention** Photosan-3 was given intravenously at a dose of 2 mg/kg bw 48 hr before laser irradiation. A flexible cylindrical diffuser probe was used. The probe was mounted on a 400-μm quartz fibre with an active length of 4cm and a radiopaque marker at the distal fibre tip. A diode laser system with a maximum power output of 2W and a wavelength of 633 ± 3 nm was used as light source. Irradiation time was calculated for a light energy density of 200 J/cm^2. In most cases this was around 550 s. the power density was 450–500 mW/cm and energy dose was 250–275 J/cm of diffuser length. For transpapillary PDT the light applicator was inserted through the working channel of a duodenoscope. For percutaneous PDT the quartz fibre was guided in four patients through the partially removed percutaneous catheter and in one patient through the working channel of a cholangioscope. The 1st PDT session was performed at a median of 4.5 mth (1–9) after diagnosis of BDC. Nine patients received a 2nd PDT session after 3–9 mth and one patient a 3rd session 6 mth after the 2nd session. Further PDT parameters were not reported. All patients were provided with plastic endoprostheses immediately after the PDT treatment **Comparator** The aim of the endoprosthetic treatment was bilateral hilar drainage. Endoprostheses were regularly changed every 3 mth or earlier in case of clotting or dislocation	**Mortality** The PDT group had a longer survival time compared to the endoprosthesis group (21 mth vs 7 mth, $p = 0.01$). In the PDT group, 30-d mortality was 0% and 6% in the endoprosthesis group. At the time of evaluation, three patients in the PDT group and one in the endoprosthesis group were still alive. The PDT patients were deemed to be in good clinical condition without significant cholestasis. No details were provided on the survivor in the endoprosthesis group. In the PDT group 12 patients died of tumour-related causes, and one patient of a perforated gastric ulcer. Causes of death were not reported for the endoprosthesis group **Morbidity** 4 wk after initial PDT, most PDT patients showed an almost complete elimination of bile duct stenosis in the treated area as shown with cholangiography (data not provided). Median bilirubin level after 1st intervention was not significantly different between the groups **QoL and return to normal activity** QoL as assessed by the Karnofsky scale did not significantly improve after PDT **AEs** Three patients developed an infected bilioma with prolonged cholangitis after PDT treatment, which could be managed by antibiotic treatment. Another patient developed cholecystitis 2 mth after a 2nd treatment session, which led to surgical laparoscopic cholecystectomy. There was no skin phototoxicity observed in any of the three patients. One patient developed severe bacterial cholangitis during endoprosthetic therapy, which was successfully treated by standard antibiotic therapy **Resource use** Not assessed	**Authors' conclusions** PDT is minimally invasive but there is a considerable risk of cholangitis after the procedure. PDT was found to result in a substantial prolongation of survival time but this would need confirmation in further patient series. PDT has the potential to result in a changeover of current palliative treatment of BDC **Brief study appraisal** A small trial with clear reporting of procedures. The results appear to be reliable but would need confirmation in a larger trial

Appendix 20

Brain cancer data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Eljamel *et al.* (2008)[139] **Data source** Full published paper **Country** UK **Language** English **Study design** RCT **No. of participants** Total: 27 analysed (42 randomised?) Intervention: 13 Comparator: 14 **No. of recruiting centres** One **Follow-up period and frequency** 3-monthly, until death	**Treatment intention** Curative **Type(s) of cancer and histology** GBM **Main Eligibility Criteria** Patients over 17 yr, with a new MRI diagnosis of GBM and a Karnofsky score ≥ 60 **Patient characteristics** % Male: 67 Mean age: 59.8 yr Mean Karnofsky performance score: 70 **Concomitant treatment** Some study patients received additional treatments such as chemotherapy and further surgery. However, there were no statistically significant differences between the groups in patients receiving additional treatments	**Trial treatments** Fluorescence-guided resection and repetitive PDT and radiotherapy vs standard resection and radiotherapy **Intervention** PDT: Patients were given 2 mg/kg Photofrin intravenously 48 h before surgery, and 20 mg/kg ALA orally 3 h before surgery. After removal of bulk of tumour violet-blue light (375–440 nm) with a 440-nm observation filter was used to illuminate the cavity with fluorescence detected by a high-quality photodiagnosis camera, and detected tumour was removed until no further fluorescence was detected. A laser-based (405 nm) protoporphyrin-IX spectroscopy detection system was used to detect any remaining tumour cells at the margins, which were removed. A size-10 balloon catheter was inflated to fit the cavity with 0.8% intralipid solution. After the patient awoke from surgery the 1st PDT treatment, using 630-nm diode laser (600 mW), was given in theatre recovery at 100 J/cm^2; more PDT was given at 72, 96, 120 and 144 hr. Patients also received standard radiotherapy. Advice was given on sun protection measures **Comparator** Tumour removal using the same neuronavigation and surgical microscope as the PDT group. Patients also received standard radiotherapy	**Mortality** Mean survival in the PDT group was 52.8 wk vs 24.2 wk in the surgery group ($p < 0.001$) **Morbidity** There was no residual tumour on discharge scan in 10/13 PDT patients vs 4/14 surgery patients. Mean time to tumour progression was 8.6 mth in the PDT group vs 4.8 mth in the surgery group ($p < 0.01$) **QoL and return to normal activity** The Karnofsky score at 6 mth had improved from 70 (at baseline) to 80 in the PDT group, although the authors reported an improvement of 20 points. The scores remained the same for the surgery group (at 70) **AEs** Three patients had deep vein thrombosis, two of which were in the PDT group. No infections or seizures occurred **Resource use** There was no difference between the groups in length of hospital stay (both had a mean stay of 7 d)	**Authors' conclusions** ALA and Photofrin fluorescence-guided resection with repetitive PDT offer a worthwhile survival advantage, without added risk, to patients with GBM **Brief study appraisal** The Karnofsky results were reported inconsistently within the paper, making interpretation difficult. It was unclear how many patients had actually been randomised and treated, as 14 patients with negative biopsy results were subsequently excluded from analyses. The analysed population does not therefore appear to reflect the population presenting clinically (patients with an MRI diagnosis). Although the study made use of blinding to assess outcomes, it was nevertheless unclear whether suitable methods had been used to randomise and allocate participants to treatments. No results were reported on possible photosensitisation effects. The authors did though acknowledge the need for a much larger study

GBM, glioblastoma multiforme; MRI, magnetic resonance imaging.

Study details	Population details	Treatment details	Results	Interpretation
Authors Krishnamurthy *et al.* (2000)[138] **Data source** Full published paper **Country** USA **Language** English **Study design** Non-RCT **No. of participants** Total: 18 Intervention: Six Comparator: Six 2nd Comparator: Six **No. of recruiting centres** One **Follow-up period and frequency** Days 1 and 2, at discharge from hospital, at 1, 4 and 6 wk, then at 3-mth intervals	**Treatment intention** Curative Palliative **Type(s) of cancer and histology** 12 glioblastoma, five anaplastic astrocytoma, one malignant ependymoma **Main eligibility criteria** Patients aged 18–75 yr, with supratentorial primary malignant brain tumours ≤ 5 cm in diameter, a Karnofsky rating ≥ 60, and who had recurrent or residual tumours were eligible. Patients had to have received radiation therapy > 3 mth prior to PDT treatment. Further eligibility criteria were reported **Patient characteristics** Age range: 32–70 yr Median Karnofsky score: 90 Tumour locations also reported. All patients had initial surgery, radiation therapy and chemotherapy before recurrence **Concomitant treatment** Steroid therapy if required	**Trial treatments** PDT 1500–3700 J vs PDT 3700–4400 J vs PDT 4400–5900 J **Intervention** PDT 1500–3700 J (group 1): Intravenous Photofrin at 2 mg/kg, followed 24 hr later by anaesthetic and CT or MRI scan which locates tumour using stereotactic arc system. Six optical diffusion tip fibres (1.6 mm) and central fibre inserted through drill holes into skull. Red light (630 nm) from an argon pumped-dye laser was delivered through optical fibres and beam splitters to individual diffusion tip fibres. Tumours were biopsied (and if no malignancy was found the patient was excluded from the study). Patients were advised about sunlight protection, and about avoiding direct sunlight and bright artificial light for 6 wk **Comparator** PDT 3700–4400 J (group 2): See above **2nd comparator** PDT 4400–5900 J (group 3): See above	**Mortality** Mean survival time was 314 d (sd = 106) in group 2 vs 238 d in group 3 (sd = 61). Group 1 not stated **Morbidity** 16 patients had recurrence after PDT (four in group 1, six in group 2 and six in group 3), and two did not. Time to tumour recurrence was a mean of 150 d in group 2 vs 131 d in group 3. Group 1 not stated **QoL and return to normal activity** Median Karnofsky rating changed from 90 (pre-PDT) to 85 (post PDT) **AEs** Five patients had postoperative permanent neurological defects (zero in group 1, two in group 2, and three in group 3) **Resource use** Not assessed	**Authors' conclusions** Increasing the light dose increases the odds of having permanent neurological deficit, but does not increase survival time, or time to tumour progression. There was no difference in recurrence with increasing light dose **Brief study appraisal** This non-randomised study appeared to have far too small a sample size to provide clinically meaningful results. Results were not always provided for all three groups

Appendix 21

Head and neck cancer data extraction

Study details	Population details	Treatment details	Results	Interpretation
Authors Li *et al.* (2006)[141] **Data source** Full published paper **Country** China **Language** English **Study design** RCT **No. of participants** Total: 30 Intervention: 15 Comparator: 15 **No. of recruiting centres** Not stated **Follow-up period and frequency** FU at 1, 3 and 6 mth	**Treatment intention** Not stated, appears palliative **Type(s) of cancer and histology** Nasopharyngeal carcinoma **Main eligibility criteria** Patients who had relapsed and who had failed radiotherapy **Patient characteristics** % Male: 80 Age range: 28–72 Mean age: 54 yr Cancer stage: All stage IV and had local relapse. All had prior (failed) radiotherapy; some also had prior chemotherapy, 6–12 mth before trial treatment **Concomitant treatment** Anti-vomiting treatment for chemotherapy group. Chinese herbs (unspecified)	**Trial treatments** PDT vs Chemotherapy (cisplatin and 5-FU) **Intervention** Intravenous Photofrin of 2 mg/kg. Local anaesthetic (lidocaine) before light (630 nm) at 200–300 J/cm from a diode laser through a cylindrical diffuser (1–5 cm) 48 hr after injection. Light was applied to one to three overlapping segments for 12 min per segment. Segments had at least a 0.5-cm margin beyond the lesion. After 48-hr necrotic tissue removed by biopsy forceps and newly exposed lesions were re-treated after cleaning. Cleaning was repeated when necessary. Patients asked to avoid sunlight for 4–6 wk after treatment. Maximum number of sessions was not stated **Comparator** Cisplatin 80 mg/m^2 and 5-FU 500 mg/m^2, both divided into five. Each cycle lasted 4 wk. Two cycles were given	**Mortality** Not assessed **Morbidity** Overall clinical response was statistically significantly better with PDT than chemotherapy ($p = 0.001$). No patients achieved CR. The PDT group had more patients with a significant response (i.e. 50% reduction for 1 mth, 12 vs 2). In those patients with nasal obstructions PDT produced more effective debulking ($p = 0.04$) (subgroup of 16 patients, 7/8 improved vs 2/8) **QoL and return to normal activity** PDT group had a statistically significant greater improvement in Karnofsky score ($p = 0.02$). PDT group increased from 45 to 70 vs chemotherapy group increased from 40 to 50 **AEs** All PDT related adverse effects and reactions were tolerable. Treatment to the laryngopharynx area resulted in slight pain and increased nasal cavity secretion – resolved in 3–5 d One case of severe laryngopharynx swelling and pain. Resolved with treatment 1 wk later, may be related to light exposure One case of photosensitivity dermatitis after accidental exposure to daylight. Resolved after treatment, 1 wk later One case of skin pigmentation, no treatment required	**Authors' conclusions** PDT is effective and safe for the treatment of advanced nasal pharyngeal cancer and the management of nasal obstruction **Brief study appraisal** This small pilot study provided no details on randomisation, blinding and other study quality parameters raising questions about the validity of the results. Treatment details were well described. It does not appear to have led on to a larger study, though the authors rightly stated that further investigation was needed

Study details	Population details	Treatment details	Results	Interpretation
Authors Loukatch *et al.* (1995)[142] **Data source** Abstract **Country** Ukraine **Language** English **Study design** Non-RCT **No. of participants** Total: 145 Intervention: 42 Comparator: 51 2nd Comparator: 52 **No. of recruiting centres** Not stated **Follow-up period and frequency** 3 yr	**Treatment intention** Curative **Type(s) of Cancer and Histology** Planocellular cancer of larynx **Main eligibility criteria** Not stated **Patient characteristics** Cancer stage: Stage Ib, 79; stage IIa, 66. All cancers were of middle localisation. No further characteristics were reported **Concomitant treatment** Not stated	**Trial treatments** Surgery/ intraoperative PDT vs Surgery/ intraoperative PDT without laser vs Surgery alone **Intervention** Cordectomy with local anaesthetic, followed by administration of 0.4% solution of methylene blue photosensitiser. A He-Ne laser of wavelength 633 nm emitting at 25–30 mW/cm^2 for 5 min was used. Further PDT parameters were not reported **Comparator** Cordectomy with local anaesthetic followed by laser only (same parameters as PDT group) **2nd comparator** Cordectomy with local anaesthetic only	**Morbidity** After 3 yr there was recurrence in one patient (2%) and no cases of metastasis in the PDT group, four cases of recurrence (8%) in the laser group and one case of metastasis, and five cases of recurrence (10%) and two cases of metastasis in the Surgery-alone group **QoL and return to normal activity** Not assessed **AEs** PDT group: Some patients had oedema of laryngeal mucous membrane and one patient had a small haemorrhage. Surgery-alone group: One patient had a small haemorrhage. Both haemorrhages were managed by conservative treatment	**Authors' conclusions** Intraoperative PDT in patients with stages I and II laryngeal cancer could be effective for preventing recurrence and metastasis of tumours **Brief study appraisal** This study used comparator treatments such that the results offer little insight to how PDT compares to other treatments adjunctive to surgery. The study also examined few outcomes and there was sparse reporting of methods, patient characteristics and results

Study details	Population details	Treatment details	Results	Interpretation
Authors Loukatch *et al.* (1996)[143] **Data source** Abstract **Country** Ukraine **Language** English **Study design** Non-RCT **No. of participants** Total: 49 Intervention: 19 Comparator: 15 2nd Comparator: 15 **No. of recruiting centres** Not stated **Follow-up period and frequency** 3 yr	**Treatment intention** Curative **Type(s) of cancer and histology** SCC in laryngeal part of pharynx **Main eligibility criteria** Not stated **Patient characteristics** Cancer stage: Stage II, 25; stages III and IV, 24 No further characteristics were reported **Concomitant treatment** Pharyngotomy for stage II patients and hemilaryngopharyngotomy for stage III–IV patients with general anaesthetic. Postoperative cobalt therapy (45-Gy dose). Neck dissection operation for patients developing metastases	**Trial treatments** PDT vs PDT with Laser only vs PDT with Photosensitiser only **Intervention** PDT with methylene blue (injected locally) as photosensitiser, followed by 633-nm light for 5 min from a He-Ne laser at 25–30 mW/cm^2. Further PDT parameters were not reported **Comparator** As for PDT group but without photosensitiser **2nd comparator** As for PDT group but without laser	**Mortality** *2-yr survival* PDT group, 100% (stage II), 89% (stages III and IV); Laser-only group: 88% (stage II), 86% (stages III and IV); Photosensitiser-only group: 71% (stage II), 75% (stages III and IV) *3-yr survival* PDT group, 100% (stage II), 67% (stages III and IV); Laser-only group: 43% (stages III and IV); Photosensitiser-only group: 38% (stages III and IV). Stage II results not available for last two groups **Morbidity** After 1 year, none of the stage II patients had recurrence or metastasis. For stage III and stage IV patients, there was recurrence in one patient (11%) in the PDT group, two patients (29%) in the Laser-only group and two patients (25%) in the Photosensitiser-only group After 2 yr, in the PDT group: recurrence in 10% (stage II) and 11% (stages III and IV); in the Laser-only group: recurrence in 25% (stage II), and 43% (stages III and IV); in the Photosensitiser-only group: recurrence in 43% (stage II), and 50% (stages III and IV) During the 3-yr period there were regional metastases in 0% of PDT group (stage II), 11% in PDT (stages III and IV), 13% of Laser-only group (stage II), 14% Laser-only (stages III and IV), 14% Photosensitiser-only (stage II), 25% Photosensitiser-only (stages III and IV) **QoL and return to normal activity** Not assessed **AEs** No complications postoperatively, except some patients had minor oedema of the pharyngeal mucous membrane (resolved within 5 d)	**Authors' conclusions** PDT appears effective in treating tumours of the pharynx, but larger studies with longer FU are needed **Brief study appraisal** This study used comparator treatments such that the results offer little insight to how PDT compares with other treatments adjunctive to surgery. There was sparse reporting of methods and patient characteristics, and results were sometimes incomplete

Study details	Population details	Treatment details	Results	Interpretation
Authors Vakulovskaya (2007)[144] Linked publications[213] **Data source** Abstract **Country** Russia **Language** English **Study design** Non-RCT **No. of participants** Total: 52 Intervention: Not stated Comparator: Not stated **No. of recruiting centres** Not stated **Follow-up period and frequency** Not stated (although survival monitored up to 3 yr)	**Treatment intention** Not stated **Type(s) of cancer and histology** Oral cancer (SCC) **Main eligibility criteria** Not stated **Patient characteristics** Patients had tumours in the oral cavity, oropharynx or lower lip. Further patient characteristics were not reported **Concomitant treatment** Not stated	**Trial treatments** PDT with Photosense vs PDT with Radachlorin **Intervention** Intravenous Photosense (0.4–0.8 mg/kg) with semiconductive lasers (Milon 660, Biospec 672) at a total light dose of 400–600 J/cm^2. Further PDT parameters were not reported **Comparator** Intravenous Radachlorin (1.2–2.4 mg/kg) with semiconductive lasers (Milon 660, Biospec 672) at a total light dose of 200–300 J/cm^2. Further PDT parameters were not reported	**Mortality** Not broken down by treatment group **Morbidity** For Photosense a CR was seen in 57% of patients and a PR in 38%. For Radachlorin a CR was seen in 20% and a PR in 50% **QoL and return to normal activity** Not assessed **AEs** Main side effect with Photosense was increased skin sensitivity to direct sunlight, with Radachlorin skin sensitivity is short term. No further details were given	**Authors' conclusions** Our experience showed pronounced efficacy of PDT with high functional and cosmetic effects for oral cancer of different localisations **Brief study appraisal** Minimal reporting of both methods and results means little can be deduced from this conference abstract

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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