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Photodynamic therapy for skin carcinomas: A systematic review and meta-analysis

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Background: Photodynamic therapy (PDT) is increasingly used for the treatment of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). However, it is unknown whether photodynamic therapy is more effective than other commonly used treatment modalities for these cancers.

Purpose: The aim of this study was to determine the relative efficacy and safety of PDT compared with placebo or other interventions for the treatment of skin carcinomas.

Methods: Searches were performed in PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials databases. We included randomized controlled trials comparing the PDT with other interventions in adults skin BCC or SCC that reported on lesion response, recurrence, cosmetic appearance, or safety outcomes.

Results: Seventeen unique randomized controlled trials, representing 22 study arms from 21 publications were included. The included trials included 2,166 participants, comparing methyl aminolevulinic (MAL) PDT (six studies) or aminolevulinic acid (ALA) PDT (two studies). Comparators included placebo, surgery, hexaminolevulinic (HAL) PDT, erbium: yttrium-aluminum-garnet ablative factional laser (YAG-AFL) PDT, fluorouracil, and imiquimod. There were few studies available for each comparison. Mantel-Haenszel fixed effects risk ratios were calculated for response, recurrence, cosmetic outcomes, and adverse events. MAL-PDT had similar response rates to surgery, ALA-PDT, fluorouracil and imiquimod at 3- and 12 months post-intervention. The rate of recurrence was similar, showing few differences at 12 months, but at later time points (24–60 months), fewer lesions recurred with surgery and imiquimod than with PDT. PDT also caused more adverse events and pain than other interventions. However, PDT treatment was more likely to receive a "good" or "excellent" rating for cosmetic appearance than surgery or cryotherapy.

Conclusion: This systematic review and meta-analysis demonstrates that the choice of treatment modality for BCC or SCC is best chosen in the context of the location and size of the lesion, the socioeconomic circumstances of the patient, as well as the patient's preferences. We call for more high quality studies to be done, in order to enable more reliable interpretations of the data.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=368626, identifier CRD42022368626.

KEYWORDS

basal cell carcinoma, squamous cell carcinoma, photodynamic therapy, skin cancer, systematic review, meta-analysis

Introduction

Non-melanoma skin cancers are the most commonly occurring cancer in Caucasian populations, and the incidence of both basal and squamous cell carcinomas in Europe have been increasing (1). From 1969 to 2000, 61% of the deaths associated with non-melanoma skin cancer occurred as a result of primary tumors arising on non-genital skin, and the age-adjusted mortality rate among men and women with non-genital non-melanoma skin cancer was 0.69 and 0.30 deaths per 105 at-risk individuals per year, respectively (2). For genital non-melanoma skin cancers, the rate was 0.30 per 105 at-risk individuals per year for men and 0.54 per 105 at-risk individuals per year for women (2).

The conventional treatments for non-melanoma skin cancers include surgical procedures, radiation, cryotherapy, fluorouracil, and imiquimod. Although surgery is the most common treatment for basal and squamous cell carcinomas, other less invasive methods such as fluorouracil or cryotherapy are sometimes used. Radiation may be considered as treatment for patients in whom surgery is contraindicated (3). Imiquimod has commonly been used in the treatment of various forms of basal cell carcinoma, such as nodular basal cell carcinoma and sclerodermiform basal cell carcinoma, and for various forms of squamous cell carcinoma, such as Bowen's disease and keratoacanthoma (4, 5). Although the current treatments are effective to varying degrees, they tend to lack specificity and often do not target the tumor itself or the environment in which it exists (6). They are also associated with a high incidence of adverse effects and yield undesirable cosmetic results (7, 8). As such, alternative treatments options for patients with these conditions are needed.

Photodynamic therapy represents a safe alternative for treatment of these conditions. Photodynamic therapy uses a source of visible light to activate a photosensitizing agent (commonly aminolaevulinic acid or methyl aminolevulinic acid) applied on the skin, which releases reactive oxygen species that destroy the lesions (9). The safety and efficacy profile of photodynamic therapy in treating basal cell carcinoma and squamous cell carcinoma is well known (5). However, the relative efficacy of different modes of treatment for basal cell or squamous cell carcinomas is unknown. As such, we undertook a systematic review and meta-analysis of photodynamic therapies compared with each other, placebo, surgery, cryotherapy, imiquimod, or fluorouracil.

Materials and methods

This systematic review and meta-analysis was performed according to the guidelines given in the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) (10). The protocol for this review was registered in the International Prospective Register of Systematic Review (PROSPERO) under the registration number CRD42022368626.

Search strategy

We searched PubMed, Web of Science, Embase, and the Cochrane Library from inception to October 10, 2022. We had no limitations on the date of publication or language. The search strategy used for PubMed is given in **Supplementary Table 1** and was altered for use in the other databases. The citations of included studies were searched manually to identify studies that were not returned using the search strategies.

Inclusion/exclusion criteria

Studies were included if they met the follow criteria: randomized, controlled trial (RCT) in patients with basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), who were treated with any form of photodynamic therapy (PDT), compared with another form of PDT, other therapies or placebo, followed for a period of at least 3 months in an outpatient setting. At least one of the following outcomes must have been reported: treatment success, cosmetic acceptability, pain, or adverse events.

Studies were excluded if the trial was not an RCT, the skin cancers were not BCC or SCC, if the treatments did not include PDT, if the treatment duration was too short, or if none of the required outcomes was reported. Comparisons of different protocols within a single technology (e.g., cycle number, wavelength, light source comparisons within MAL-PDT) were excluded, as were trials of recurrent cancers, and protocols that involved substantial debulking of the tumors prior to treatment. Trials adding PDT to other treatments were also excluded.

Inclusion and exclusion at the title and abstract level were carried out by two authors (YY and YZ) independently. In the case of disagreements between two authors, the article was discussed between the authors and a consensus decision was taken. After inclusion of potentially relevant abstracts, full texts of the articles were obtained and subjected to the inclusion and exclusion criteria independently by two authors (YY and YZ) using. Disagreements were resolved by consensus. Data collection was performed by one author (YY) using electronic data collection forms and extracted data was then cross checked with the articles by a second author (KM) to ensure the accuracy of the information.

Quality assessment

The risk of bias of the included studies was carried out using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (11). The risk of bias was assessed over seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting bias, and other bias. The quality assessment was carried out by YY and checked by KM. Conflicts were resolved by consensus.

Data extraction and data synthesis

The study characteristics and outcome data were extracted into a pre-designed Excel spreadsheet by YZ and checked by KM. Where data were reported by both the clinician and the patient (e.g., cosmetic appearance), we extracted the patient-reported data. Response rates were calculated at the end of the treatment period, regardless of the number of treatments each group received. If data were available at the patient level, we extracted this; if data were only available at the lesion level, we extracted lesion-level data.



All outcomes were reported as dichotomous data; we therefore calculated Mantel-Haenszel risk ratios with 95% confidence intervals using a random effects model. A random effects model was chosen as we expected the heterogeneity between studies to arise mostly by factors other than chance, such as differences in carcinoma size, location, or depth, treatment protocols, and differences in the populations. Where a study reported on more than two arms and both were used in a single analysis, the arms were separated into subgroups, and the overall meta-analyzed result was removed from the analysis.

Subgroup analysis was used to differentiate between the location of the lesion. Meta-regression was undertaken using type of carcinoma (SCC or BCC) and comparators as covariates. Metaregression was carried out using OpenMetaAnalyst (12) on outcomes that had nine or more study arms comparing any type of PDT with a non-PDT comparator.

Results

Studies

The database searches identified 621 citations, of which 123 were duplicates (**Figure 1**). The remaining 498 citations were subjected to inclusion and exclusion at the abstract level. This resulted in the exclusion of 412 abstracts. The remaining full texts for the remaining 86 abstracts were sourced and subjected to the inclusion and exclusion criteria. Of these, 21 publications reporting on 22 study arms from 17 individual RCTs were included (13–33).

The included studies involved 2,166 participants (Table 1). Twelve trials were in people with basal cell carcinomas, and five trials involved people with squamous cell carcinomas. Most studies used methyl aminolevulinic acid (MAL) as the photosensitizing agent in PDT. These studies compared MAL-PDT with aminolevulinic acid

TABLE 1 Characteristics of included studies.

| Study ID | Authors | Clinical trial identifier | Carcinoma type | PDT-n | Control-n | PDT type | Control | Follow up times | Average/Median age | % female |
|------------------------|--------------------|------------------------------|-------------------|-------|-----------|----------|--------------|--------------------|-----------------------|----------|
| EudraCT-2013-003241-42 | Morton 2018 | EudraCT-2013-003241-42 | BCC | 110 | 121 | MAL-PDT | ALA-PDT | 3 m, 12 m | 67 | 43.3 |
| ISRCTN 79701845 | Arits 2013/1 | ISRCTN 79701845 | BCC | 202 | 198 | MAL-PDT | Imiquimod | 3 m, 12 m | 63 | 50.5 |
| ISRCTN 79701845 | Arits 2013/2 | ISRCTN 79701845 | BCC | 202 | 201 | MAL-PDT | Fluorouracil | 3 m, 12 m | 63 | 48.0 |
| ISRCTN 79701845 | Jansen 2018 | ISRCTN 79701845 | BCC | 153 | 157 | MAL-PDT | Fluorouracil | 5 y | 63 | 48.0 |
| ISRCTN 79701845 | Jansen 2018 | ISRCTN 79701845 | BCC | 153 | 148 | MAL-PDT | Imiquimod | 5 y | 63 | 50.5 |
| ISRCTN 79701845 | Roozeboom 2014 | ISRCTN 79701845 | BCC | 202 | 198 | MAL-PDT | Imiquimod | 12 m | 63 | 50.6 |
| ISRCTN 79701845 | Roozeboom 2016/1 | ISRCTN 79701845 | BCC | 202 | 198 | MAL-PDT | Imiquimod | 36 m | 63 | 50.6 |
| ISRCTN 79701845 | Roozeboom 2016/2 | ISRCTN 79701845 | BCC | 202 | 201 | MAL-PDT | Fluorouracil | 36 m | 63 | 48.0 |
| Basset-Seguin 2008 | Basset-Seguin 2008 | N/A | BCC | 66 | 58 | MAL-PDT | Cryotherapy | 5 y | | |
| Berroeta 2007 | Berroeta 2007 | N/A | BCC | 21 | 19 | ALA-PDT | Surgery | 3 m, 6 m, 12 m | 72 | 38.7 |
| Foley 2009 | Foley 2009 | N/A | BCC | 66 | 65 | MAL-PDT | Placebo | 3 m | 66 | 24.4 |
| Ko 2013 | Ko 2013 | N/A | SCC | 19 | 19 | MAL-PDT | YAG-AFL-PDT | 3 m, 12 m | 52.4 | 39 |
| Morton 1996 | Morton 1996 | N/A | SCC | 20 | 20 | ALA-PDT | Cryotherapy | 3 m, 12 m | 76 | 84.0 |
| Morton 2006/1 | Morton 2006/1 | N/A | SCC | 96 | 17 | MAL-PDT | Placebo | 3 m, 12 m | 72 | 62.8 |
| Morton 2006/2 | Morton 2006/2 | N/A | SCC | 96 | 82 | MAL-PDT | Cryotherapy | 3 m, 12 m | 73 | 60.7 |
| Morton 2006/3 | Morton 2006/3 | N/A | SCC | 96 | 30 | MAL-PDT | Fluorouracil | 3 m, 12 m | 72 | 62.7 |
| Mosterd 2008 | Mosterd 2008 | N/A | BCC | 83 | 88 | ALA-PDT | Surgery | 3 m, 36 m | 65 | 49.7 |
| Rhodes 2004 | Rhodes 2004 | N/A | BCC | 52 | 49 | MAL-PDT | Surgery | 12 m, 24 m | 68 | 39.6 |
| Rhodes 2004 FU | Rhodes 2007 | N/A | BCC | 52 | 49 | MAL-PDT | Surgery | 5 y | 68 | 39.6 |
| Salim 2003 | Salim 2003 | N/A | SCC | 20 | 20 | ALA-PDT | Fluorouracil | 3 m, 12 m | 76 | 80.0 |
| Szeimie 2008 | Szeimie 2008 | N/A | BCC | 100 | 96 | MAL-PDT | Surgery | 3 m, 12 m | 64 | 33.7 |
| Wang 2001 | Wang 2001 | N/A | BCC | 47 | 41 | ALA-PDT | Cryotherapy | 12 m | NR | 50.0 |
| NCT01491711 | Kessels 2017 | NCT01491711 | BCC | 80 | 82 | MAL-PDT | ALA-PDT | 3 m, 12 m | 65 | 53.7 |
| NCT02018679 | Choi 2016 | NCT02018679 | BCC | 19 | 20 | MAL-PDT | YAG-AFL-PDT | 3 m, 12 m | 65 | 45.9 |
| NCT02367547 | Salmivuori 2020 | NCT02367547 | BCC | 31 | 33 | MAL-PDT | ALA-PDT | 3 m | 72 | 28.3 |
| NCT02367547 | Salmivuori 2020 | NCT02367547 | BCC | 31 | 31 | MAL-PDT | HAL-PDT | 3 m | 72 | 43.1 |
| NCT02666534 | Choi 2017 | NCT02666534 | SCC | 24 | 21 | MAL-PDT | YAG-AFL-PDT | 3 m, 12 m, 24 m | 76 | 62.2 |

ALA-PDT, aminolevulinic acid photodynamic therapy; BCC, basal cell carcinoma; HAL-PDT, hexaminolevulinic acid photodynamic therapy; m, months; MAL-PDT, methyl aminolevulinic acid photodynamic therapy; N/A, not applicable; NR, not reported; PDT, photodynamic therapy; y, years; YAG-AFL-PDT, erbium: yttrium-aluminum-garnet ablative factional laser photodynamic therapy.

| Study or Subgroup 1.1.1 MAL-PDT vs placebo | Events Tota | al Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% CI |
|---|------------------------------------|----------------------|-----------------------|---------------------------------|---|---|
| Foley 2009 Morton 2006 Subtotal (95% CI) Total events | 55 7 103 11 18 158 | 1 4 | 75 19 94 | 81.5% 18.5% 100.0% | 2.75 [1.84, 4.10] 4.41 [1.84, 10.54] 3.00 [2.05, 4.39] | |
| Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 5. | | |).31); I | 2 = 4% | | |
| 1.1.2 MAL-PDT vs surgery Szeimie 2008 Subtotal (95% CI) Fotal events Heterogeneity: Not applicabli | | 8 117 | | 100.0% 100.0% | 0.93 [0.88, 0.98] 0.93 [0.88, 0.98] | • |
| Fest for overall effect: Z = 2. 1.1.3 MAL-PDT vs fluoroura SRCTN 79701845 | | | 198 | 62.5% | 0.96 [0.88, 1.04] | |
| Morton 2006 Subtotal (95% CI) Fotal events | 103 11 30 268 | 1 24 7 198 | 29 227 | 37.5% 100.0% | 1.12 [0.94, 1.33] 1.02 [0.88, 1.18] | ▲ |
| Heterogeneity: Tau ² = 0.01; Fest for overall effect: Z = 0. | | r = 1 (P = 0) |).11); r | - = 62% | | |
| L .1.4 MAL-PDT vs imiquim SRCTN 79701845 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable | 165 19 19 165 e | | | 100.0% 100.0% | 0.94 [0.87, 1.01] 0.94 [0.87, 1.01] | • |
| est for overall effect: Z = 1. | | | | | | |
| Basset-Seguin 2008 Morton 2006 Subtotal (95% CI) Fotal events | 46 6 103 11 17 149 | 1 73 | 58 85 143 | | 2.53 [1.62, 3.95] 1.08 [0.98, 1.19] 1.63 [0.53, 4.99] | |
| Heterogeneity: Tau ² = 0.63; Fest for overall effect: Z = 0. | Chi ² = 24.08, | df = 1 (P < | 0.000 | 01); $I^2 = 90$ | 6% | |
| 1.1.6 MAL-PDT vs YAG-AFI <o 2013<="" td=""><td></td><td>9 17</td><td>19</td><td>56.9%</td><td>0.76 [0.54, 1.08]</td><td></td></o> | | 9 17 | 19 | 56.9% | 0.76 [0.54, 1.08] | |
| NCT02018679 NCT02666534 Subtotal (95% CI) Total events | 8 1 9 1 | 9 15 9 16 7 48 | 20 21 | 19.5% | 0.56 [0.31, 1.01] 0.62 [0.37, 1.06] 0.69 [0.53, 0.89] | |
| Heterogeneity: $Tau^2 = 0.00$; Test for overall effect: $Z = 2$. | $Chi^2 = 1.09, d^2$ | f = 2 (P = 0) |).58); I | ² = 0% | | |
| 1.7 MAL-PDT vs HAL-PD ICT02367547 Jubtotal (95% CI) | 29 3 | 1 27 1 | | 100.0% 100.0% | 1.07 [0.91, 1.27] 1.07 [0.91, 1.27] | |
| iotal events leterogeneity: Not applicable est for overall effect: Z = 0. | 29 e | 27 | 51 | 100.070 | 1.07 [0.51, 1.27] | |
| L.1.8 MAL-PDT vs ALA-PDT EudraCT-2013-003241-42 | r 101 11 | 0 113 | 121 | 40.8% | 0.98 [0.91, 1.06] | |
| NCT01491711 NCT02367547 Subtotal (95% CI) | 75 7 | 9 76 1 30 | 79 33 | 48.4% | 0.99 [0.92, 1.06] 1.03 [0.89, 1.19] 0.99 [0.94, 1.04] | - |
| Fotal events Heterogeneity: Tau ² = 0.00; Fest for overall effect: Z = 0. | | 219 f = 2 (P = 0 | | | | |
| 1.1.9 ALA-PDT vs cryothera Morton 1996 | 20 2 | 0 20 | | 100.0% | 1.00 [0.91, 1.10] | |
| Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 0. | 20 e | 0 20 | 20 | 100.0% | 1.00 [0.91, 1.10] | Ī |
| 1.1.10 ALA-PDT vs fluorou Salim 2003 | 29 3 | 3 22 | | 100.0% | 1.32 [1.00, 1.73] | |
| Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fort for overall offect: 7 – 1 | 29 e | 3 22 | 33 | 100.0% | 1.32 [1.00, 1.73] | |
| Test for overall effect: Z = 1. 1.1.11 ALA-PDT vs surgery | | 2 | 05 | 100.00 | | _ |
| Mosterd 2008 Subtotal (95% CI) Total events | 8 78 | 3 68 3 68 | | 100.0% 100.0% | 1.22 [1.07, 1.38] 1.22 [1.07, 1.38] | • |
| Heterogeneity: Not applicable Test for overall effect: Z = 3. | | | | | L | |
| Fest for subgroup difference | s: Chi ² = 64.24 | 1, df = 10 (| (P < 0.0 | 00001), I ² : | = 84.4% | 0.2 0.5 1 2 5 10 Favours control Favours PDT |

| Study or Subgroup | PDT Events | | Contre | | Weight | Risk Ratio M-H, Random, 95% Cl | Risk Ratio M–H, Random, 95% Cl |
|---|----------------------------|------------------|-----------|----------------------------------|-----------------|-----------------------------------|---|
| 1.2.1 MAL-PDT vs surgery | Lvents | TULAI | Lvents | Totai | weight | M-II, Kalidolli, 55% Cl | |
| Rhodes 2004 | 44 | 53 | 50 | 52 | 100.0% | 0.86 [0.76, 0.99] | - |
| Subtotal (95% CI) | | 53 | 50 | | 100.0% | 0.86 [0.76, 0.99] | → |
| Total events | 44 | | 50 | | | | |
| Heterogeneity: Not applicable | e | | | | | | |
| Test for overall effect: $Z = 2$. | 16 (P = 0.0) | 03) | | | | | |
| 1.2.2 MAL-PDT vs fluoroura | acil | | | | | | |
| ISRCTN 79701845 | 135 | 156 | 154 | 169 | 100.0% | 0.95 [0.88, 1.03] | |
| Subtotal (95% CI) | | 156 | | | 100.0% | 0.95 [0.88, 1.03] | • |
| Total events | 135 | | 154 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: $Z = 1$. | 30 (P = 0.1) | 19) | | | | | |
| 1.2.3 MAL-PDT vs imiquim | od | | | | | | |
| ISRCTN 79701845 | 135 | 156 | 153 | 165 | 100.0% | 0.93 [0.87, 1.01] | |
| Subtotal (95% CI) | | 156 | | | 100.0% | 0.93 [0.87, 1.01] | • |
| Total events | 135 | | 153 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: $Z = 1$. | 80 (P = 0.0 | 07) | | | | | |
| 1.2.4 MAL-PDT vs YAG-AFL | L-PDT | | | | | | |
| Ko 2013 | 9 | 19 | 16 | 19 | 50.8% | | |
| NCT02018679 | 4 | 19 | 14 | 20 | 27.5% | 0.30 [0.12, 0.75] — | |
| NCT02666534 | 3 | 19 | 14 | 21 | 21.8% | 0.24 [0.08, 0.70] | |
| Subtotal (95% CI) | 1.0 | 57 | | 60 | 100.0% | 0.39 [0.22, 0.71] | |
| Total events Heterogeneity: Tau ² = 0.11; • | 16 Chi ² 2 2 | ر م ر | 2 (10 0 | 201.12 | 2.00/ | | |
| Test for overall effect: $Z = 3$. | | | 2(P = 0 | .20), 1 | = 39% | | |
| | | 50L) | | | | | |
| 1.2.5 MAL-PDT vs ALA-PD | | | | | | | \bot |
| EudraCT-2013-003241-42 | 86 | 94 | 98 | 107 | 53.8% | 1.00 [0.92, 1.09] | |
| NCT01491711 Subtotal (95% CI) | 65 | 74 168 | 72 | 75 | 46.2% 100.0% | 0.91 [0.83, 1.01] | |
| Total events | 151 | 100 | 170 | 102 | 100.0% | 0.96 [0.88, 1.05] | • |
| Heterogeneity: Tau ² = 0.00; | | 0. df = | | .18) [.] 1 ² | = 45% | | |
| Test for overall effect: $Z = 0$. | | | 100 | | 13/0 | | |
| 1.2.6 ALA-PDT vs cryothera | nv | | | | | | |
| Wang 2001 | ару 33 | 44 | 33 | 39 | 100.0% | 0.89 [0.71, 1.10] | - |
| Subtotal (95% CI) | 20 | 44 | | | 100.0% | 0.89 [0.71, 1.10] | — |
| Total events | 33 | | 33 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: $Z = 1$. | 09 (P = 0.2) | 28) | | | | | |
| 1.2.7 ALA-PDT vs surgery | | | | | | | |
| Berroeta 2007 | 13 | 21 | 15 | 19 | 100.0% | 0.78 [0.52, 1.18] | |
| Subtotal (95% CI) | | 21 | | | 100.0% | 0.78 [0.52, 1.18] | |
| Total events | 13 | | 15 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: $Z = 1$. | 17 (P = 0.2) | 24) | | | | | |
| | | | | | | <u> </u> | |
| | | | | | | 0.1 | 0.2 0.5 1 2 5 10 Favours control Favours PDT |
| Test for subgroup difference | s: $Chi^2 = 1$ | 1.11, 0 | df = 6 (P | = 0.09 |), $1^2 = 46$ | 5.0% | |
| | | | | | | | |
| | | | | | | | |

(ALA) PDT, erbium: yttrium-aluminum-garnet ablative fractional laser-assisted (YAG-AFL) PDT, hexaminolevulinic (HAL) PDT, surgical excision, cryotherapy, imiquimod, fluorouracil, and placebo. Five studies compared ALA-PDT with surgical excision, cryotherapy, and fluorouracil. The mean age of the participants was 67.3 years, and on average 49.7% of participants were female.

Study quality as determined by the Cochrane Collaboration's tool for the assessment of risk of bias in interventions studies was generally good (Supplementary Figure 1). However, due to the nature of the interventions, it was often impossible to blind the participants to their intervention. To compensate for this, the outcome assessors were frequently blinded to the allocation of the patients they assessed. Five of the clinical trials were funded by companies with a financial interest in the outcomes; these trials

usually had at least one company employee on the author list of the publication(s).

Response

All clinical trials reported on response at 3 months post-treatment (**Figure 2**). MAL-PDT was significantly superior to placebo (two studies; RR: 3.00 (95% CI: 2.05 to 4.39); P < 0.00001), but statistically less effective than surgery (one study) and YAG-AFL-PDT (three studies). No other comparisons were statistically significant.

At 12 months post-treatment, similar results were observed (Figure 3). MAL-PDT was less effective than surgery (one study) and YAG-AFL-PDT (three studies). At 24–60 months post-intervention (Supplementary Figure 2), MAL-PDT was statistically inferior to

| 2.1.1 MAL-PDT vs placebo Subtail (95% C) 103 2 4 100.0% 0.29 [0.10, 0.85] Subtail (95% C) 103 2 4 100.0% 0.29 [0.10, 0.85] Here reprintly the uplicable Total events 15 2 1.2.2 MAL-PDT vs iniquined ISCITN 770145 12 156 7 165 100.0% 1.31 [0.73, 4.49] Subtail (95% C) 12 156 7 165 100.0% 1.31 [0.73, 4.49] L3 MAL-PDT vs iniquined ISCITN 770145 12 12 156 10 169 60.8% 1.30 [0.58, 2.92] Morino 2006 15 103 4 24 39 2% 0.37 [0.32, 2.40] Subtail (95% C) 27 7 14 Here repending lefter: $Z = 1.29 (P = 0.20)$ 2.1.3 MAL-PDT vs fluoromatil ISCITN 770145 112 156 10 169 60.8% 1.30 [0.58, 2.92] Morino 2006 15 103 4 24 39 2% 0.37 [0.32, 2.40] Subtail (95% C) 27 7 14 Here repending Tat' = 0.00, Ch' = 0.36, df = 1 (P = 0.55); t' = 0% Test for overall effect: $Z = 0.39 (P = 0.74)$ 2.1.4 MAL-PDT vs chorematel ISCITN 770145 112 103 15 73 100.0% 0.71 [0.37, 1.36] Subtail (95% C) 7 53 1 02 100.0% 6.87 [0.88, 53.89] Morino 2006 15 103 15 73 100.0% 0.71 [0.37, 1.36] Subtail (95% C) 7 53 1 52 100.0% 6.87 [0.88, 53.89] Here repending Nat applicable Test for overall effect: $Z = 1.04 (P = 0.30)$ 2.1.5 MAL-PDT vs the control is 1.38 [1.53 [1.55 [1.53 [1.55 [1.53 [1.55 [1.53 [1.55 [| | PDT vents Total | Conti Events | | Weight | Risk Ratio M-H, Random, 95% Cl | Risk Ratio M-H, Random, 95% Cl |
|--|--|--------------------|-----------------|----------|--------------------|-----------------------------------|-----------------------------------|
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| Test for overall effect: $2 = 2.3 \ (P = 0.03)$ 2.1.2 MAL-PDT vs imiguined ISRCH7 9701454 Total events Total events Total events 1.2 7 2.1.3 MAL-PDT vs Cryptherap Morton 2006 1.5 103 1.2 156 1.0 169 1.3 10.058, 2.921 Morton 2006 1.3 10 1058, 2.921 Morton 2006 1.5 103 1.5 73 100.056, 0.71 [0.37, 1.36] 1.5 Mol-PDT vs cryptherapy Morton 2006 1.5 103 1.5 100.056, 2.921 Morton 2006 1.5 103 1.5 100.056, 2.921 Morton 2006 1.5 103 1.5 100.056, 0.71 [0.37, 1.36] 1.5 Mol-PDT vs cryptherapy Morton 2006 1.5 103 1.5 100.056, 6.87 [0.88, 53.89] Morton 2004 1.5 10.056, 2.3 1.5 1.5 Heterogenetic, Not applicable Test for overall effect: $2 = 1.83 \ (P = 0.07)$ 2.1.6 MAL-PDT vs urgety Heterogenetic, Not applicable Total events 1.3 1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.1 1.5 1.5 8.6 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 | | 15 | 2 | | | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | (P = 0.03) | | | | | |
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| 2.1.3 MAL-PDT vs fluorouradi SRCTN 79701845 12 156 10 169 60.8% 1.30 [0.58, 2.92] Marton 2006 12 103 14 24 39.2% 0.67 [0.32, 2.40] Subtotal (95% Ct) 2 29 193 100.0% 1.11 [0.59, 2.99] Total events 27 14 Heterogeneity: Tau ² = 0.0; Ch ² = 0.36 df = 1 ($P = 0.55$); $l2 = 0$ % Test for overall effect: $Z = 0.3 (P = 0.74)$ 2.1.4 MAL-PDT vs cryotherapy Morton 2006 15 103 15 73 100.0% 0.71 [0.37, 1.36] Subtotal (95% Ct) 103 15 73 100.0% 0.71 [0.37, 1.36] Subtotal (95% Ct) 7 53 152 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Heterogeneity: Not applicable Test for overall effect: $Z = 1.04 (P = 0.30)$ 2.1.5 MAL-PDT vs surgery Rhodes 2004 77 53 1 52 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: $Z = 1.81 (P = 0.67)$ 2.1.6 MAL-PDT vs VAC-AFL-PDT Kot 2013 66 18 1 18 18.5% 6.00 [0.80, 44.94] NCT02066534 12 19 3 21 61.7% 4.42 [1.47, 13.31] Subtotal (95% Ct) 56 59 100.0% 5.66 [2.38, 13.46] Total events 29 5 Total events 17 12 Heterogeneity: Tau ² = 0.02 (Ch ² = 0.69) 17 5 8.3% 1.01 [0.41, 2.52] NCT0140171 20 9 240 - 42 (9 - 0.0001) 2.1.7 MAL-PDT vs (MAL-PDT Exit for overall effect: $Z = -0.86 (P = 0.39)$ 2.1.8 AL-PDT vs cryotherapy Morton 196 0 20 2 20 27.0% 0.20 [0.01, 3.92] Total events 17 12 Heterogeneity: Tau ² = 0.29; Ch ² = 1.93, df = 1 (P = 0.17); l ² = 48% Test for overall effect: $Z = -0.86 (P = 0.39)$ 2.1.8 ALA-PDT vs surgery Barcenta 2007 5 2.1 0 19 100.0% 10.00 [0.59, 169.63] Total events 5 1 1 8 8 Subtotal (95% Ct) 2 1 1 4 46 39 77.0% 1.53 [0.66, 3.98] Total events 5 0 Heterogeneity: Tau ² = 1.02; Ch ² = 1.81, df = 1 (P = 0.17); l ² = 45% Test for overall effect: $Z = -0.08 (P = 0.39)$ 2.1.8 ALA-PDT vs surgery Barcenta 2007 5 2.1 0 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Tau ² = 1.02; Ch ² = 1.81, df = 1 (P = 0.17); l ² = 45% Test for overall effect: $Z = -1.9 (P = 0.11)$ 2.1.0 ALA-PDT vs surgery Barcenta 2007 5 2.1 0 19 100.0% 10.00 [0.59, 169.63] | | | | | | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | Test for overall effect: $Z = 1.29$ (| (P = 0.20) | | | | | |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | | | | | | | |
| Subtoal (95% C) 259 193 100.0% 1.11 [0.59, 2.09] Heterogeneity: Tau ² = 0.0; Chi ² = 0.36 (F = 0.74) 2.1.4 MAL-POT vs (ryotherap) Morton 2006 15 103 15 73 100.0% 0.71 [0.37, 1.36] Otto 2006 15 103 73 100.0% 0.71 [0.37, 1.36] Total events 15 15 Heterogeneity: Not applicable Test for overall effect: Z = 1.04 (P = 0.30) 2.1.5 MAL-POT vs surgery Rhodes 2004 7 53 152 100.0% 6.87 [0.88, 53.89] Subtoal (95% Ct) 7 53 52 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: Z = 1.38 (P = 0.07) 2.1.6 MAL-POT vs YAG-AFL-POT Ko 2013 6 18 1 18 18.5% 6.00 [0.80, 44.94] NCT02018679 11 19 12 01 9.8% 11.58 [1.65, 81.26] NCT02018679 11 19 12 01 9.8% 11.58 [1.65, 81.26] NCT02018679 11 93 321 61.7% 4.42 [1.47, 13.31] Subtoal (95% Ct) 56 59 100.0% 5.66 [2.38, 13.46] Total events 29 5 Total events - 0.76, df = 2 (P = 0.69); P^2 0% Test for overall effect: Z = 3.92 ($P < 0.001$) 2.1.7 MAL-POT vs (AA-POT Heterogeneity: Tau ² = 0.03; Chi ² = 0.76, df = 2 ($P = 0.69$); P^2 0% Test for overall effect: Z = 3.92 ($P < 0.001$) 2.1.7 MAL-POT vs (AA-POT Heterogeneity: Tau ² = 0.03; Chi ² = 0.73, df = 1 ($P = 0.17$); P^2 48% Test for overall effect: Z = 0.36 ($P = 0.39$) 1.64 539 100.0% 1.60 [0.55, 4.66] 1.64 539 100.0% 0.20 [0.01, 3.92] Morton 1966 0 20 2 27.0% 0.20 [0.01, 3.92] Morton 1965 0 10 20 2 20 27.0% 0.20 [0.01, 3.92] Morton 1965 (D) 64 539 100.0% 0.32 [0.14, 5.50] Total events - 1.0 1 8 8 Heterogeneity: Tau ² = 0.03 ($P = 0.39$) 2.1.9 AL-POT vs surgery Berroeta 2007 5 2.1 0 19 100.0% 10.00 [0.59, 169.63] Subtoal (95% Ct) 2 1 19 100.0% 10.00 [0.59, 169.63] Total events - 5 0 Heterogeneity: Tau ² = 1.59 ($P = 0.11$) 2.1.9 AL-POT vs functural Subtoal (95% Ct) 2 1 3 10.00% 0.33 [0.07, 1.53] 3.0000 (0.59, 169.63] Total events - 5 0 Heterogeneity: Tau ² = 1.59 ($P = 0.11$) 2.1.9 AL-POT vs functural Subtoal (95% Ct) 2 3 3 6 33 100.0% 0.33 [0.07, 1.53] 3.0000 (0.59, 169.63] 3.0000 (0.59, 169.63] 3.0000 (0.59, 169.63] 3.0000 | | | | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.36, df = 1 (P = 0.55); l ² = 0% Test for overall effect: Z = 0.33 (P = 0.74) Morton 2006 15 103 73 100.0% 0.71 [0.37, 1.36] Total events 15 15 Heterogeneity: Not applicable Test for overall effect: Z = 1.04 (P = 0.30) 2.1.5 MAL-POT vs surgery Rhodes 2004 7 53 152 100.0% 6.87 [0.88, 53.89] Subtotal (95% C) 53 52 100.0% 6.87 [0.88, 53.89] Subtotal (95% C) 53 52 100.0% 6.87 [0.88, 53.89] Subtotal (95% C) 53 52 100.0% 5.66 [0.88, 53.89] Subtotal (95% C) 53 52 100.0% 5.67 [0.88, 53.89] Subtotal (95% C) 53 52 100.0% 5.66 [2.88, 153.82] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: Z = 1.83 (P = 0.07) 2.1.5 MAL-POT vs YACA-FL-POT Ko 2013 6 18 1 18 18.5% 6.00 [0.80, 44.94] NCT02066534 12 19 3 221 6.7% 4.42 [1.47, 13.31] Subtotal (95% C) 56 59 100.0% 5.66 [2.38, 13.46] Total events 20 5 Total events 20 5 Heterogeneity: Tau ² = 0.00; Chi ² = 0.76, df = 2 (P = 0.69); l ² = 0% Test for overall effect: Z = 3.92 (P < 0.000) 2.1.7 MAL-POT vs AAL-POT EadraCT-2013-003241-42 8 94 9 107 58.3% 1.01 [0.41, 2.52] NorT014 [9711 9 74 3 75 4.1.7% 3.04 [0.65, 13.91] Subtotal (95% C) 168 128 100.0% 1.60 [0.55, 4.66] Total events 17 12 Heterogeneity: Tau ² = 0.29; Chi ² = 1.93, df = 1 (P = 0.17); l ² = 48% Test for overall effect: Z = 0.80 (P = 0.39) 2.1.8 ALA-PDT vs surgery Morton 1996 0 220 2 20 27.0% 0.20 [0.01, 3.92] 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% C) 21 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% C) 21 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% C) 21 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% C) 2 33 6 33 100.0% 0.33 [0.07, 1.53] 3.100.0% 0.33 [0.07, 1.53] Subtotal (95% C) 2 33 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% C) 2 3 6 | | | | | | | |
| Test for overall effect: $Z = 0.33 (P = 0.74)$ 2.1.4 MAL-PDT vs cryotherapy Morton 2006 0.71 [0.37, 1.36] Subtotal (95% C) 15 103 15 73 100.0% 0.71 [0.37, 1.36] Total events 15 15 Heterogeneity: Not applicable Test for overall effect: $Z = 1.04 (P = 0.30)$ 2.1.5 MAL-PDT vs surgery Rhodes 2004 7 53 152 100.0% 6.87 [0.88, 53.89] Subtotal (95% C) 7 53 152 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: $Z = 1.33 (P = 0.07)$ 2.1.6 MAL-PDT vs YAG-AFL-PDT Ko 2013 6 18 1 18 18.5% 6.00 [0.80, 44.94] NCT02018679 11 19 1 20 19.8% 11.58 [1.65, 81.26] Total events 29 5 Total events 17 12 Heterogeneity: Tau' = 0.00; Ch' = 0.76; df = 2 (P = 0.69); l' = 0%. Test for overall effect: $Z = 1.392 (P < 0.0001)$ 2.1.7 MAL-PDT vs ALA-PDT Eutoractic 2 = 0.86 (P = 0.39) 2.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] Total events 17 12 Heterogeneity: Tau' = 0.29; Ch' = 1.93, df = 1 (P = 0.17); l' = 48%. Test for overall effect: $Z = -0.86 (P = 0.39)$ 2.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] 3.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] 3.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 0.27, 0% 0.20 [0.01, 3.92] 3.1.8 ALA-PDT vs argent Ext for overall effect: $Z = -0.86 (P = 0.39)$ 2.1.9 ALA-PDT vs argent Heterogeneity: Tau' = 1.02; Ch' = 1.81, df = 1 (P = 0.17); l' = 45% Test for overall effect: $Z = -0.80 (P = 0.39)$ 2.1.9 ALA-PDT vs fulcorural 3.1 00.0% 0.33 [0.07, 1.53] 3.1 00.0% 0 | | | | | | | |
| Morton 2006 15 103 15 73 100.0% 0.71 [0.37, 1.36] Total events 15 15 Total events 15 15 Total events 15 15 Total events 104 ($P = 0.30$) 2.1.5 MAL-PDT vs surgery Rhodes 2004 7 53 152 100.0% 6.87 [0.88, 53.89] Subtatal (95% C) 53 52 100.0% 6.87 [0.88, 53.89] Subtatal (95% C) 53 52 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: $Z = 1.83 (P = 0.07)$ 2.1.6 MAL-PDT vs VAC-AFL-PDT Kok 2013 6.87 [0.88, 51.86] NCT02618679 11 19 1 20 19.8% 11.58 [1.65, 81.26] NCT02666534 12 19 3 21 61.7% 4.42 [1.47, 13.31] Subtatal (95% C) 56 59 100.0% 5.66 [2.38, 13.46] Total events 29 5 Heterogeneity: Tau ² = 0.00; Ch ² = 0.76, df = 2 (P = 0.69); l ² = 0% Test for overall effect: $Z = 3.92 (P < 0.0001)$ 2.1.7 MAL-PDT vs ALA-PDT EudraCT-2013-003241-42 8 94 9 107 58.3% 1.01 [0.41, 2.52] Subtatal (95% C) 166 179 Total events 17 12 Heterogeneity: Tau ² = 0.29, Ch ² = 1.93, df = 1 (P = 0.15); l ² = 45% Test for overall effect: $Z = 0.86 (P = 0.39)$ 2.1.8 ALA-PDT vs curgetry Marga 2001 11 44 6 39 73.0% 1.63 [0.66, 3.98] 0.32 [0.14, 5.90] Notron 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] 1.3 ALA-PDT vs surgetry Barroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] 3.4 JONOM 0.33 [0.07, 1.53] 3.1 JONOM 1.1 JON | | | = 1 (P = 0 |).55); I | $^{2} = 0\%$ | | |
| Subtotal (95% C) 103 73 100.0% 0.71 [0.37, 1.36] Heterogeneity: Not applicable Test for overall effect: $Z = 1.04$ ($P = 0.30$) 2.15 MAL-POT vs surgery Rhodes 2004 7 53 152 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: $Z = 1.63$ ($P = 0.07$) 2.16 MAL-POT vs YAG-AFL-PDT Ko 2013 6 18 1 18 18.5% 6.00 [0.80, 44.94] NCT02018679 11 19 2 20 19.8% 11.58 [1.65, 81.26] NCT02018679 11 19 2 20 19.8% 11.58 [1.65, 81.26] NCT02018679 12 9 5 5 Total events 29 5 5 Total events 2004 100.0% 1.00 [0.55, 4.66] Total events 17 12 Heterogeneity: Tau ² = 0.02; ($h^2 = 0.69$); $h^2 = 0.%$ Test for overall effect: $Z = 3.92$ ($P < 0.0001$) 2.1.7 MAL-POT vs ($h = 0.76$, df = 2 ($P = 0.69$); $h^2 = 0.%$ Total events 17 12 Heterogeneity: Tau ² = 0.30; ($h = 1.1$ ($P = 0.77$); $h^2 = 48\%$ Test for overall effect: $Z = 0.86$ ($P = 0.39$) 2.1.8 ALA-POT vs cryotherapy Morton 1996 0 20 27 0% 0.20 [0.01, 3.92] 2.1.9 ALA-POT vs cryotherapy Morton 1996 0 20 20 27.0% 0.20 [0.01, 3.92] 2.1.9 ALA-POT vs cryotherapy Morton 1996 0 20 20 27.0% 0.20 [0.01, 3.92] 2.1.9 ALA-POT vs cryotherapy Morton 1996 0 20 20 27.0% 0.20 [0.01, 3.92] 2.1.9 ALA-POT vs cryotherapy Morton 1996 0 20 20 27.0% 0.20 [0.01, 3.92] 2.1.9 ALA-POT vs cryotherapy Meterogeneity: Tau ² = 1.02; ($h^2 = 1.81$, df = 1 ($P = 0.18$); $h^2 = 45\%$ Total events 5 0 Heterogeneity: Tau ² = 0.036 ($P = 0.39$) 2.1.9 ALA-POT vs cryotherapy Meterogeneity: Natapilicable Total events 5 0 Heterogeneity: Natapilicable Total events 2 6 6 | | | | | | | |
| Total events 15 15 Heterogeneity: Not applicable Test for overall effect: $Z = 1.04 (P = 0.30)$ 2.1.5 MAL-PDT vs surgery Rhodes 2004 7 53 1 52 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: $Z = 1.83 (P = 0.07)$ 2.1.6 MAL-PDT vs YAG-FL-PDT Ko 2013 6 18 1 18 18.5% 6.00 [0.80, 44.94] NCT02018679 11 19 1 20 19.8% 11.58 [1.65, 81.26] NCT02018673 12 19 3 20 19.8% 11.58 [1.65, 81.26] NCT02018673 12 19 3 20 19.8% 11.58 [1.65, 81.26] NCT02018673 12 19 3 20 5 Heterogeneity: Tau ² = 0.00; Ch ² = 0.76, df = 2 (P = 0.69); l ² = 0% Test for overall effect: $Z = 3.92 (P < 0.0001)$ 2.1.7 MAL-PDT vs ALA-PDT EudraCT-2013-003241-42 8 94 9 107 58.3% 1.01 [0.41, 2.52] NCT01491711 9 74 3 725 41.7% 3.04 [0.86, 10.79] Lobutotal (95% Ct) 17 12 Heterogeneity: Tau ² = 0.29; Ch ² = 1.93, df = 1 (P = 0.17); l ² = 48% Test for overall effect: $Z = 0.86 (P = 0.39)$ 2.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] Total events 11 8 Heterogeneity: Tau ² = 0.29; Ch ² = 1.81, df = 1 (P = 0.18); l ² = 45% Test for overall effect: $Z = 0.08 (P = 0.39)$ 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 2 1 0 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% Ct) 2 1 1 81 Subtotal (95% Ct) 2 1 1 9 100.0% 10.00 [0.59, 169.63] Subtotal (95% Ct) 2 1 1 9 100.0% 10.00 [0.59, 169.63] Subtotal (95% Ct) 2 3 3 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 1 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 1 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 3 100.0% 0.33 [0.07, 1.53] Subtotal (95% Ct) 3 3 | | | | | | | 1 |
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| 2.1.5 MAL-PDT vs surgery Rhodes 2004 7 53 1 52 100.0% 6.87 [0.88, 53.89] Total events 7 1 Heterogeneity: Not applicable Test for overall effect: Z = 1.83 ($P = 0.07$) 2.1.6 MAL-PDT vs YAG-AFL-PDT Ko 2013 6 18 1 18 18.5% 6.00 [0.80, 44.94] NCT02018679 11 19 1 20 19.8% 11.58 [1.65, 81.26] NCT020666534 12 19 3 21 61.7% 4.42 [1.47, 13.31] Subtotal (95% Cl) 56 59 100.0% 5.66 [2.38, 13.46] Total events 29 5 Heterogeneity: Tau ² = 0.00 ² = 0.6, 6f = 2 ($P = 0.69$); $I2 = 0%$ Test for overall effect: Z = 3.92 ($P < 0.0001$) 2.1.7 MAL-PDT vs ALA-PDT EudraCT-2013-003241-42 8 94 9 107 58.3% 1.01 [0.41, 2.52] NCT02140201 17 9 74 3 75 41.7% 3.04 [0.86, 10.79] Subtotal (95% Cl) 168 182 100.0% 1.60 [0.55, 4.66] Total events 17 12 Heterogeneity: Tau ² = 0.29; Ch ² = 1.39, df = 1 ($P = 0.17$); $I2 = 48%$ Test for overall effect: Z = 0.86 ($P = 0.39$) 2.1.8 LAA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] Wang 2001 11 44 6 39 77.30% 1.63 [0.66, 3.98] Subtotal (95% Cl) 51 18 8 Heterogeneity: Tau ² = 1.02; Ch ² = 1.39, df = 1 ($P = 0.18$); $I2 = 45\%$ Total events 1 8 L1.8 LAA-PDT vs scryotherapy Morton 1996 0 20 2 10 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Tau ² = 1.02; Ch ² = 1.51 ($P = 0.18$); $I2 = 45\%$ Total events 5 0 Heterogeneity: Tota ² = 1.02; Ch ² = 0.11) 2.1.0 ALA-PDT vs flurourcail Subtotal (95% Cl) 21 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Not applicable Test for overall effect: Z = 1.59 ($P = 0.11$) 2.1.10 ALA-PDT vs flurourcail Subtotal (95% Cl) 21 0 19 100.0% 0.33 [0.07, 1.53] Subtotal (95% Cl) 2 3 3 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% Cl) 33 3 100.0% 0.33 [0.07, 1.53] | Heterogeneity: Not applicable | | 10 | | | | |
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| Subtotal (95% Cl) 168 182 100.0% 1.60 [0.55, 4.66] Total events 17 12 Heterogeneity: Tau ² = 0.29; Chi ² = 1.93, df = 1 (P = 0.17); l ² = 48% Test for overall effect: Z = 0.86 (P = 0.39) 2.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] Wang 2001 11 44 6 39 73.0% 1.63 [0.66, 3.98] Subtotal (95% Cl) 64 59 100.00% 0.92 [0.14, 5.90] Total events 11 8 Heterogeneity: Tau ² = 1.02; Chi ² = 1.81, df = 1 (P = 0.18); l ² = 45% Test for overall effect: Z = 0.08 (P = 0.93) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% Cl) 21 19 100.0% 10.00 [0.59, 169.63] 10.00 10.00 10.59, 169.63] Subtotal (95% Cl) 2 3 33 100.0% 0.33 [0.07, 1.53] 10.00 Subtotal (95% Cl) 33 33 100.0% 0.33 [0.07, 1.53] 10.00 | | | | | | | _ |
| Total events 17 12 Heterogeneity: Tau ² = 0.29; Chi ² = 1.93, df = 1 ($P = 0.17$); I ² = 48% Test for overall effect: Z = 0.86 ($P = 0.39$) 2.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] Wang 2001 11 44 6 39 73.0% 1.63 [0.66, 3.98] Subtotal (95% CI) 64 59 100.0% 0.92 [0.14, 5.90] Total events 11 8 Heterogeneity: Tau ² = 1.02; Chi ² = 1.81, df = 1 ($P = 0.18$); I ² = 45% Test for overall effect: Z = 0.08 ($P = 0.93$) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% CI) 21 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Not applicable Test for overall effect: Z = 1.59 ($P = 0.11$) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 33 6 33 100.0% 0.33 [0.07, 1.53] Total events 2 6 | | | | | | | |
| Test for overall effect: $Z = 0.86$ (P = 0.39) 2.1.8 ALA-PDT vs cryotherapy Morton 1996 0 20 2 20 27.0% 0.20 [0.01, 3.92] Wang 2001 11 44 6 39 73.0% 1.63 [0.66, 3.98] Subtotal (95% CI) 64 59 100.0% 0.92 [0.14, 5.90] Total events 11 8 Heterogeneity: Tau ² = 1.02; Chi ² = 1.81, df = 1 (P = 0.18); l ² = 45% Test for overall effect: $Z = 0.08$ (P = 0.93) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Not applicable Test for overall effect: $Z = 1.59$ (P = 0.11) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 33 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% CI) 33 33 100.0% 0.33 [0.07, 1.53] | | | | | | . , | |
| Morton 1996 0 20 2 20 27.0% 0.20 $[0.01, 3.92]$ Wang 2001 11 44 6 39 73.0% 1.63 $[0.66, 3.98]$ Subtotal (95% CI) 64 59 100.0% 0.92 $[0.14, 5.90]$ Total events 11 8 Heterogeneity: Tau ² = 1.02; Chi ² = 1.81, df = 1 (P = 0.18); l ² = 45% Test for overall effect: Z = 0.08 (P = 0.93) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 $[0.59, 169.63]$ Subtotal (95% CI) 21 19 100.0% 10.00 $[0.59, 169.63]$ Total events 5 0 Heterogeneity: Not applicable Test for overall effect: Z = 1.59 (P = 0.11) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 33 6 33 100.0% 0.33 $[0.07, 1.53]$ Subtotal (95% CI) 33 33 100.0% 0.33 $[0.07, 1.53]$ | | | = 1 (P = 0 |).17); I | ² = 48% | | |
| Wang 2001 11 44 6 39 73.0% 1.63 $[0.66, 3.98]$ Subtotal (95% CI) 64 59 100.0% 0.92 $[0.14, 5.90]$ Total events 11 8 Heterogeneity: Tau ² = 1.02; Chi ² = 1.81, df = 1 (P = 0.18); l ² = 45% Test for overall effect: $Z = 0.08$ (P = 0.93) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 $[0.59, 169.63]$ Subtotal (95% CI) 2 1 19 100.0% 10.00 $[0.59, 169.63]$ Total events 5 0 Heterogeneity: Not applicable Test for overall effect: $Z = 1.59$ (P = 0.11) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 33 6 33 100.0% 0.33 $[0.07, 1.53]$ Subtotal (95% CI) 33 33 100.0% 0.33 $[0.07, 1.53]$ | 2.1.8 ALA-PDT vs cryotherapy | | | | | | |
| Subtotal (95% Cl) 64 59 100.0% 0.92 [0.14, 5.90] Total events 11 8 Heterogeneity: Tau ² = 1.02; Chi ² = 1.81, df = 1 (P = 0.18); I ² = 45% Test for overall effect: Z = 0.08 (P = 0.93) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% Cl) 21 19 100.0% 10.00 [0.59, 169.63] 10.00 [0.59, 169.63] Total events 5 0 0 10.00 [0.59, 169.63] 10.00 [0.59, 169.63] Subtotal (95% Cl) 21 19 100.0% 10.00 [0.59, 169.63] 10.00 [0.59, 169.63] Total events 5 0 0 10.00 [0.59, 169.63] 10.00 [0.59, 169.63] Subtotal (95% Cl) 21 33 100.0% 0.33 [0.07, 1.53] 10.00 [0.59, 169.63] Salim 2003 2 33 6 33<100.0% | | | | | | | |
| Total events 11 8 Heterogeneity: Tau ² = 1.02; Chi ² = 1.81, df = 1 ($P = 0.18$); $I2 = 45\%$ Test for overall effect: $Z = 0.08$ ($P = 0.93$) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Not applicable Test for overall effect: $Z = 1.59$ ($P = 0.11$) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 33 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% Cl) 33 33 100.0% 0.33 [0.07, 1.53] | | | | | | | |
| Test for overall effect: Z = 0.08 (P = 0.93) 2.1.9 ALA-PDT vs surgery Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% Cl) 21 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Not applicable Test for overall effect: Z = 1.59 (P = 0.11) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 33 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% Cl) 33 33 100.0% 0.33 [0.07, 1.53] 100.0% 10.00 [0.59, 169.63] | Total events | 11 | 8 | | | | |
| Berroeta 2007 5 21 0 19 100.0% 10.00 [0.59, 169.63] Subtotal (95% Cl) 21 19 100.0% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Not applicable | | | = 1 (P = 0 | 0.18); I | ² = 45% | | |
| Subtotal (95% Cl) 21 19 10.00% 10.00 [0.59, 169.63] Total events 5 0 Heterogeneity: Not applicable | • / | | | | | | _ |
| Total events 5 0 Heterogeneity: Not applicable 0 Test for overall effect: Z = 1.59 (P = 0.11) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 Subtotal (95% Cl) 33 33 33 Total events 2 | | | | | | | |
| Heterogeneity: Not applicable Test for overall effect: Z = 1.59 (P = 0.11) 2.1.10 ALA-PDT vs fluorouracil Salim 2003 2 33 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% Cl) 33 33 100.0% 0.33 [0.07, 1.53] Total events 2 6 | | | | 19 | 100.0% | 20:00 [0:39, 103:03] | |
| Salim 2003 2 33 6 33 100.0% 0.33 [0.07, 1.53] Subtotal (95% Cl) 33 33 100.0% 0.33 [0.07, 1.53] Total events 2 6 4 | Heterogeneity: Not applicable | | 5 | | | | |
| Subtotal (95% CI) 33 33 100.0% 0.33 [0.07, 1.53] Image: Comparison of the comparison | 2.1.10 ALA-PDT vs fluorouraci | I | | | | | _ |
| Total events 2 6 | | | | | | | |
| | | | | 55 | 100.0% | 0.33 [0.07, 1.33] | |
| | Heterogeneity: Not applicable | | 5 | | | | |
| Test for overall effect: Z = 1.41 (P = 0.16) | | (P = 0.16) | | | | | |
| | | | | | | 0.01 | |
| Test for subgroup differences: Chi ² = 30.17, df = 9 (P = 0.0004), I ² = 70.2% Favours PDT Favours control | Test for subgroup differences: C | hi² = 30.17, | df = 9 (P | = 0.0 | 004), $I^2 = 3$ | 70.2% | Favours PDT Favours control |
| | | | | | | | |

surgery and YAG-AFL-PDT at 24 m (one study), and imiquimod at 36 m (one study).

Analyses by location of the original lesion found few differences at 3 months (**Supplementary Figure 3**). MAL-PDT was more effective than placebo on the extremities, but less effective than surgery on the neck/trunk. At 12 months, imiquimod was statistically superior to MAL-PDT for lesions on the trunk, whereas MAL-PDT was superior to imiquimod for lesions on the extremities (**Supplementary Figure 4**). However, each of these findings resulted from a single trial, so interpretations should be made with caution.

| Study or Subaroup | PDT | Total | Cont | | Waight | Risk Ratio M-H, Random, 95% Cl | Risk Ratio M-H, Random, 95% Cl |
|--|---------------|--------------------|-----------|----------|-------------------------|---|-----------------------------------|
| Study or Subgroup 2.2.1 ALA-PDT vs sur | | | events | TOLAI | weight | M-H, Randolli, 95% Cl | M-H, Kandom, 95% Ci |
| Mosterd 2008 Subtotal (95% CI) | 21 | 83 83 | 2 | | 100.0% 100.0% | 11.13 [2.69, 46.01] 11.13 [2.69, 46.01] | |
| Total events | 21 | | 2 | | | | |
| Heterogeneity: Not app Test for overall effect: | | (P = 0. | 0009) | | | | |
| 2.2.2 MAL-PDT vs sur | gery 24 | m | | | | | |
| Rhodes 2004 Subtotal (95% CI) | 10 | 53 53 | 2 | | 100.0% 100.0% | 5.00 [1.15, 21.74] 5.00 [1.15, 21.74] | |
| Total events | 10 | | 2 | | | | |
| Heterogeneity: Not app Test for overall effect: | | (P = 0. | 03) | | | | |
| 2.2.3 MAL-PDT vs sur | gery 60 | m | | | | | _ |
| Rhodes 2004 Subtotal (95% CI) | 7 | 49 49 | 2 | | 100.0% 100.0% | 3.71 [0.81, 17.02] 3.71 [0.81, 17.02] | |
| Total events Heterogeneity: Not app Test for overall effect: 3 | | (P = 0. | 2 09) | | | | |
| 2.2.4 MAL-PDT vs flu | orouracil | 36 m | | | | | |
| ISRCTN 79701845 Subtotal (95% CI) | 34 | 126 126 | 29 | | 100.0% 100.0% | 1.36 [0.88, 2.10] 1.36 [0.88, 2.10] | |
| Total events Heterogeneity: Not app Test for overall effect: 3 | | (P = 0. | 29 17) | | | | |
| 2.2.5 MAL-PDT vs imi | quimod | 36 m | | | | | |
| ISRCTN 79701845 Subtotal (95% CI) | 34 | 126 126 | 10 | | 100.0% 100.0% | 3.91 [2.02, 7.60] 3.91 [2.02, 7.60] | 4 |
| Total events | 34 | | 10 | | | | |
| Heterogeneity: Not app Test for overall effect: | | (P < 0 | 0001) | | | | |
| 2.2.6 MAL-PDT vs cry | otherapy | 60 m | | | | | \bot |
| Basset-Seguin 2008 Subtotal (95% CI) | 15 | 66 66 | 12 | | 100.0% 100.0% | 1.10 [0.56, 2.15] 1.10 [0.56, 2.15] | |
| Total events Heterogeneity: Not app Test for overall effect: 3 | | (P = 0. | 12 78) | | | | |
| 2.2.7 MAL-PDT vs YA | G-AFL-P | DT 24 | m | | | | |
| NCT02666534 | 14 | 19 | 4 | | 100.0% | 3.87 [1.54, 9.72] | |
| Subtotal (95% CI) | | 19 | | 21 | 100.0% | 3.87 [1.54, 9.72] | |
| Total events Heterogeneity: Not app | 14 licable | | 4 | | | | |
| Test for overall effect: | | (P = 0) | 004) | | | | |
| | | | | | | 0.01 | |
| Test for subgroup diffe | erences: C | Chi ² = | 19.68, d | f = 6 (F | P = 0.003 |), $I^2 = 69.5\%$ | Favours PDT Favours control |
| | | | | | | | |

Meta-regression of all active control studies revealed no significant differences between imiquimod, cryotherapy, fluorouracil, and surgery (Supplementary Table 2). We therefore undertook a meta-regression of all active control studies by type of carcinoma (Supplementary Table 3). There were no significant differences between basal cell and squamous cell carcinomas for this outcome, suggesting that the treatments are similarly effective for both carcinoma types.

Recurrence

At 12 months post-intervention, MAL-PDT was more effective than placebo (one study), but YAG-AFL-PDT was more effective than MAL-PDT (three studies; **Figure 4**). The risk of recurrence after MAL-PDT was 5.66 times (95% CI: 2.38, 13.46) that of YAG-AFL-PDT (P < 0.00001). At 24 months, this increased risk of recurrence remained (one study per comparison; Figure 5). In addition, both MAL-PDT and ALA-PDT were inferior to surgery at 24- and 36-month post-intervention, respectively, and MAL-PDT was inferior to YAG-AFL-PDT and imiquimod at 24- and 36-month post-intervention, however there was only one study per comparison, so these results should be interpreted with caution.

Analyses by location of the original lesion showed few differences (**Supplementary Figure 5**). MAL-PDT was superior to cryotherapy on the face/scalp, superior to placebo on the neck/trunk, and superior to imiquimod on the extremities. In contrast, imiquimod was significantly less likely than MAL-PDT to result in lesion recurrence on the body trunk. However, each of these findings resulted from a single trial, so interpretations should be made with caution. There were too few studies to undertake meta-regression.

| Study or Subgroup 3.1.1 MAL-PDT vs placebo | MAL-PDT Events To | | Contro vents T | | Weight | Risk Ratio M-H, Random, 95% Cl | Risk Ratio M-H, Random, 95% Cl | |
|---|--|--|--|---|--|--|-----------------------------------|--|
| Solutional (95% CI) Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.63 | 42 42 2 (P = 0.53 | 43 43 | 14 14 | | 100.0% 1 00.0% | 1.05 [0.91, 1.21] 1.05 [0.91, 1.21] | # | |
| 3.1.2 MAL-PDT vs surgery Rhodes 2004 Szeimie 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; CI Test for overall effect: Z = 2.5 | 118 157 hi ² = 0.72, | | 131 | 117 161 1 | 27.6% 72.4% 100.0% = 0% | 1.05 [0.89, 1.24] 1.15 [1.04, 1.27] 1.12 [1.03, 1.22] | ₹ | |
| 3.1.3 MAL-PDT vs fluorourac ISRCTN 79701845 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.90 | :il 116 116 | 186 1 86 | | | 100.0% 1 00.0% | 1.08 [0.92, 1.28] 1.08 [0.92, 1.28] | Ŧ | |
| 3.1.4 MAL-PDT vs imiquimoc ISRCTN 79701845 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.19 | 116 1 116 | 186 | | | 100.0% 100.0% | 1.02 [0.87, 1.19] 1.02 [0.87, 1.19] | * | |
| 3.1.5 MAL-PDT vs ALA-PDT EudraCT-2013-003241-42 NCT02367547 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.01; CI Test for overall effect: Z = 0.7 | 24 60 hi ² = 1.39, | | 67 | 33 103 1 | 46.1% 53.9% 100.0% = 28% | 0.81 [0.60, 1.10] 1.02 [0.78, 1.34] 0.92 [0.72, 1.17] | - <u>+</u> - | |
| 3.1.6 MAL-PDT vs HAL-PDT NCT02367547 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.3 | 24 24 | 31 31 | 19 19 | | 100.0% 100.0% | 1.26 [0.90, 1.77] 1.26 [0.90, 1.77] | - | |
| Test for subgroup differences: | | | | | | 0.2 | 0.5 1 2 5 | |
| rest for subgroup unreferices. | Chi ² = 4.0 |)4, df = | = 5 (P = | 0.54), I | l ² = 0% | | Favours control Favours MAL-PDT | |
| В | PDT | | Contro | bl | | Risk Ratio | Risk Ratio | |
| B <u>Study or Subgroup</u> <u>3.2.1 MAL-PDT vs surgery</u> Rhodes 2004 Szeimie 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; C | PDT Events T 41 118 159 hi ² = 1.42, | <u>otal E</u> 42 128 170 , df = 1 | Contro Events 36 83 119 | ol Total 43 117 160 | Weight 46.4% 53.6% 100.0% | M-H, Random, 95% Cl 1.17 [1.01, 1.34] 1.30 [1.15, 1.47] | | |
| B <u>Study or Subgroup</u> <u>3.2.1 MAL-PDT vs surgery</u> Rhodes 2004 Szeimie 2008 Subtotal (95% CI) Total events | PDT Events T 41 118 159 hi ² = 1.42, 1 (P = 0.00 Py 77 77 | otal E 42 128 170 | Contro Events 36 83 119 | ol Total 43 117 160 23); I ² 65 | Weight 46.4% 53.6% 100.0% | M-H, Random, 95% Cl 1.17 (1.01, 1.34) 1.30 (1.15, 1.47) 1.24 (1.10, 1.38) 1.42 (1.18, 1.70) | Risk Ratio | |
| B Study or Subgroup 3.2.1 MAL-PDT vs surgery Rhodes 2004 Szeimie 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 3.7 3.2.2 MAL-PDT vs cryotheral Morton 2006 Subtotal (95% CI) Total events Heterogeneity: Not applicable | PDT Events T 41 118 159 $hi^2 = 1.42$, 1 (P = 0.00 py 77 77 6 (P = 0.00 cill 77 77 77 | iotal E 42 128 170 | Contro 36 83 119 1 (P = 0. 43 | ol Total 43 117 160 23); l ² 65 65 65 | Weight 46.4% 53.6% 100.0% = 29% | M-H, Random, 95% Cl 1.17 [1.01, 1.34] 1.30 [1.15, 1.47] 1.24 [1.10, 1.38] 1.42 [1.18, 1.70] 1.42 [1.18, 1.70] 1.42 [1.18, 1.70] | Risk Ratio | |
| B Study or Subgroup 3.2.1 MAL-PDT vs surgery Rhodes 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 3.7 3.2.2 MAL-PDT vs cryotheral Morton 2006 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 3.7 3.2.3 MAL-PDT vs fluorourau Morton 2006 Subtotal (95% CI) Total events Heterogeneity: Not applicable Heterogeneity: Not applicable Subtotal (95% CI) Total events | PDT Events T 41 118 159 hi ² = 1.42, 1 (P = 0.00 77 77 6 (P = 0.00 77 77 6 (P = 0.00 77 77 77 7 (P = 0.00 77 7 (P = 0.00 11 99 11 90 11 91 11 92 11 | iotal E 42 128 128 170 , df = : 5002) 82 82 0002) 82 82 82 9) 18 19 37 , df = : 2 | Contro Svents - 36 83 119 1 (P = 0. 43 43 16 16 16 19 35 | 1 43 117 160 23); I ² 65 65 21 21 21 18 20 38 | Weight 46.4% 53.6% 100.0% = 29% 100.0% 100.0% 100.0% | M-H, Random, 95% CI 1.17 [1.01, 1.34] 1.30 [1.15, 1.47] 1.24 [1.10, 1.38] 1.42 [1.18, 1.70] 1.42 [1.18, 1.70] 1.42 [1.18, 1.70] 1.23 [0.96, 1.58] 1.23 [0.96, 1.58] 1.23 [0.96, 1.58] 1.06 [0.87, 1.30] 1.05 [0.91, 1.21] | Risk Ratio | |
| B 3.2.1 MAL-PDT vs surgery Rhodes 2004 Szeimie 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 3.7 3.2.2 MAL-PDT vs cryotheral Morton 2006 Subtotal (95% CI) Total events Heterogeneity: Nat applicable Test for overall effect: Z = 3.7 3.2.3 MAL-PDT vs fluorourad Morton 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; C | PDT Events T: 41 118 159 $hi^2 = 1.42, 1$ 1 (P = 0.000 PY 77 77 6 (P = 0.000 Cill 77 7 (P = 0.000 Cill 77 7 (P = 0.000 PDT 17 19 $hi^2 = 0.001$ 11 (P = 0.000 PDT 17 36 $hi^2 = 0.001$ 19 $hi^2 = 0.001$ 19 $hi^2 = 0.001$ 10 $hi^2 = 0.001$ 10 $hi^2 = 0.002$ PDT 10 $hi^2 = 0.002$ PDT 10 $hi^2 = 0.002$ PDT 10 $hi^2 = 0.002$ PDT 10 $hi^2 = 0.002$ PDT 10 $hi^2 = 0.002$ PDT 10 $hi^2 = 0.002$ $hi^2 = 0.002$ hi^2 | otal E 42 128 120 6 002) 82 82 82 002) 82 82 82 002) 82 82 82 002) 82 82 82 002) 82 82 82 002) 82 82 82 001 18 19 37 50 57 72 129 off = 1 10 | Contro ivents 36 83 119 1 (P = 0. 43 43 16 16 16 19 35 1 (P = 0. 35 1 (P = 0. 41 58 99 | 21 21 21 21 21 21 21 21 21 21 21 21 21 2 | Weight 46.4% 53.6% 100.0% = 29% 100.0% 100.0% 57.4% 100.0% 32.6% 67.4% 100.0% | M-H, Random, 95% CI 1.17 [1.01, 1.34] 1.30 [1.15, 1.47] 1.24 [1.10, 1.38] 1.42 [1.18, 1.70] 1.42 [1.18, 1.70] 1.42 [1.18, 1.70] 1.23 [0.96, 1.58] 1.23 [0.96, 1.58] 1.06 [0.87, 1.30] 1.05 [0.91, 1.21] 1.05 [0.94, 1.18] 0.93 [0.74, 1.18] 0.84 [0.69, 1.03] | Risk Ratio | |
| B 3.2.1 MAL-PDT vs surgery Rhodes 2004 Szeimie 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 3.7 3.2.2 MAL-PDT vs cryotheral Morton 2006 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 3.7 3.2.3 MAL-PDT vs fluorourad Morton 2006 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.6 3.2.4 MAL-PDT vs YAG-AFL- Ko 2013 NCT02018679 Subtotal (95% C) Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 0.9 3.2.5 MAL-PDT vs ALA-PDT EudraCT-2013-003241-42 NCT01491711 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; C | PDT Events T 41 118 159 $hi^2 = 1.42, 1$ 1 (P = 0.000 PY 77 77 6 (P = 0.000 cill 77 7 (P = 0.000 Cill 77 7 (P = 0.000 PDT 17 36 hi^2 = 0.01, 1 1 (P = 0.360 39 48 hi^2 = 0.01, 0 7 (P = 0.01, 0) 1 (P = 0.01, 0) 39 48 hi^2 = 0.01, 0 7 (P = 0.01, 0) 39 39 39 | $\begin{array}{c} \hline \textbf{otal} & \textbf{I} \\ 42 \\ 42 \\ 128 \\ 170 \\ 002) \\ 82 \\ 82 \\ 82 \\ 002) \\ 82 \\ 82 \\ 82 \\ 9) \\ 18 \\ 19 \\ 37 \\ 37 \\ 129 \\ 0 \\ df = 1 \\ 129 \\ 0 \\ df = 1 \\ 129 \\ 0 \\ 42 \\ 42 \end{array}$ | Contro ivents 36 83 119 1 (P = 0. 43 43 16 16 16 19 35 1 (P = 0. 35 1 (P = 0. 41 58 99 | 1 117 160 23); ² 65 65 21 21 21 18 20 38 92); ² 56 73 129 50); ² 37 | Weight 46.4% 53.6% 100.0% = 29% 100.0% 100.0% 57.4% 100.0% 32.6% 67.4% 100.0% | M-H, Random, 95% CI | Risk Ratio | |

FIGURE 6

Meta-analy ratios with 95% confidence intervals.

Cosmetic outcomes

After 3 months, there were no differences in the chance of good/excellent ratings for cosmetic appearance of lesions between MAL-PDT and ALA-PDT (two studies), HAL-PDT, imiquimod,

fluorouracil, and placebo (one study per comparison; Figure 6A). The only exception to this was the comparison of MAL-PDT with surgery, which significantly favored MAL-PDT (two studies; RR: 1.12 (95% CI: 1.03, 1.22); p = 0.01). At 12 months, ALA-PDT showed superiority over cryotherapy (one study), and MAL-PDT was

| Study or Subgroup | Events | Total | Events | Total | Weight M | -H, Random, 95% CI | M-H, Random, 95% Cl |
|---|------------------------|-------------------|-------------|----------------------|-------------------------|--|---------------------------------|
| 4.1.1 MAL-PDT vs placebo | Litento | | | · o tu: | neight h | | |
| Foley 2009 | 60 | 66 | 43 | 65 | 77.1% | 1.37 [1.14, 1.66] | _ _ |
| Morton 2006 | 60 | 96 | 10 | 17 | 22.9% | 1.06 [0.69, 1.63] | |
| Subtotal (95% CI) | | 162 | | | 100.0% | 1.30 [1.04, 1.61] | ◆ |
| Total events | 120 | | 53 | | | | |
| Heterogeneity: $Tau^2 = 0.01$; C | $hi^2 = 1.2$ | 4, df = | = 1 (P = 0) | .27); I ² | = 19% | | |
| Test for overall effect: $Z = 2.3$ | 3 (P = 0.0 |)2) | | | | | |
| 4.1.2 MAL-PDT vs surgery | | | | | | | |
| Rhodes 2004 | 27 | 52 | 14 | 49 | 53.1% | 1.82 [1.09, 3.04] | _ |
| Szeimie 2008 | 37 | 100 | 14 | 96 | 46.9% | 2.54 [1.47, 4.39] | |
| Subtotal (95% CI) | | 152 | | 145 | 100.0% | 2.12 [1.46, 3.09] | |
| Total events | 64 | | 28 | | | | |
| Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 3.9 | | | = 1 (P = 0 | .38); l² | = 0% | | |
| 4.1.3 MAL-PDT vs cryothera | ру | | | | | | |
| Morton 2006 Subtotal (95% CI) | 60 | 96 96 | 40 | | 100.0% 100.0% | 1.28 [0.98, 1.68] 1.28 [0.98, 1.68] | |
| Total events | 60 | 50 | 40 | 02 | 100.070 | 1.20 [0.50, 1.00] | |
| Heterogeneity: Not applicable | | | 40 | | | | |
| Test for overall effect: $Z = 1.8$ | |)7) | | | | | |
| 4.1.4 MAL-PDT vs fluoroura | | | | | | | _ |
| Morton 2006 Subtotal (95% CI) | 60 | 96 96 | 23 | | 100.0% 100.0% | 0.82 [0.63, 1.05] 0.82 [0.63, 1.05] | |
| Total events | 60 | | 23 | | | | |
| Heterogeneity: Not applicable Test for overall effect: Z = 1.6 | 0 (P = 0.3 | 1) | | | | | |
| 4.1.5 MAL-PDT vs ALA-PDT | | | | | | | |
| EudraCT-2013-003241-42 Subtotal (95% CI) | 143 | 143 143 | 138 | | 100.0% 100.0% | 1.00 [0.99, 1.01] 1.00 [0.99, 1.01] | — |
| Total events | 143 | | 138 | -55 | | | |
| Heterogeneity: Not applicable | | | 150 | | | | |
| Test for overall effect: $Z = 0.0$ | |)0) | | | | | |
| 4.1.6 MAL-PDT vs YAG-AFL- | -PDT | | | | | | |
| Ko 2013 | 18 | 18 | 18 | 18 | 32.2% | 1.00 [0.90, 1.11] | + |
| NCT02018679 | 18 | 18 | 16 | 16 | 28.6% | 1.00 [0.89, 1.12] | + |
| NCT02666534 Subtotal (95% CI) | 19 | 19 55 | 21 | 21 55 | 39.2% 100.0% | 1.00 [0.91, 1.10] 1.00 [0.94, 1.06] | * |
| Total events | 55 | | 55 | | | | Ţ |
| Heterogeneity: $Tau^2 = 0.00$; C Test for overall effect: $Z = 0.0$ | $hi^2 = 0.0$ | | = 2 (P = 1 | .00); l ² | = 0% | | |
| | | | | | | | <u> </u> |
| | | | | | | | 0.2 0.5 1 2 5 |
| Test for subgroup differences | : Chi ² = 2 | 6.63, | df = 5 (P | < 0.00 | 01), $I^2 = 81$ | .2% | Favours MAL-PDT Favours control |
| 7 | | | | | | | |

superior to surgery (two studies) and cryotherapy (one study) for this outcome (Figure 6B). There were too few studies to undertake meta-regression.

Adverse events

The rates of any adverse event were relatively high in all studies (**Figure 7**). There were no significant differences between the different forms of PDT (MAL vs. ALA (one study) and MAL vs. YAG-AFL (three studies)). However, MAL-PDT caused significantly more adverse events than surgery (two studies; RR: 2.12; 95% CI: 1.46 to 3.09; P < 0.0001).

The incidence of pain during the procedure was higher in people who had MAL-PDT than imiquimod, fluorouracil, or placebo (one study per comparison; **Figure 8**), and lower in those undergoing ALA-PDT than cryotherapy (one study). There was no difference in the incidence of pain between MAL-PDT and ALA-PDT (one study), between ALA-PDT and fluorouracil (one study), and between MAL-PDT and surgery (two studies). There were too few studies to undertake meta-regression. Peak pain severity showed a slightly different picture. The only statistically significant difference in pain intensity was between ALA-PDT and surgery (one study; **Supplementary Figure 6**).

Publication bias

The potential for publication bias was examined by visual examination of funnel plots produced for response, recurrence, cosmetic outcomes, and adverse events (Supplementary Figure 7). All plots appeared symmetrical, with little obvious skew in data. We attempted to undertake an analysis of bias by comparing industry-funded with government/university funded studies (Supplementary Figure 8). We used studies reporting on response at 3 months for comparisons that showed a statistically significant advantage toward PDT in the overall meta-analysis. We found no statistically significant differences between the

| Study or Subgroup | MAL-PDT Events To | | Contro Events | | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M–H, Random, 95% Cl |
|--|---------------------------|--------------------|------------------|---------------------|-------------------------|---|--|
| 4.2.1 MAL-PDT vs placebo | Lvents rt | | Lvents | TOLAT | weight | M-II, Kalidolli, 55% Cl | M-II, Kalidolii, 35% Ci |
| Foley 2009 Subtotal (95% CI) | 12 | 66 66 | 3 | | 100.0% 100.0% | 3.94 [1.17, 13.32] 3.94 [1.17, 13.32] | |
| Total events | 12 | 00 | 3 | 05 | 100.0% | 5.94 [1.17, 15.52] | |
| Heterogeneity: Not applicable Test for overall effect: Z = 2. | |) | | | | | |
| 4.2.2 MAL-PDT vs surgery | | | | | | | |
| Rhodes 2004 | 7 | 52 | 3 | 49 | 56.3% | 2.20 [0.60, 8.03] | |
| Szeimie 2008 Subtotal (95% CI) | | 100 L 52 | 4 | 96 145 | 43.7% 100.0% | 0.48 [0.09, 2.56] 1.13 [0.26, 4.97] | |
| Total events | 9 | | 7 | | | | |
| Heterogeneity: Tau ² = 0.58; Test for overall effect: Z = 0. | | | 1 (P = 0. | 16); I ² | = 50% | | |
| 4.2.3 MAL-PDT vs fluoroura | acil | | | | | | |
| ISRCTN 79701845 Subtotal (95% CI) | | 190 L 90 | 14 | | 100.0% 100.0% | 1.95 [1.06, 3.60] 1.95 [1.06, 3.60] | |
| Total events Heterogeneity: Not applicable Test for overall effect: Z = 2. | |) | 14 | | | | |
| 4.2.4 MAL-PDT vs imiquim | od | | | | | | |
| ISRCTN 79701845 Subtotal (95% CI) | 27 1 | 190 L 90 | 9 | | 100.0% 100.0% | 2.98 [1.44, 6.17] 2.98 [1.44, 6.17] | |
| Total events Heterogeneity: Not applicable | 27 e | | 9 | | | | |
| Test for overall effect: $Z = 2$. | 95 (P = 0.00 | 3) | | | | | |
| 4.2.5 MAL-PDT vs ALA-PDT | г | | | | | | |
| EudraCT-2013-003241-42 Subtotal (95% CI) | | 143 L 43 | 134 | | 100.0% 100.0% | 1.03 [1.00, 1.06] 1.03 [1.00, 1.06] | - |
| Total events | 143 | | 134 | | | | |
| Heterogeneity: Not applicable Test for overall effect: $Z = 1$. | |) | | | | | |
| 4.2.6 ALA-PDT vs cryothera | ару | | | | | | _ |
| Morton 1996 Subtotal (95% CI) | 11 | 20 20 | 19 | | 100.0% 100.0% | 0.58 [0.38, 0.87] 0.58 [0.38, 0.87] | |
| Total events | 11 | | 19 | | | - · · | - |
| Heterogeneity: Not applicable Test for overall effect: Z = 2. | | 9) | | | | | |
| 4.2.7 ALA-PDT vs fluoroura | cil | | | | | | |
| Salim 2003 Subtotal (95% CI) | 14 | 19 19 | 10 | | 100.0% 100.0% | 1.11 [0.71, 1.73] 1.11 [0.71, 1.73] | 1 |
| Total events | 14 | 1.7 | 10 | 13 | 100.0/0 | 1.11 [0.7 1, 1.7 5] | |
| Heterogeneity: Not applicable Test for overall effect: Z = 0. | e |) | | | | | |
| | | | | | | - | |
| Test for subgroup difference | s: Chi ² = 24. | 76, d [.] | f = 6 (P | = 0.00 | 004), I ² = | |).05 0.2 İ İ ZO Favours MAL-PDT Favours control |
| | | | | | | | |
| alysis of the risk of pain du | | | | | | | |

two subgroups, however, heterogeneity was extremely high (96 and 85% for industry-funded and non-industry-funded, respectively). This heterogeneity was likely a result of combing different control types.

Discussion

Our systematic review and meta-analysis demonstrates for the first time the evidence for the relative efficacy and safety of PDT compared with other potential treatments. We found that MAL-PDT was superior to placebo, and ALA-PDT was superior to surgery, but PDT, surgery, fluorouracil, and imiquimod have similar rates of response and recurrence over the short and medium term. However, over the longer term (24–60 m), PDTtreated lesions are significantly more likely to recur than those that were surgically resected, or those treated with imiquimod. PDT is also more likely to cause intra-procedural pain and adverse events. However, PDT is more likely to be rated "good" or "excellent" compared with cryotherapy and surgery. Given the small number of available studies, the choice of treatment for any particular lesion is best left to the discretion of the treating physician, taking into account the individual patient's preferences.

Interestingly, differences between the photosensitizing agents used with PDT emerged. Whereas MAL-PDT was significantly less likely than surgery to result in response of a lesion at 3 months (32), ALA-DT was significantly more likely than surgery to result in response (25). Whether these differences are real and robust, however, is unclear, as Szeimie et al. (32) treated small superficial lesions, whereas Mosterd et al. (25) treated nodular BCCs. Furthermore, three head-to-head trials failed to show any differences between MAL-PDT and ALA-PDT (20, 24, 31). Intriguingly, the meta-analysis indicates that YAG-AFL-PDT may be superior to MAL-PDT for response and recurrence, without compromising on cosmetic outcomes or risk of adverse events (16, 17, 21). However, larger studies will be required to confirm this result.

Although cosmetic concerns are sometimes minimized or dismissed, they can have serious effects on patients. Patients with visible and unpleasant scarring can suffer from embarrassment, isolation and a modification of social activities (34), along with self-consciousness, unhappiness and insecurity (35). Nevertheless, excision, especially of melanomas and SCCs, does lead to an increase in quality of life, probably due to a reduction in the anxiety associated with a diagnosis of skin cancer (34). It is thus vital that the location of the lesion, the likely size and visibility of the resulting scar, and the personal circumstances, activities, and preferences of the individual patient are considered when choosing the treatment for any particular lesion.

Conclusion

Basal cell carcinoma and SCC lesions cause significant economic burdens for health organizations all around the world. This disease also leads to chronic discomfort and a reduction in quality of life for patients, as it can cause poor cosmetic effects. Finding an appropriate method for treatment of these lesions has remained a challenge as the number of treatment methods increases. Our results suggest that PDT is can be an effective method for treatment of these lesions. However, further studies are required before any strong recommendations can be made.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Author contributions

YO-Y and YZ did the database searching, citation management, and inclusion and exclusion of records. YZ did the data extraction, study quality assessment, which was checked by KM. KM did the meta-analysis and meta-regression in consultation with YO-Y and YZ. KM wrote the manuscript in consultation with YO-Y and YZ. All authors contributed to the article and approved the submitted version.

Conflict of interest

YZ was employed by Guangdong Nuohui Hospital Management LLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1089361/ full#supplementary-material

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