



# University of Dundee

# Conventional and combination topical photodynamic therapy for basal cell carcinoma

Collier, N. J.; Haylett, A. K.; Wong, T. H.; Morton, C. A.; Ibbotson, S. H.; McKenna, K. E.

Published in: British Journal of Dermatology

DOI: 10.1111/bjd.16838

Publication date: 2018

Document Version Peer reviewed version

Link to publication in Discovery Research Portal

*Citation for published version (APA):* Collier, N. J., Haylett, A. K., Wong, T. H., Morton, C. A., Ibbotson, S. H., McKenna, K. E., ... Rhodes, L. E. (2018). Conventional and combination topical photodynamic therapy for basal cell carcinoma: systematic review and meta-analysis. British Journal of Dermatology, 179(6), 1277-1296. https://doi.org/10.1111/bjd.16838

**General rights** 

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

#### British Journal of Dermatology



# Conventional and combination topical photodynamic therapy for basal cell carcinoma: systematic review and meta-analysis

British Journal of Dermatology
BJD-2018-1072
Systematic Review
16-May-2018
Collier, Nick; University of Manchester, Dermatology Centre Haylett, Ann; Salford Royal NHS Foundation Trust, Photobiology Unit Wong, Terence; NHS Forth Valley, Dermatology Morton, Colin; Falkirk Royal Infirmary, Dermatology Ibbotson, Sally; Photobiology Unit, University Department of Dermatology McKenna, Kevin; Belfast City Hospital, Department of Dermatology Mallipeddi, Raj; St. Thomas' Hospital, Department of Cell and Molecular Pathology Moseley, Harry; Photobiology Unit Seukeran, Daron; South Tees Hospitals NHS Foundation Trust Ward, Anne; Cannock Chase Hospital Mohd Mustapa, M. Firouz; British Association of Dermatoloigsts, Clinical Standards Unit Exton, Lesley Green, Adele; Cancer Research UK Manchester Institute Rhodes, Lesley; University of Manchester, Photobiology Unit, Dermatology Centre
Photodynamic therapy, Basal Cell Carcinoma, Cosmesis, Imiquimod, Fluorouracil



This is the peer reviewed version of the following article: Collier, N., et al. (2018) 'Conventional and combination topical photodynamic therapy for basal cell carcinoma: systematic review and meta-analysis', *British Journal of Dermatology*, which has been published in final form at http://dx.doi.org/10.1111/bjd.1683. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Conventional and combination topical photodynamic therapy for basal cell carcinoma: systematic review and meta-analysis

N.J. Collier<sup>1</sup>, A.K. Haylett<sup>1</sup>, T.H. Wong<sup>2</sup>, C.A. Morton<sup>2</sup>, S.H. Ibbotson<sup>3</sup>, K.E. McKenna<sup>4</sup>, R. Mallipeddi<sup>5</sup>, H. Moseley<sup>3</sup>, D. Seukeran<sup>6</sup>, K.A. Ward<sup>7</sup>, M.F. Mohd Mustapa<sup>8</sup>, L.S. Exton<sup>8</sup>, A.C. Green<sup>1,9</sup>, L.E. Rhodes<sup>1</sup>

<sup>1</sup>Photobiology Unit, Dermatology Centre, The University of Manchester & Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK. <sup>2</sup>Stirling Community Hospital, Stirling, UK. <sup>3</sup> The Photobiology Unit, Department of Dermatology, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK. <sup>4</sup>Department of Dermatology, Belfast City Hospital, Belfast, UK. <sup>5</sup>St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK. <sup>6</sup>The James Cook University Hospital, Middleborough, UK. <sup>7</sup>Cannock Chase Hospital, Cannock, UK. <sup>8</sup>British Association of Dermatologists, Willan House, 4 Fitzroy Square, London, UK. <sup>9</sup>CR-UK Manchester Institute, The University of Manchester, Manchester, UK and QIMR Berghofer Medical Research Institute, Brisbane, Australia.

ORCID ID: NJ Collier 0000-0002-4377-9398; AK Haylett 0000-0001-6625-7640; TH Wong 0000-0002-3711-2976; CA Morton 0000-0002-6035-0737; SH Ibbotson 0000-0001-5685-752X; R Mallipeddi 0000-0001-5962-5759; AC Green 0000-0002-2753-4841; LE Rhodes 0000-0002-9107-6654

Running head: Photodynamic therapy for basal cell carcinoma

Corresponding author: Lesley E. Rhodes

E-mail: lesley.e.rhodes@manchester.ac.uk

Funding sources: None

**Conflicts of interest**: CAM: Invited speaker - Galderma, Biofrontera/Spirit (specific), Astellas, Almirall, LEO Pharma (non-specific); Advisory board - Spirit/Biofrontera (specific), Almirall, Astellas, LEO Pharma (non-specific); Investigator participating in a study sponsored by Biofrontera (specific); HM: Runs a UKAS Laboratory calibrating UV meters for phototherapy (specific); SHI: Invited speaker - Galderma, Spirit healthcare (specific); Investigator participating in Biofrontera - sponsored study (specific); DS: Sponsorship to attend EADV meeting - Galderma (non-specific); Advisory board - Galderma (non-specific); KAW; Sponsorship to attend 2014 Euro PDT meeting – Galderma (specific).

# What is already known about this topic?

- Topical photodynamic therapy (PDT) is one of a range of established treatment options for low-risk basal cell carcinoma (BCC).
- BCC clearance is reported to be higher with imiquimod than with single-cycle PDT

# What does this study add?

- This is the largest systematic review and meta-analysis to-date of PDT for BCC and incorporates NICE-approved GRADE assessment of evidence quality including 15 RCTs (2,327 patients with 3,509 BCCs).
- Serious adverse reactions are less common with PDT than imiquimod.
- Peak pain is higher with PDT than topical therapies but is of shorter duration.
- Fractionated PDT offers superior clearance to conventional PDT.
- Combination PDT treatments show promise but require further study.

# 

# Abstract

**Background:** Topical photodynamic therapy (PDT) is an established treatment option for low-risk basal cell carcinoma (BCC).

**Objectives:** Compare efficacy, cosmesis and tolerability of PDT for BCC with alternative treatments.

*Methods*: MEDLINE/PubMed/EMBASE/CENTRAL databases were searched from inception until 1 September 2017. Included studies were randomised controlled trials (RCTs) of PDT for nodular (n) and superficial (s) BCC reporting at least one of the outcomes: clearance at 3 months, and sustained at 1 or 5 years; recurrence at ≥1 year; cosmesis; adverse events; tolerability.

**Results:** From 2,331 search results, 15 RCTs (2,327 patients; 3,509 BCCs) were included. PDT efficacy (5-year sustained clearance) was high although inferior to excisional surgery (nBCC pooled RR 0.76; 95% CI 0.63–0.91), and without re-treatment of partially-responding lesions, was modestly inferior to imiquimod (sBCC: RR 0.81; 95% CI 0.70-0.95) and similar to fluorouracil (sBCC: RR 0.88; 95% CI 0.75-1.04). Five-year sustained clearance was inferior with conventional versus fractionated PDT (sBCC: RR 0.76; 95% CI 0.68-0.84). PDT cosmesis was superior to surgery (sBCC: RR 1.68; 95% CI 1.32-2.14; nBCC: RR 1.82; 95% CI 1.19-2.80) and cryosurgery (BCC: RR 3.73; 95% CI 1.96-7.07), and without re-treatment of partially-responding lesions was similar to imiquimod (sBCC: RR 1.01; 95%CI 0.85-1.19) and fluorouracil (sBCC: RR 1.04; 95% CI 0.88-1.24). Peak pain was higher but of shorter duration with PDT than topical treatments. Serious adverse reactions were rarer with PDT than imiquimod (sBCC: RR 0.05; 95% CI 0.00-0.84) and fluorouracil (sBCC: RR 0.11; 95% CI 0.01-2.04). Combination PDT regimens demonstrated reduced recurrence and improved cosmesis; however, results from these small studies were often non-significant.

**Conclusions:** PDT is an effective treatment for low-risk BCC, with excellent cosmesis and safety. Imiquimod has higher efficacy than single-cycle PDT though more adverse effects. Highest efficacy is with excisional surgery. Fractionated and combination PDT options warrant further study.

#### Introduction

Basal cell carcinoma (BCC) is the commonest cancer worldwide, with reported incidence increasing.<sup>1</sup> BCCs form a substantial and growing proportion of a dermatologist's workload and are a large burden to Western health services.<sup>2</sup> An effective treatment armamentarium is required, alongside prevention strategies. This systematic review examines randomized controlled trials (RCTs) comparing conventional topical photodynamic therapy (PDT) with alternative treatments, including fractionated PDT and combination regimens.

Mortality from BCC is low and BCCs almost never metastasise. Advanced tumours, however, cause considerable morbidity through local tissue destruction, leading to disfigurement and functional compromise.<sup>3</sup> The risk of morbidity depends on tumour location and subtype. The majority of BCCs are low-risk, i.e. less aggressive subtypes, superficial BCC (sBCC) and nodular BCC (nBCC), located in anatomical areas that allow uncomplicated resection without substantially impairing function or cosmesis.<sup>4</sup>

Surgical excision allows unparalleled cure rates but the cosmetic outcome depends on BCC size and location, reconstruction method, and expertise.<sup>4-6</sup> One of several nonsurgical treatments available for nBCC and sBCC<sup>7,8</sup> is topical PDT with 5-aminolaevulinic acid (ALA) or methyl aminolaevulinate (MAL).<sup>9</sup> The licensed MAL-PDT protocol uses a cycle of two treatments, 1 week apart, with outcome reviewed at 3 months, where it is usual practice to re-treat partially-responding lesions.<sup>10</sup> High clearance rate (although lower for nBCC than sBCC), excellent cosmesis and low adverse event (AE) rate are reported.<sup>9</sup>

The objective of this systematic review and meta-analysis of RCTs was to evaluate PDT as a treatment for BCC. Treatment choice is based not only on efficacy but tailored to patients' preferences with respect to cosmesis and AE.<sup>11,12</sup> This review aims to provide clinicians with comprehensive, up-to-date evidence regarding these outcomes from a

review of all available published RCTs of PDT and comparator topical, surgical and combination treatments for low-risk BCC. A further purpose of this work was to inform the development of the updated British Association of Dermatologists and British Photodermatology Group guidelines for topical PDT (2018).

# Materials and methods

 This systematic review was performed in accordance with PRISMA guidelines<sup>13</sup> and registered with PROSPERO International prospective register of systematic reviews

(2017:CRD42017055804).

#### Eligibility criteria

Eligible studies are listed in Table 1. These were published RCTs evaluating topical PDT in adults with BCC with one or more of the following outcomes: clearance of BCCs at 3 months, sustained clearance at 1 year and 5 years; recurrence rates at 1 year or more; cosmesis; severe pain (leading to break in treatment/use of local analgesia); other AE and treatment tolerability.

# Data sources and search strategy

A systematic search of the MEDLINE, PubMed, EMBASE and CENTRAL databases was conducted from inception until 1 September 2017 (see Table S1 for search terms and strategies). Only studies reported in English were included. The National Library of Medicine (www.clinicaltrials.gov) and European Clinical Trials Database (www.clinicaltrialsregister.eu) were reviewed for additional details of clinical trials. Reference lists of included studies were reviewed for further eligible trials. Titles and abstracts of studies were independently screened by three investigators and disagreements were resolved in consultation with a further investigator. Full-text articles were reviewed

 against an *a priori* protocol (PROSPERO number 2017:CRD42017055804) and excluded if ineligible (see Table 2 for inclusion/exclusion criteria and Table S2 for details of excluded studies).

#### Data extraction and quality assessment

Data were independently extracted by two investigators using a standard form to record study details (country and setting, randomisation unit, study duration, follow-up duration and funding source); population details (patient characteristics, inclusion criteria, exclusion criteria, stratified or subgroup analyses); intervention details (outcome measure, treatment regimen) and results (numbers of patients randomised, analysed, with missing data, and with outcome). Differences were resolved by consensus. Methodological quality of each study was assessed using the Cochrane Risk of Bias tool (see Table S3) and quality of evidence for each outcome was assessed by the GRADE criteria (see Table S4).<sup>14</sup>

#### Data analysis

Extracted outcomes were combined for the meta-analysis, where possible, using Review Manager (RevMan 5.3.5) and analysed on an intention-to-treat (ITT) basis, using patient data if available and lesion data otherwise. Inconsistency and heterogeneity between studies was assessed using the  $l^2$  test and the Chi-squared tests where p < 0.05 was considered statistically significant.

#### Results

#### Study selection

The 2,331 results from the systematic search gave 155 articles for full-text assessment resulting in 15 eligible RCTs published between 2001-2017 (Figure 1) involving 2,327 patients and 3,509 BCCs. Most study populations were white, middle-aged and elderly

patients with all but one trial occurring in North America, Europe or Australia. The followup ranged from 3 months to >5 years. Treatment protocols for the included studies are summarised in Table 3.

#### PDT vs. Placebo cream-PDT

Two RCTs, involving 150 primary nBCC, were reported together.<sup>15</sup> A cycle of two treatments, 1 week apart was performed; at 3 months, partially-responding lesions were retreated with a second cycle. All lesions were excised and examined histologically. MAL-PDT showed superior clearance at 3 months post-final treatment compared with placebo-PDT (risk ratio (RR) 2.75; 95% confidence interval (CI) 1.84–4.10, Table 4) and better cosmesis (RR 3.00; 95% CI 1.80–5.01; Table 5), while manageable pain was worse (RR 1.37; 95% CI 1.14–1.66; Table 6).

#### PDT vs. Cryosurgery

Two RCTs compared PDT and cryosurgery; both involved only a single session of PDT (Table 3).<sup>16,17</sup> One compared ALA-PDT in both sBCC and nBCC with cryosurgery (two freeze-thaw cycles, 25–30 seconds, thawing period 2–4 min). Recurrence was evaluated by biopsy 12 months after final treatment.<sup>16</sup> The other RCT compared MAL-PDT with cryosurgery ( $\leq$ 20 seconds freeze, repeated 2-3 times; Table 3).<sup>17</sup>

For sBCC there was no significant difference between MAL-PDT and cryosurgery for initial lesion clearance or sustained clearance at 1 year, or in ALA-PDT recurrence rate at 1 year (Table 4). Our ITT analysis demonstrated a reduced sustained clearance at 5 years with single-session MAL-PDT compared with cryosurgery (RR 0.72; 95% CI 0.55–0.95; Table 4). This contrasted with the per-protocol analysis reported of recurrence rates of 20% with cryosurgery and 22% with PDT. This discrepancy is influenced by non-treatment-related AEs affecting seven patients treated with PDT but only two with cryosurgery. PDT gave superior

investigator-assessed cosmesis compared with cryosurgery at all assessment time points up to 5 years (RR 2.54; 95% CI 1.15–5.59; p < 0.0001; Figure 2). Patient-assessed excellent cosmesis following PDT was superior to cryosurgery at 3 months (RR 2.13; 95% CI 1.15–3.92) but not at 1 or 2 years (Table 5). There was no significant difference in treatment tolerability between PDT and cryosurgery (Table 6). <sup>17</sup>

For nBCC there was no difference in 1-year recurrence rates between cryosurgery and ALA-PDT.<sup>16</sup> ALA-PDT demonstrated better cosmesis than cryosurgery in sBCC and nBCC at 1 year (RR 3.73; 95% CI 1.96–7.07).

# PDT vs. Surgical excision

Three studies of nBCC compared PDT with surgical excision; two studies used ALA and one, MAL (Table 2). Meta-analysis showed modestly reduced rates of clearance at 3 months with PDT (RR 0.94; 95% CI 0.89–0.99; p = 0.03; Figure 3), and a slightly greater difference at 1 year (RR 0.90; 95% CI 0.84–0.97; p = 0.006; Figure 4). One study compared MAL-PDT with surgical excision of sBCC;<sup>18</sup> PDT did not show inferior rates of clearance at 3 months, but did so at 1 year (RR 0.91; 95% CI 0.85–0.96; p = 0.001; Table 4).

Two nBCC studies (one MAL, one ALA) included recurrence rate at > 1 and showed PDT had more recurrences than excision (pooled RR 13.19; 95% CI 2.58–67.37; p = 0.002; Figure 5). Clinical recurrence of sBCC after 1 year following the last treatment was 9.3% in the PDT arm and zero in the surgical excision arm, although 7% of excisions showed positive histological margins.<sup>18</sup>

Those studies reporting cosmetic outcome (investigator-assessed) showed an advantage of PDT over surgical excision at 1-year for both sBCC (RR 1.68; 95% Cl 1.32–2.14; p < 0.0001) and nBCC (RR 1.82; 95% Cl 1.19–2.80; p = 0.006; Table 5).<sup>18,19</sup>

Low-to-manageable pain was greater for MAL-PDT than for excision (RR 1.81; 95% Cl 1.09-3.01; p = 0.02; Table 6).<sup>19</sup>

### PDT vs. Topical Treatments

 A single RCT compared MAL-PDT with repeated applications of imiquimod or fluorouracil for sBCC.<sup>20-22</sup> This large RCT involved 601 patients, however 310 of 911 eligible patients declined to participate, 44% due to treatment preference. One cycle (two treatments) of MAL-PDT was used, but partially cleared sBCC at 3 months were not re-treated. There was no significant difference between one cycle of MAL-PDT or fluorouracil in clearance at 3 months, 1 or 5 years. MAL-PDT (one cycle) did not show inferior clearance rates to imiquimod at 3 months, but did at 1 year (RR 0.91; 95% CI 0.83–0.99; p=0.03) and 5 years (RR 0.81; 95% CI 0.70–0.95; p = 0.01; Table 4).

Compared with PDT, treatment with fluorouracil or imiquimod resulted in more prolonged pain, which intensified throughout the treatment course. The number of patients reporting severe pain per week during each treatment course, calculated using a cumulative measurement (2 weeks for PDT, 4 for fluorouracil, and 6 for imiquimod) indicated no difference in severe pain between imiquimod and MAL-PDT (RR 0.93: 95% CI 0.61-1.41; p = 0.72), while fluorouracil demonstrated fewer episodes of severe pain than PDT (RR 1.93: 95% CI 1.13-3.30; Table 6).

Suspected unexpected serious adverse reactions (SUSARs) reported with imiquimod included influenza-type symptoms (4%) and local wound infections (1%). SUSAR reported with fluorouracil included erysipelas (2%), local wound infection (1%) and leg ulceration (1%). No SUSARs were reported with PDT (see Tables 6 and S5 for pain and non-pain AEs respectively).<sup>20</sup>

# 

# PDT vs. Fractionated PDT

Two RCTs compared conventional PDT with fractionated ALA-PDT for sBCC (for protocols see Table 3).<sup>23-25</sup> The first involved 195 patients (573 lesions), with single-illumination ALA-PDT as the conventional arm.<sup>23,24</sup> Fractionated PDT showed greater sustained clearance, together with greater pain, than with single-illumination, with the 1-year clearance being 96% vs. 87% (RR 1.11; 95% Cl 1.05–1.17; p = 0.0002), and at 5 years, 80% vs. 60% (RR 1.33; 95% Cl 1.19–1.47; p < 0.00001; Table 4).<sup>23,24</sup> The second RCT, involving 162 patients with one primary sBCC treated per patient, used the one-cycle MAL-PDT protocol without retreatment of partially-responding lesions at 3 months. Treatment failures were excised and scored cosmetically poor. At 12 months' follow-up, 13 treatment failures occurred with MAL-PDT and six with fractionated ALA-PDT, but this was not a statistically significant difference (Table 4). Good-to-excellent cosmesis occurred more frequently with fractionated PDT (Table 5). There was significantly more pain during the second illumination (Table 6).<sup>25</sup>

# PDT vs. Laser or vs. Laser-enhanced PDT

Three RCTs compared conventional MAL-PDT and MAL-PDT with prior ablative laser treatment.<sup>26-28</sup> The largest (286 patients), a within-patient design, compared treatments in patients with three recurrent nBCCs in three arms: MAL-PDT, erbium-doped yttriumaluminium-garnet (Er:YAG)-laser ablation, and Er:YAG-laser ablation plus MAL-PDT.<sup>26</sup> The within-patient design precluded meta-analysis with the other RCTs.<sup>27,28</sup> A 1-year clearance rate of approximately 75% was seen with no significant differences between the three arms (Table 4). Superior cosmesis of the combined treatment to PDT alone was indicated at 3, 6, and 9 months, while the laser alone varied (best at 3 months, equal second at 6 months, and

Page 12 of 97

worst at 9 months); these results were all statistically significant (see Table 5 and Appendix S1).

The other, smaller, trials involved facial nBCC treatments with prior ablative fractional laser (AFL) treatment; one used CO<sub>2</sub>-AFL, the other Er:YAG-AFL.<sup>27,28</sup> The clearance rates at 3 months were, CO<sub>2</sub>-AFL–PDT 100% vs. PDT 88% and Er:YAG-AFL–PDT 76% vs. PDT 43% (RR 1.78; 95% CI 1.03–3.08).<sup>27,28</sup> One-year sustained clearance showed no significant difference in the CO<sub>2</sub>-AFL trial (CO<sub>2</sub>-laser–PDT 81% vs. PDT 64%). The CO<sub>2</sub>-AFL–PDT versus PDT trial showed excellent cosmetic outcome in both arms with a tendency towards superior cosmesis with combined treatment (Table 5). The AEs in the two trials (Table 6) were typical of PDT treatment, with mild-moderate pain during illumination, quickly resolving after illumination, together with a range of self-limiting, transient symptoms.<sup>27,28</sup>

One RCT compared ALA-PDT and imiquimod versus ALA-PDT and placebo-cream for recurrent BCC. This was a small study (34 patients) and the clearance results reported did not meet our inclusion criteria. However, greater clearance and fewer recurrences were noted in the PDT plus imiquimod arm. Cosmesis was very good in both groups (Table 5).

# Risk of bias

The overall risk of bias for the individual outcomes of each included study varied from low (13, 24%), to high (35, 65%), to very high (6, 11%). One half of the outcomes with very high overall risk of bias related to the within-patient study.<sup>26</sup> Regarding performance bias, high risk predominated (39, 72%) due to blinding being precluded by nature of the treatment; the remainder were low risk (15, 28%). All studies showed low risk of detection and other biases. Low risk predominated for the 54 study outcomes in respect of selection (50, 93%), attrition (51, 94%), and outcome-reporting (51, 94%) biases (see Table S3). For outcomes

 assessable by the GRADE criteria, the overall quality of evidence per outcome, varied from moderate to very low, the latter due mainly to imprecision and risk of bias (see Table S4).

#### Discussion

Overall, this systematic review found clearance and recurrence rates with conventional PDT were largely similar to alternative treatments, except for excision which showed distinctly improved rates.<sup>18,19,29-32</sup> Modestly reduced efficacy was seen with PDT versus imiquimod in a study where PDT was limited to only one treatment cycle. Strengths of PDT included its excellent cosmesis and lack of serious AEs. Although pain was of higher peak intensity than with topical treatments, it was typically of short duration and limited to the treatment session.

The results from the meta-analyses and the included RCTs indicate that surgical excision is more effective than PDT in both sustained clearance and reducing recurrence. Results were not always statistically significant, with shorter follow-up times, but there was a consistent tendency favouring surgery in both nBCC and sBCC. The data indicate that PDT and cryosurgery have similar clearance and recurrence rates. Whilst higher clearance of sBCC in comparison to nBCC after PDT is widely reported<sup>9,10</sup> this was not clear from the RCTs analysed and they were not designed to examine this; the single study involving both histological subtypes reported a statistically non-significant higher recurrence rate with superficial lesions at 1 year (38% vs. 13%).<sup>16</sup>

One RCT compared MAL-PDT with imiquimod or fluorouracil for sBCC.<sup>20-22</sup> Lesions partially responding to PDT at 3 months were regarded as treatment failures and surgically excised rather than re-treated. There was no significant difference in clearance rates between one cycle of MAL-PDT and courses of either fluorouracil (at 3 months, 1 or 5 years)

 or imiquimod (at 3 months), while at 1 and 5 years imiquimod showed advantage over PDT. Interestingly, PDT showed substantially greater sustained clearance than imiquimod in treating lower-extremity lesions in older patients; this was, however, a post-hoc subgroup analysis and requires corroboration.<sup>21</sup>

Results from included trials demonstrated that, with respect to good-to-excellent cosmesis, PDT for nBCC was superior to placebo and to cryosurgery. Meta-analysis of the two cryosurgery RCTs showed investigator-assessed excellent outcome favouring PDT. An earlier systematic review concluded cosmetic outcome for PDT was significantly better than for surgery; this was confirmed by the four included RCTs.<sup>33</sup> For sBCC, a single RCT showed MAL-PDT gave equivalent cosmesis to imiquimod or fluorouracil, although incompletely responding lesions were not re-treated with PDT but were excised, which was then defined as a poor aesthetic result for PDT.<sup>16</sup> Cosmetic differences between therapies were smaller in patient assessments, and diminished with time.<sup>17,19,31</sup> The cosmetic advantages of PDT and other topical treatments over surgery can make these more preferable to patients, particularly for sBCC.

Pain is a predictable feature of a PDT session and, although generally tolerable, this sometimes required a break in treatment or use of infiltrative local anaesthetic. Low or manageable pain was significantly worse with MAL-PDT than surgical excision, whereas severe AEs, such as wound dehiscence, were avoided with PDT. Modalities differed in the number of treatment sessions, from a single surgical episode to 56 applications of fluorouracil.<sup>16</sup> Pain intensified with treatment repetition;<sup>16</sup> however, pain was primarily evaluated by peak rather than cumulative values, which underestimated the pain experienced over a course of treatment. With PDT, pain was mostly limited to the irradiation period and, although peak pain was greater, it was of much shorter duration than

#### British Journal of Dermatology

with either imiquimod or fluorouracil. Calculation of cumulative pain showed that there was no difference between imiquimod and MAL-PDT, while fluorouracil was less painful than PDT.<sup>20</sup> Recent PDT studies utilising low irradiance protocols (≤35 mWcm<sup>-2</sup>, compared with 50-200 mWcm<sup>-2</sup> in this review) show reduced pain with apparent preservation of efficacy.<sup>34-38</sup>

Treatment-related AEs, excluding pain, were widely reported in RCTs. Severe local AEs seldom occurred with PDT and mild-to-moderate AEs predominated. Secondary infection was reported following surgery in 0-5% of patients, following fluorouracil in 2%, and imiquimod in 0.5%, of patients; in contrast, infection following PDT was reported in just a single patient throughout all trials, speculatively attributable to the potent antimicrobial action of topical PDT.<sup>18,20,39</sup> Following PDT, effects including weeping, crusting, erosion and ulceration were less severe and resolved more rapidly than with cryosurgery, imiquimod or fluorouracil.<sup>16,17,20</sup> MAL-PDT had fewer reports of moderate-to-severe local swelling, itching, crusting or erosion than either imiquimod or fluorouracil.<sup>20-22</sup> The non-pain-related AEs were largely transient and of mild-to-moderate intensity after PDT and cryosurgery, and were less frequent following PDT.<sup>16,17</sup> Of all the treatments, other than placebo cream, superiority was indicated for PDT with respect to non-pain AEs, particularly compared with imiquimod.

In practice, advantages of therapeutic options may vary depending on lesion location, lesion and patient characteristics.<sup>12,40,41</sup> Patient preferences did not directly feature as outcomes in reviewed RCTs, but it was noted that differences in cosmesis were often less marked when recorded by patients than clinicians.<sup>17,19</sup> A study of patient preferences showed cure and cosmesis were first priorities, whereby those with head/neck BCCs showed a willingness to trade risk of recurrence for better cosmetic outcome.<sup>11</sup> A

systematic review of the needs and experiences of patients with skin cancer found only three studies of keratinocyte carcinoma; no RCT included here considered the psychosocial effects of BCC or its treatment, and the need for further research in this area is evident.<sup>40,41</sup> Cosmesis and AEs need to be taken into account as well as clearance, to reflect patient's views.<sup>11,42,43</sup>

The reviewed RCTs also included recent approaches to enhancing clearance with PDT, i.e. fractionation of light dose, assisted penetration of prodrug by skin pre-treatment with ablative fractional lasers, and combination of PDT with another modality. Fractionated illumination showed higher sustained clearance of BCC than single illumination PDT, but greater pain was seen with fractionation, particularly during the second illumination  $^{23,24,25}$  The RCTs comparing conventional PDT versus PDT with laser pre-treatment showed a tendency towards improved clearance in the combination arm,  $^{26-28}$  while the RCT of conventional PDT versus PDT plus imiquimod suggested greater clearance and fewer recurrences in the combined treatment arm.<sup>44</sup> These findings indicate that combination PDT warrants further study.

Strengths of this systematic review include assessment of quality of studies using the Cochrane Risk of Bias tool and GRADE criteria, with presentation of ITT analyses and metaanalyses when possible. The scope included all RCTs comparing topical PDT directly with any other treatment for low-risk BCC; hence this is the most comprehensive systematic review of PDT for BCC to date.<sup>45,46</sup> Non-English language studies were not included. The major limitations reflected those of the reviewed studies, including no systematic reporting of patient concerns.<sup>41,42</sup> A challenge in evaluating clinical trials of PDT is that protocols have varied including in regard to pro-drug used and incubation time; the light source, dosage and irradiance; and number of treatment sessions or cycles given. This severely restricted

#### British Journal of Dermatology

the ability to pool trial data. The included RCTs partially answered the need, identified in a Cochrane review 10 years ago, for head-to-head trials of effectiveness of BCC treatments, with long-term follow-up.<sup>33</sup> Future RCTs would benefit from including PDT re-treatment of partially responding lesions, as in usual clinical practice, and from reporting subgroup analyses according to anatomical site, lesion size and patient age, particularly as major differences were shown between PDT and imiquimod in older patients with lower leg lesions.

In conclusion, this systematic review shows that topical PDT, amongst a range of treatment options, can be used appropriately for low-risk BCCs. The included RCTs demonstrated PDT is a favourable treatment option for cases of superficial and nodular BCC where patients place a high importance upon cosmesis, avoidance of ongoing AEs or potential for severe treatment-related complications. New approaches to improve upon conventional topical PDT outcomes, namely prior use of AFL, fractionated irradiation in PDT, or the combination of PDT with other topical treatments, show promise and warrant further exploration in BCC.

#### Acknowledgments

This systematic review and meta-analysis was supported by the British Association of Dermatologists and used to inform the 2018 clinical guidelines for topical PDT.

# **Supporting Information**

Supporting Information may be found in the online version of this article at the publisher's website: **Table S1** Search strategy, **Table S2** Papers excluded from quantitative analysis, **Table S3** Cochrane risk of bias, **Table S4** GRADE evidence, **Table S5** Non-pain AEs, **Appendix S1** Forest plots.

# References

1	Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of
	nonmelanoma skin cancer. Br J Dermatol 2012; 166: 1069-80.

- 2 Wu X, Elkin EE, Marghoob AA. Burden of basal cell carcinoma in USA. Future Oncol 2015; 11: 2967-74.
- von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. Journal of the American Academy of Dermatology 1984; 10: 1043-60.
- 4 Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002; 147: 41-7.
- 5 McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. Arch Dermatol 1997; 133: 593-6.
- 6 van Loo E, Mosterd K, Krekels GA et al. Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow-up. Eur J Cancer 2014; 50: 3011-20.
- 7 Trakatelli M, Morton C, Nagore E et al. Update of the European guidelines for basal cell carcinoma management. Eur J Dermatol 2014; 24: 312-29.
- 8 Clark CM, Furniss M, Mackay-Wiggan JM. Basal cell carcinoma: an evidence-based treatment update. Am J Clin Dermatol 2014; 15: 197-216.
- Morton CA, McKenna KE, Rhodes LE et al. Guidelines for topical photodynamic therapy:
   update. Br J Dermatol 2008; 159: 1245-66.
- 10 Morton C, Szeimies RM, Sidoroff A et al. European Dermatology Forum Guidelines on topical photodynamic therapy. Eur J Dermatol 2015; 25: 296-311.

11	Martin I, Schaarschmidt ML, Glocker A et al. Patient Preferences for Treatment of Basal Cell
	Carcinoma: Importance of Cure and Cosmetic Outcome. Acta Derm Venereol 2016; 96: 355-
	60.
12	de Haas ER. Treatment of choice in superficial basal cell carcinoma. Br J Dermatol 2015; 172:
	563.
13	Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and
	meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-41.
14	Guyatt GH, Ebrahim S, Alonso-Coello P et al. GRADE guidelines 17: assessing the risk of bias
	associated with missing participant outcome data in a body of evidence. J Clin Epidemiol
	2017; 87: 14-22.
15	Foley P, Freeman M, Menter A et al. Photodynamic therapy with methyl aminolevulinate for
	primary nodular basal cell carcinoma: results of two randomized studies. International
	journal of dermatology 2009; 48: 1236-45.
16	Wang I, Bendsoe N, Klinteberg CA et al. Photodynamic therapy vs. cryosurgery of basal cell
	carcinomas: results of a phase III clinical trial. Br J Dermatol 2001; 144: 832-40.
17	Basset-Seguin N, Ibbotson SH, Emtestam L et al. Topical methyl aminolaevulinate
	photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year
	randomized trial. Eur J Dermatol 2008; 18: 547-53.
18	Szeimies RM, Ibbotson S, Murrell DF et al. A clinical study comparing methyl aminolevulinate
	photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with
	a 12-month follow-up. Journal of the European Academy of Dermatology and Venereology
	2008; 22: 1302-11.
19	Rhodes LE, de Rie M, Enstrom Y et al. Photodynamic therapy using topical methyl
	aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter
	randomized prospective trial. Arch Dermatol 2004; 140: 17-23.

- 20 Arits AH, Mosterd K, Essers BA et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. The lancet oncology 2013; 14: 647-54.
  - 21 Roozeboom M, Arits A, Mosterd K et al. Three-year follow-up results of photodynamic therapy vs. Imiquimod vs. Fluorouracil for treatment of superficial basal cell carcinoma: a single-blind, noninferiority, randomized controlled trial. In: Journal of investigative dermatology, Vol. 136. 2016; 1568-74.
- Jansen MHE, Mosterd K, Arits A et al. Five-Year Results of a Randomized Controlled Trial
   Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5 Fluorouracil in Patients with Superficial Basal Cell Carcinoma. J Invest Dermatol 2017.
- 23 de Haas ER, Kruijt B, Sterenborg HJ et al. Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy. J Invest Dermatol 2006; 126: 2679-86.
- Vijlder H, Sterenborg H, Neumann H et al. Light fractionation significantly improves the response of superficial basal cell carcinoma to aminolaevulinic acid photodynamic therapy: five-year follow-up of a randomized, prospective trial. In: Acta dermato-venereologica, Vol. 92. 2012; 641-7.
- 25 Kessels J, Kreukels H, Nelemans PJ et al. Treatment of superficial basal cell carcinoma by topical photodynamic therapy with fractionated 5-aminolevulinic acid 20% versus two stage topical methylaminolevulinic acid: results of a randomized controlled trial. Br J Dermatol 2017.
- 26 Smucler R, Vlk M. Combination of Er:YAG laser and photodynamic therapy in the treatment of nodular basal cell carcinoma. Lasers in Surgery and Medicine 2008; 40: 153-8.
- 27 Haak C, Togsverd-Bo K, Thaysen-Petersen D et al. Fractional laser-mediated photodynamic therapy of high-risk basal cell carcinomas--a randomized clinical trial. In: The British journal of dermatology, Vol. 172. 2015; 215-22.

28	Choi SH, Kim KH, Song KH. Er:YAG ablative fractional laser-primed photodynamic therapy
	with methyl aminolevulinate as an alternative treatment option for patients with thin
	nodular basal cell carcinoma: 12-month follow-up results of a randomized, prospective,
	comparative trial. J Eur Acad Dermatol Venereol 2016; 30: 783-8.
29	Berroeta L, Clark C, Dawe RS et al. A randomized study of minimal curettage followed by
	topical photodynamic therapy compared with surgical excision for low-risk nodular basal cel
	carcinoma. Br J Dermatol 2007; 157: 401-3.
30	Mosterd K, Thissen MR, Nelemans P et al. Fractionated 5-aminolaevulinic acid-
	photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma:
	results of a randomized controlled trial. Br J Dermatol 2008; 159: 864-70.
31	Rhodes LE, de Rie MA, Leifsdottir R et al. Five-year follow-up of a randomized, prospective
	trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal
	cell carcinoma. Arch Dermatol 2007; 143: 1131-6.
32	Roozeboom MH, Aardoom MA, Nelemans PJ et al. Fractionated 5-aminolevulinic acid
	photodynamic therapy after partial debulking versus surgical excision for nodular basal cell
	carcinoma: a randomized controlled trial with at least 5-year follow-up. Journal of the
	American Academy of Dermatology 2013; 69: 280-7.
33	Bath-Hextall FJ, Perkins W, Bong J et al. Interventions for basal cell carcinoma of the skin.
	Cochrane Database Syst Rev 2007: CD003412.
34	Zeitouni NC, Sunar U, Rohrbach DJ et al. A prospective study of pain control by a 2-step
	irradiance schedule during topical photodynamic therapy of nonmelanoma skin cancer.
	Dermatol Surg 2014; 40: 1390-4.
35	Zeitouni NC, Paquette AD, Housel JP et al. A retrospective review of pain control by a two-
	step irradiance schedule during topical ALA-photodynamic therapy of non-melanoma skin
	cancer. Lasers Surg Med 2013; 45: 89-94.
	21

36	Moseley H, Allen JW, Ibbotson S et al. Ambulatory photodynamic therapy: a new concept in
	delivering photodynamic therapy. Br J Dermatol 2006; 154: 747-50.
37	Ibbotson SH, Ferguson J. Ambulatory photodynamic therapy using low irradiance inorganic
	light-emitting diodes for the treatment of non-melanoma skin cancer: an open study.
	Photodermatol Photoimmunol Photomed 2012; 28: 235-9.
38	Kessels J, Dzino N, Nelemans PJ et al. Ambulatory Photodynamic Therapy for Superficial
	Basal Cell Carcinoma: An Effective Light Source? Acta Derm Venereol 2017; 97: 649-50.
39	Loebel N, Andersen R, Dawson T et al. CHAPTER 28 Antimicrobial Photodynamic Therapy: A
	Decade of Development and Clinical Study. In: Photodynamic Medicine: From Bench to
	Clinic: The Royal Society of Chemistry. 2016; 519-48.
40	Bath-Hextall F, Nalubega S, Evans C. The needs and experiences of patients with skin cancer:
	a qualitative systematic review with metasynthesis. Br J Dermatol 2017; 177: 666-87.
41	Kelleners-Smeets NW, Mosterd K, Nelemans PJ. Treatment of Low-Risk Basal Cell Carcinoma.
	J Invest Dermatol 2017; 137: 539-40.
42	Tinelli M, Ozolins M, Bath-Hextall F et al. What determines patient preferences for treating
	low risk basal cell carcinoma when comparing surgery vs imiquimod? A discrete choice
	experiment survey from the SINS trial. BMC Dermatol 2012; 12: 19.
43	Weston A, Fitzgerald P. Discrete choice experiment to derive willingness to pay for methyl
	aminolevulinate photodynamic therapy versus simple excision surgery in basal cell
	carcinoma. Pharmacoeconomics 2004; 22: 1195-208.
44	Osiecka B, Jurczyszyn K, Ziolkowski P. The application of Levulan-based photodynamic
	therapy with imiquimod in the treatment of recurrent basal cell carcinoma. Med Sci Monit
	2012; 18: PI5-9.
45	Zou Y, Zhao Y, Yu J et al. Photodynamic therapy versus surgical excision to basal cell
	carcinoma: meta-analysis. J Cosmet Dermatol 2016; 15: 374-82.

1		
2		
3	46	Roozeboom MH, Arits AH, Nelemans PJ et al. Overall treatment success after treatment of
4		
5 6		primary superficial basal cell carcinoma: a systematic review and meta-analysis of
0 7		randomized and nonrandomized trials. Br J Dermatol 2012; 167: 733-56.
8		
9	47	Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma.
10	.,	
11		British Association of Dermatologists. Br J Dermatol 1999; 141: 415-23.
12		-
13 14		
15		
16		
17		
18		
19		
20		
21		
22 23		
23		
25		
26		
27		
28		
29		
30 31		
32		
33		
34		
35		
36		
37		
38 39		
40		
41		
42		
43		
44		
45 46		
40		
48		
49		
50		
51		
52 53		
53 54		
55		
56		
57		
58		23
59		

# Table 1 Trials comparator arms

Comparator arm(s)	BCC type	Trial
Placebo-PDT	nBCC	Foley 2009 <sup>15</sup> (2 RCTs)
Cryosurgery	sBCC	Basset-Seguin 2008 <sup>17</sup>
Cryosurgery	nBCC, sBCC	Wang 2001 <sup>16</sup>
	nBCC	Berroeta 2007 <sup>29</sup>
Surgery	nBCC	Mosterd 2008 <sup>30</sup> , Roozeboom 2013 <sup>32</sup>
Surgery	nBCC	Rhodes 2004 <sup>19</sup> , Rhodes 2007 <sup>31</sup>
	sBCC	Szeimies 2008 <sup>18</sup>
Topical treatments	sBCC	Arits 2013 <sup>20</sup> , Roozeboom 2016 <sup>21</sup> , Jansen 2017 <sup>22</sup>
Fractionated PDT	sBCC	De Haas 2006 <sup>23</sup> , De Vijlder 2012 <sup>24</sup>
	sBCC	Kessels 2017 <sup>25</sup>
Laser enhanced PDT	high-risk nBCC	Haak 2015 <sup>27</sup>
	nBCC	Choi 2016 <sup>28</sup>
Laser enhanced PDT, and laser	recurrent nBCC	Smucler 2008 <sup>26</sup> (3 arm)
PDT then imiquimod	recurrent nBCC	Osiecka 2012 <sup>44</sup>

Abbreviations: BCC, basal cell carcinoma; PDT, photodynamic therapy; RCT, randomized controlled trial; nBCC, nodular basal cell carcinoma; sBCC, superficial basal cell carcinoma.

# Table 2 Study characteristics and inclusion/exclusion criteria

9 10	Study	Population (age in years)	Lesion characteristics	Inclusion and exclusion criteria
11 12 13	Foley 2009 <sup>15</sup> Parallel groups 2 RCTs Australia and USA	n = 131 (150 nBCC); <b>PDT</b> : 47 M 19 F, mean age 66 (range 28–88), skin type I (41%), II (39%), III and IV (20%); <b>Placebo-PDT</b> : 52 M,13 F, mean age 67 (range 39–88) skin type I (29%), II (43%), III and IV (28%)	Primary nBCC: <b>PDT</b> : face/scalp 25%, neck 12%, trunk 43%, extremities 20%, largest diameter (mm) 8.8 (range 6–20), depth (mm) 1.3 (range 0–5.0): <b>Placebo-PDT</b> : face/scalp 31%, neck 1%, trunk 45%, extremities 23%, largest diameter (mm) 9.0 (range 6–22), depth (mm) 1.2 (range 1–3.0)	Standard, plus the exclusions: Periorbital, ears or nasolabial fold; diameter < 6 mm (any site) or > 15 mm (face or scalp) > 20 mm (extremities or neck) or > 30 mm (trunk),
14 15	Basset-Seguin 2008 <sup>17</sup> Parallel groups RCT 13 European centres		Primary sBCC: PDT: face/scalp 6%, trunk/neck 72%, extremities 22%, largest diameter (mm) 5–10 43%, 11–19 42%, $\geq$ 20 16%: Cryosurgery: face/scalp 4%, trunk/neck 76%, extremities 20%, largest diameter (mm) 5–10 42%, 11–19 42%, $\geq$ 20 16%	<b>Standard, plus the Inclusions:</b> Patients with $\leq$ 10 eligible lesions verified by histology and suitable for cryosurgery. Diameter > 6 mm but < 15 mm (face, scalp), < 20 mm (extremities, neck), < 30 mm (trunk).
10	Wang 2001 <sup>16</sup> Parallel groups RCT Sweden	n = 88 (88 lesions: 39 sBCC, 49 nBCC); 44 F: 44 M. Age range 42-88	nBCC and sBCC: <b>PDT</b> : 22 sBCC, 25 nBCC: <b>Cryosurgery</b> : 17 sBCC, 24 nBCC; <b>Location</b> : 54% trunk, 28% head and neck, 11% legs and 7% arms.	Standard, plus the exclusions: daily intake of vitamins E or C, beta carotene, iron preparations, NSAIDs or strong analgesics at higher doses, BCC on nose, abdominal pain of unknown aetiology.
19	Berroeta 2007 <sup>29</sup> Parallel groups RCT UK	n = 31 (40 nBCC); 12 F: 19 M; Median age 72 (range 50–83)	nBCC; Largest diameter $\leq$ 20mm on anatomically noncritical sites	Standard, plus the exclusions: high risk sites, recurrent BCC, BBC largest diameter > 20 mm
21 22	Mosterd 2008 <sup>30</sup> Roozeboom 2013 <sup>32</sup> Parallel groups RCT Netherlands	n = 149 (171 nBCC); 74 F: 75 M; Age, mean ± SD, 64.7 ± 13	Primary nBCC; Size (mm), mean ± SD, 9.1 ± 4.1; <b>Location</b> : Facial 52% (forehead or temple, 22.8%; nose or perinasal zone, 14.0%), nonfacial 48% (back, 14.6%)	Standard, plus the inclusion: Maximum diameter 20 mm. and plus the exclusions: Life expectancy of < 5 years, Recurrent BCC, histological subtypes other than nodular, localisation on concave or hairy parts of the skin
24 25 26	Rhodes 2004 <sup>19</sup> Rhodes 2007 <sup>31</sup> ; Parallel groups RCT European University Dermatology Departments	n = 101 (110 nBCC); 40 F: 61 M; Mean age: group 1; 69 (range 40–95), group 2; 67 (range 38–82).	Primary nBCC; <b>Location</b> : 50% face or scalp; 40% trunk or neck; 10% extremities. Largest diameter (mm), ≤ 10 60%; > 10 and < 20 31%; ≥ 20 5%.	Standard, plus the inclusions: suitable for simple excision surgery and, plus the exclusions: Tumours on extremely concave areas or hairy skin. Patients > 10 eligible lesions, < 6 mm or > 15 mm (face or scalp), > 20 mm (extremities or neck), or > 30 mm (trunk); probable poor compliers; life expectancy < 5 years.
28 29	Szeimies 2008 <sup>18</sup> Parallel groups RCT Multicentre; UK/ Germany/ Austria/ Switzerland	n = 196 (267 sBCC); 66 F: 130 M; Mean age 63.8 (range 31–92); White Caucasian	Primary sBCC: Location: 65% trunk and neck; 27% extremities; 8% face and scalp. White Caucasian 100% Diameter (mm) mean $\pm$ SD: PDT = 12.5 $\pm$ 3.7; Surgery = 12.6 $\pm$ 3.7. Number per patient, mean $\pm$ SD, 1.4 $\pm$ 0.9	Standard, plus the inclusions: Largest diameter ≥ 8 mm and ≤ 20 mm.; and plus the exclusions Suitable for simple excision. Midface region (nose, nasolabial or orbital areas), > 5, In sun damaged skin where surgery unsuitable due to BCC's.
32	Arits 2013 <sup>20</sup> Roozeboom 2016 <sup>21</sup> Jansen 2017 <sup>22</sup> ;Parallel groups RCT; Netherlands	n = 601 (601 sBCC); 298 F: 303 M; Mean age 63 (range 26–91); One BCC per patient (largest).	Primary sBCC, histologically verified: <b>Location</b> : 13% head or neck; 60% trunk; 14% upper extremities; 13% lower extremities. Median size (mm <sup>2</sup> ) 59 (range 5–5,472); median size (mm <sup>2</sup> ) was 52 in MAL-PDT group and 63 in both imiquimod and fluorouracil groups.	
34 35 36	Smucler 2008 <sup>26</sup> Within patient RCT Czech Republic	n = 286 (858 recurrent nBCC); 94 F: 192 M; Age, mean $\pm$ SD, 65.1 $\pm$ 7.3; Skin type I 29%, II 69.9%, III 1.1%	Recurrent nBCC	<b>Inclusions:</b> At least 3 recurring nBCCs (histologically verified). At least 30mm between tumours. Refractory to at least one surgical excision, cryosurgery or laser ablation. <b>Exclusions:</b> Inability to attend regular checkups (patients from abroad were excluded from the study).
	Haak 2015 <sup>27</sup> Parallel groups RCT Denmark	n = 32 (32 nBCC); 17 F: 15 M; Median age 66 (range 57–73.5) Skin type II (20), III (12)	Primary nodular facial 'high-risk' BCC which was histologically confirmed. Location: 17% nose; 25% forehead; 9% cheek; 9% oral area; 9% periorbital area. Single lesion per patient. Median tumour size: AFXL-PDT, 7 mm; PDT, 8.5 mm.	<b>Standard, plus the inclusions:</b> High-risk facial tumour due to either (i) diameter > 15mm, (ii) located in high-risk facial H zone, or (iii) located on severely sun damaged skin with ≥ 1 actinic lesions requiring treatment. <b>and, plus the exclusions:</b> Skin type IV–VI, risk of poor compliance
40 41			25	

Study	Population (age in years)	Lesion characteristics	Inclusion and exclusion criteria
		Primary nBCC of maximum depth ≤ 2 mm; histologically verified.	Standard, plus the inclusions: Patients where surgical excision would be difficult because of bleeding abnormalities or cardiac problems. and, plus the exclusions: Midface region, nose orbital areas or ears; longest diameter > 15mm; > 5 eligible lesions; active systemic infectious disease; indication of poor compliance
Dsiecka 2012 <sup>44</sup> Parallel groups RCT Poland		Recurrent BCC, confirmed histopathologically: Location: Face (nose, nasolabial sulcus, cheek, suborbital region) Mean diameter 5 mm	Standard, plus the inclusions: Facial BCC previously treated with cryosurgery, laser therapy or surgical excision without satisfactory results. Good health and, plus the exclusions: Systemic disease.
		sBCC	Inclusions: Clinically or histologically diagnosed sBCC (with at least one histologically diagnosed primary sBCC per patient). Exclusions: Child or not white-Caucasian.
	by fractionated illumination): <b>Single illumination</b> , Age, mean 56.7 (range 31–88): <b>Fractionated illumination</b> , Age, mean 56.9 (range 32–84): <b>Fractionated illumination with later enrolment</b> , Age, mean 65.5 (range 39–	sBCC	Inclusions: Clinically or histologically diagnosed sBCC (with at least one histologically diagnosed primary sBCC per patient). Exclusions: Child or not white-Caucasian.
Kessels 2017 <sup>25</sup>	(range 38–85)		Standard, plus the inclusions: One sBCCper patient selected (largest- diameter eligible). and, plus the exclusions: Prior treatment at the same site. sBCC localized in the hairy scalp and convex or concave areas such as the ears or fingers.
	Choi 2016 <sup>28</sup> Parallel groups RCT South Korea Desiecka 2012 <sup>44</sup> Parallel groups RCT Parallel groups RCT Pa	n = 39 (42 nBCC): MAL-PDT: 7 F: 12 M; Age, mean ± SD, 63.3 ± 10.7; Skin         arallel groups RCT         South Korea         De Valle (2012 <sup>44</sup> )         n = 34 (34 recurrent); Age range 50–68.         Parallel groups RCT         Poland         De Haas 2006 <sup>23</sup> n = 155 patients (505 sBCC): Single illumination, Age, mean 57 (range 32– 81): Fractionated illumination, Age, mean 56 (range 31–83)         De Vijlder 2012 <sup>24</sup> n = 195 patients (573 sBCC) (plus further 50 patients with 172 sBCC treated by fractionated illumination). Single illumination, Age, mean 65.7 (range 31–88): Fractionated illumination, Age, mean 65.9 (range 32–84): Fractionated illumination with later enrolment, Age, mean 65.5 (range 39– 90);         Kessels 2017 <sup>25</sup> n = 162 patients (162 sBCC): MAL-PDT: 45 F; 35 M: Age, mean 63.6 (range 28-83): ALA 2-fold fractionated illumination: 42 F; 40 M: Age, mean 65.9	Loid 2016 <sup>28</sup> Loid 2016 <sup>28</sup> n = 39 (42 nBCC): MAL-PDT: 7 F: 12 M; Age, mean ± SD, 63.3 ± 10.7; Skin type: III 15%, IV 65%, V 20%: Er:YAG AFL-PDT: 11 F: 9 M ; Age, mean ± SD, 66.9 ± 9.6; Skin type III 11%, IV 75%, V 16%Primary nBCC of maximum depth $\leq$ 2 mm; histologically verified.Disiecka 2012 <sup>44</sup> arallel groups RCTn = 34 (34 recurrent); Age range 50–68.Recurrent BCC, confirmed histopathologically: Location: Face (nose, nasolabial sulcus, cheek, suborbital region) Mean diameter 5 mmDe Haas 2006 <sup>23</sup> arallel groups RCT Noladn = 155 patients (505 sBCC): Single illumination, Age, mean 57 (range 32– 81): Fractionated illumination, Age, mean 56 (range 31–83)sBCCDe Vijlder 2012 <sup>24</sup> n = 195 patients (573 sBCC) (plus further 50 patients with 172 sBCC treated by fractionated illumination, Single illumination, Age, mean 65.7 (range 32– 90);sBCCSeesels 2017 <sup>25</sup> n = 162 patients (162 sBCC): MAL-PDT: 45 F; 35 M: Age, mean 63.6 (range 28-83): ALA 2-fold fractionated illumination: 42 F; 40 M: Age, mean 63.6 (range 28-83): ALA 2-fold fractionated illumination: 42 F; 40 M: Age, mean 65.9 (range 32– 90);Primary sBCC: MAL-PDT: head/nack 1%, trunk 73%, upper extremities 16%, lower extremities 1

Abbreviations: M, male; F, female; n, number; skin type, Fitzpatrick skin type; MAL, methyl aminolaevulinate; ALA, 5-aminolaevulinic acid; PDT, photodynamic therapy; BCC, basal cell carcinoma; PDT, photodynamic therapy; RCT, randomized controlled trial; nBCC, nodular basal cell carcinoma; sBCC, superficial basal cell carcinoma; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation. Standard: inclusion when  $\geq$  18 years, primary histologically confirmed nBCC or sBCC, not previously treated. Exclusion: anogenital area, areas within 1 cm of H-zone, pigmented or morphoeaform or infiltrative BCC, dermatological conditions that interfere with treatment, genetic skin disorders, immunosuppressive therapy, pregnant or breastfeeding women.

# Table 3 Treatment protocols for included studies

Study	всс	Conventional PDT Treatment [Skin preparation; Prodrug; Incubation (hours); Wavelength (nm); Irradiance (mWcm <sup>-2</sup> ); Sessions; Light dose per session (Jcm <sup>-2</sup> ); PDT re-treatment]	Comparator Treatment
Foley 2009 <sup>15</sup>	nodular	Surface debridement, no LA; MAL (Metvix); 3; 570–670, noncoherent; 50–200; 2, (1 week apart); 75; 2 sessions if partial response (≥ 50% but < 100%) at 3 months, 22% of patients.	Placebo-PDT: lesion debulked with curette, PDT protocol with placebo cream.
Basset-Seguin 2008 <sup>17</sup>	superficial	Surface scrape, no LA; MAL (Metvix); 3; 570–670, noncoherent; not stated; 1; 75; 2 sessions if noncomplete response at 3 months, 30% of lesions	Cryosurgery: ice field formation with a 3 mm rim of healthy tissue. Ice field maintained for 20 seconds. Double freeze-thaw cycle.
Wang 2001 <sup>16</sup>	nodular and superficial	Surface scrape, no LA; ALA 20% (nonproprietary); 6; 635, laser; 80 ± 20; 1; 60; 1 session if noncomplete clinical response at 4, 8, or 12 months or histological response at 3 months after final treatment, 30% of lesions	Cryosurgery: 2 freeze thaw cycles comprising 25–30 seconds freeze and 2–4 minutes thaw
Berroeta 2007 <sup>29</sup>	nodular	Surface scrape, no LA, diagnostic punch biopsy for PDT only; ALA 20% (nonproprietary); 6; 635, laser; 120; 1; 125; If failure, re-treat at 3 months (1 session)	Surgery: under LA; excision with margins as recommended. <sup>47</sup>
Mosterd 2008 <sup>30</sup> Roozeboom 2013 <sup>32</sup>	nodular	Partially debulked (to level of skin) under LA, 3 weeks prior to PDT; ALA 20% (nonproprietary); 4; 585–720, noncoherent; 100; 2, (1 hour apart); fractionated, 75 + 75; No, incomplete response or recurrent tumour was re-treated surgically	Surgery: Tumour excised with a 3 mm margin under LA. Re-excised if tumour present at margins (lateral or deep) and deemed treatment failure.
Rhodes 2004 <sup>19</sup> Rhodes 2007 <sup>31</sup>	nodular	Surface scrape, no LA; MAL (Metvix); 3; 570–670, noncoherent; 50–200; 2, (1 week apart); 75; If failure, re- treat at 3 months	Surgery: Elliptical excision surgery with $\ge$ 5 mm margins under LA.
Szeimies 2008 <sup>18</sup>	superficial	Surface scrape, no LA; MAL (Metvix); 3; 630 $\pm$ 5, noncoherent; 62–88; 2, (1 week apart); 37; If failure, re-treat at 3 months	Surgery: elliptical excision with 3 mm margin.
Arits 2013 <sup>20</sup> Roozeboom 2016 <sup>21</sup> Jansen 2017 <sup>22</sup>	superficial	Surface scrape, no LA, ; MAL (Metvix); 3; $\approx$ 630, noncoherent; $\approx$ 88; 2, (1 week apart); 37; No	Imiquimod: applied 5 days a week for 6 weeks. Fluorouracil: applied twice daily for 4 weeks.
Smucler 2008 <sup>26</sup>	recurrent nodular	None mentioned; MAL (Metvix); 3; 630 ± 5, noncoherent; not stated; 2, (1 week apart); 37; No	Er:YAG laser: topical anaesthetic applied for 1 hour. Ablation using Er:YAG AFL usually with 600–1000 mJ at 7 Hz. Infiltration of LA and bipolar electrocoagulation where necessary. Er:YAG laser and PDT: Laser as above, with MAL-PDT, as per protocol on left, subsequently.
Haak 2015 <sup>27</sup>	nodular	Partially debulked under LA , ; MAL (Metvix); 3; 630 $\pm$ 5, noncoherent; $\approx$ 77; 2, (7–10 days apart); 37; No	$\rm CO_2$ AFL PDT: LA injection with partial debulking followed by CO_2 AFL with 2 stacked pulses of 40 mJ/pulse at density of 5% on tumour area plus 5 mm margin. Treatment sessions were performed twice with a 7-10 days interval.
Choi 2016 <sup>28</sup>	nodular	None; MAL (Metvix); 3; 630 $\pm$ 5, noncoherent; not stated; 2, (1 week apart); 37; No	Er:YAG AFL PDT: Topical LA applied prior to Er:YAG AFL, 2940 nm with a 550 μm ablation depth, 22% treatment density and a single pulse. Immediately following AFL, a single session of MAL-PDT as per protocol on left.
Osiecka 2012 <sup>44</sup>	recurrent	None mentioned; ALA (Levulan); 4; 635 ± 20, noncoherent; 56; 2, (2 days apart); 100; No	PDT and Imiquimod: PDT protocol followed by imiquimod cream, 3 days post irradiation and applied twice per week for 5 weeks. The placebo-PDT arm used vehicle cream instead of imiquimod.
De Haas 2006 <sup>23</sup> De Vijlder 2012 <sup>24</sup>	superficial	Surface scrape, LA in ALA preparation; ALA 20% (nonproprietary with 2% LA); 4 vs 4 + 6; Diode laser (630), LED (633) Broadband (590–650); 50; 1; 75 vs fractionated 20 + 80, (2 hours apart); Re-treated lesions excluded from analysis	Fractionated PDT: twofold ALA-PDT illumination 20 Jcm <sup>-2</sup> and 80 Jcm <sup>-2</sup> after 4 and 6 hours respectively.
Kessels 2017 <sup>25</sup>	superficial	None mentioned; MAL (Metvix); 3; 630 ± 5, LED; 75; 2 (1week apart); 75; Residual tumour at 3 months considered treatment failure and excised.	Fractionated PDT: twofold ALA-PDT illumination 20 Jcm <sup>-2</sup> and 80 Jcm <sup>-2</sup> after 4 and 6 hours respectively.

Abbreviations: PDT, photodynamic therapy; BCC, basal cell carcinoma; LA, local anaesthetic; MAL, methyl aminolaevulinate; ALA, 5-aminolaevulinic acid; Er:YAG, erbium-doped yttrium-aluminium-garnet; AFL, ablative fractional laser; LED, light emitting diode light source

# Table 4 Clearance and recurrence rates

Includeconfirmed https://confirmed.https:	Study (Comparator)	Assessment of clearance and recurrence	Clearance at 3 months	Sustained clearance at 1 year	Sustained clearance at 5 years	Recurrence rate ≥ 1 year
(Cryosurgery)       treatment:       1.01 95%CI 0.89-1.14, p = 0.90       95%CI 0.88-1.11, p = 0.82       95%CI 0.55-0.95, p = 0.02       2.20 95%CI 0.65-0.05, p = 0.02         Wang 2001 <sup>46</sup> (Cryosurgery)       Heidological assessment of punch biopsies 12 months after initial reatments:       not data meeting extraction criteria       No data meeting extraction criteria       No data meeting extraction criteria       No data meeting extraction criteria       Sector 2.20 95%CI 0.25-1.02, p = 0.05         Berroeta 2007 <sup>46</sup> (Cryosurgery)       Heidological assessment of punch biopsies 12 months after initial reatments:       No data meeting extraction criteria       No data meeting extraction criteria       No data meeting extraction criteria       Sector 2.20 95%CI 0.25-1.05, p = 0.02       2.80 95%CI 0.25-1.05, p = 0.02         Berroeta 2007 <sup>46</sup> (Surgery)       PDT repeated at 3 months if BCC cluically evident. If afte months EC       Addata meeting extraction criteria       No data meeting extraction criteria       No	, , , ,	confirmed histologically by independent laboratory (blinded). Excised at 3 months (clinical nonresponders), or 6 months (clinical responders), after	2.75 95%CI 1.84-4.10,	0	5	No data meeting extraction criteria (all excised < 1 year). Variable of interest was histologically verified complete response 6 months after last treatment.
treatment.criteria95XCI 0.85-44.78, p = 0.07 95XCI 0.25-41.78 95XCI 0.25-41.78, p = 0.07 95XCI 0.25-41.7895XCI 0.25-41.78 95XCI 0.25-41.7895XCI 0.25-41.78 95XCI 0.25-21.7895XCI 0.25-41.78 				•	•	1–3 years MAL-PDT 22 <sup>0</sup> vs Cryo 6% RR 3.45 95%Cl 1.02–11.62, p = 0.05 1–4 years MAL-PDT 22% vs Cryo 6% RR 3.45 95%Cl 1.02–11.62, p = 0.05 1–5 years MAL-PDT 22% vs Cryo 8% RR
Moster 2008 <sup>th</sup> persist referred for alternative treatment.criteria0.78 95%Cl 0.52-1.18Moster 2008 <sup>th</sup> At 3, 6, 12, 18, 24, 36, 48 and 60 months, recurring tumour (histologically confirmed 42 statist is sto to follow-up 67 months (range 0- 106)AL 33% vs Surgery 78% RR 0.25AL 35% vs Surgery 74% RR 0.71 95%Cl 95%Cl 0.82-0.991-2, years ALA 77% vs Surgery 70% RR 1.2Bhodes 2004 <sup>19</sup> Rhodes 2007 <sup>21</sup> Complete response assessed at 3 months after last treatment by the sme investigator. Lesions assessed annually for 5 years. Any clinical recurrence was histologically confirmed.MAL-PDT 91% vs Surgery 98% RR 0.92 95%Cl 0.83-1.02MAL-PDT 92% vs Surgery 71% RR 0.83 95%Cl 0.63-1.11, p = 0.2131 - 2 years MAL-PDT 7% vs Surgery 70% 95%Cl 0.37-1.60 1-5 years MAL-PDT 7% vs Surgery 71% RR 0.83 95%Cl 0.63-1.11, p = 0.2131 - 2 years MAL-PDT 7% vs Surgery 70% 95%Cl 0.37-1.60 1-5 years MAL-PDT 7% vs Surgery 71% 	Wang 2001 <sup>16</sup> (Cryosurgery)			No data meeting extraction criteria	No data meeting extraction criteria	nBCC 1-year ALA 12% vs Cryo 21% RR 0.58
2013 <sup>21</sup> (Surgery)confirmed BCC within Smm of scar) recorded. Patients lost to follow-up censored at last examination. Median follow-up 67 months (range 0- 106)95%Cl 0.82-0.990.56-0.91, p = 0.00695%Cl 0.74-23.59 1-5 years: AL17% v5 Surgery 0% RR 95%Cl 0.82-1.02, p = 0.02Rhodes 2004 <sup>13</sup> Rhodes 2007 <sup>11</sup> Complete response assessed at 3 months after last treatment by the Surgery 0% RR Surgery 0% RRMAL-PDT 91% v5 Surgery 98% RR 0.94 95%Cl 0.85-1.03MAL-PDT 60% v5 Surgery 71% RR 0.83 95%Cl 0.37-31.60 1-5 years: MAL-PDT 10% v5 Surgery 0% RR 95%Cl 0.37-31.60 1-5 years: MAL-PDT 10% v5 Surgery 0% RR 0.94 95%Cl 0.85-1.03MAL-PDT 60% v5 Surgery 71% RR 0.83 95%Cl 0.37-31.60 1-5 years: MAL-PDT 10% v5 Surgery 0% RR 20 95%Cl 0.85-1.02MAL-PDT 91% v5 Surgery 10% RR 0.94 95%Cl 0.85-1.03MAL-PDT 60% v5 Surgery 71% RR 0.83 95%Cl 0.37-31.60 1-5 years: MAL-PDT 10% v5 Surgery 0% RR 20 95%Cl 0.37-31.60 1-5 years: MAL-PDT 91% v5 Surgery 0% RR 0.94 95%Cl 0.85-0.96, p = 0.0011 year MAL-PDT 9% v5 Surgery 0% RR 16 year MAL-PDT 9% v5 Surgery 0%. RR 0.94 95%Cl 0.85-0.96, p = 0.0011 year MAL-PDT 9% v5 Surgery 0%. RR 0.94 95%Cl 0.85-0.96, p = 0.001Arits 2013 <sup>30</sup> Roozeboom 2016 <sup>41</sup> Larsen 2017 <sup>22</sup> (Imiquimod or fluorouracil)Cinically assessed (blinded) at 3 and 12 months post-treatment. MAL-PDT 82% v5 IMQ 86% RR 0.95 95%Cl 0.87-1.03, p = 0.18MAL-PDT 82% v5 IMQ 90% RR 0.91 Sustained clearance at 3 years: MAL-PDT 70% v5 IMQ 84% RR 0.84 95%Cl 0.74- 70% v5 IMQ 84% RR 0.84 95%Cl 0.74- 7	Berroeta 2007 <sup>29</sup> (Surgery)	· · · · · · · · · · · · · · · · · · ·	0	σ,	No data meeting extraction criteria	No data meeting extraction criteria
(Surgery)same investigator. Lesions assessed annually for 5 years. Any clinical recurrence was histologically confirmed.0.92 95%CI 0.84-1.020.94 95%CI 0.85-1.0395%CI 0.63-1.11, p=0.213.14 95%CI 0.37-31.60Szeimies 2008 <sup>18</sup> (Surgery)Visits at screening, baseline, 1, 13, 26 and 52 weeks (phone call week 3). If 2 MAL-PDT cycles, visits also at weeks 14, 39, 65 (phone call week 15).MAL-PDT 87% vs Surgery 89% RR 0.99 95%CI 0.90-1.08, p=0.76No data meeting extraction criteria 0.99 95%CI 0.85-1.031 year MAL-PDT 9% vs Surgery 0%. TI (9%) MAL-PDT 9% vs Surgery 0%. TI (9%) MAL-PDT 9% vs Surgery 0%. TI (9%) MAL-PDT 82% vs IMQ 86% RR 0.99 95%CI 0.87-1.04, p=0.20No data meeting extraction criteria 0.99 95%CI 0.87-1.04, p=0.211 year MAL-PDT 9% vs Surgery 0%. TI (9%) MAL-PDT 9% vs Surgery 0%. TI (9%) MAL-PDT 9% vs Surgery 0%. TI (9%) MAL-PDT 82% vs IMQ 86% RR 0.99 95%CI 0.87-1.04, p=0.001No data meeting extraction criteria 0.99 95%CI 0.87-1.04, p=0.0011 year MAL-PDT 9% vs Surgery 0%. TI (9%) MAL-PDT 82% vs IMQ 90% RR 0.91 Sustained clearance at 3 years MAL-PDT 70% vs IMQ 84% RR 0.84 95%CI 0.78-1.00, p=0.06 Sustained clearance at 5 years MAL-PDT 75% vs IMQ 73% RR 0.84 95%CI 0.78-1.00, p=0.06 Sustained clearance at 3 years MAL-PDT 59% vs FU 67% RR 0.88 95%CI 0.78-1.04, p=0.14No data meeting extraction criteria 75% vs IMQ 73% RR 0.84 95%CI 0.78-1.04, p=0.14No data meeting extraction criteria 75% vs IMQ 73% RR 0.84 95%CI 0.78-1.04, p=0.14Smucler 2008 <sup>18</sup> (Er:YAG laser/PDT)Clinical valuation at 3, 6 and 12 months independent evaluation of response at 12 months via dermoscopic images and histological examination of a shave biopsy sample.Er:YAG laser/PDT 77% vs MAL-PDT 75% vs IMAL-PDT 75% vs IMAL-PDT 7% vs MAL-PDT 75%		confirmed BCC within 5mm of scar) recorded. Patients lost to follow-up censored at last examination. Median follow-up 67 months (range 0–				1-5 years ALA 17% vs Surgery 0% RR 30.00
If 2 MAL-PDT cycles, visits also at weeks 14, 39, 65 (phone call week 15).       0.99 95%Cl 0.90-1.08, p = 0.76       0.91 95%Cl 0.85-0.96, p = 0.001       (9%) MAL-PDT lesions recurring at 1 comprised 4/15 (27%) face/scalp; 3/r (4%) trunk/neck; 4/34 (12%) extremi         Arits 2013 <sup>20</sup> Roozeboom 2016 <sup>21</sup> Clinically assessed (blinded) at 3 and 12 months post-treatment. Treatment failures histologically confirmed via 3mm punch biopsy. Median follow-up period 35 months (range 1-54 months).       MAL-PDT 82% vs IMQ 86% RR 0.95 95%Cl 0.87-1.04, p = 0.26 MAL-PDT 82% vs IL 87% RR 0.92 95%Cl 0.38-1.07, p = 0.18       Sustained clearance at 3 years MAL-PDT 70% vs IMQ 84% RR 0.84 95%Cl 0.74- PDT 82% vs ILQ 89% RR 0.92 95%Cl 0.74- D34, p = 0.03 MAL- DT 82% vs ILQ 89% RR 0.92 95%Cl 0.74- D34, p = 0.03 MAL- DT 82% vs ILQ 89% RR 0.92 95%Cl 0.74- D34, p = 0.03 MAL-PDT 75% vs IMAL-PDT 75% vs ILQ 79% RR 0.89 95%Cl 0.74- D34, p = 0.03 MAL-PDT 75% vs IMAL-PDT 75% vs ILQ 89% RR 0.92 95%Cl 0.74- D35, p = 0.01 MAL-PDT 75% vs ILQ 79% RR 0.89 95%Cl 0.74- D35, p = 0.01 MAL-PDT 75% vs ILQ 79% RR 0.89 95%Cl 0.75- D.95, p = 0.01 MAL-PDT 75% vs ILQ 79% RR 0.89 95%Cl 0.75- D.95, p = 0.01 MAL-PDT 59% vs FU 67% RR 0.88 95%Cl 0.75- D.95, p = 0.01 MAL-PDT 59% vs FU 67% RR 0.88 95%Cl 0.75- D.4, p = 0.14       No data meeting extraction criteria pDT 86% RR 1.01 95%Cl 0.94- D.49		same investigator. Lesions assessed annually for 5 years. Any clinical	<b>o</b> ,	σ,	υ,	1–5 years MAL-PDT 10% vs Surgery 4% RR
Jansen 2017 <sup>22</sup> (Imiquimod or fluorouracil)Treatment failures histologically confirmed via 3mm punch biopsy. Median follow-up period 35 months (range 1–54 months).0.95 95%Cl 0.87–1.04, p = 0.26 MAL-PDT 82% FU 87% RR 0.94 95%Cl 0.87–1.03, p = 0.1895%Cl 0.83–0.99, p = 0.03 MAL- PDT 82% vs FU 89% RR 0.92 95%Cl 0.85–1.01, p = 0.0970% vs IMQ 84% RR 0.84 95%Cl 0.74– 0.94, p = 0.03: MAL-PDT 70% vs FU 79% RR 0.89 95%Cl 0.75–1.00, p = 0.06 Sustained to possible of the second sec	Szeimies 2008 <sup>18</sup> (Surgery)				No data meeting extraction criteria	1 year MAL-PDT 9% vs Surgery 0%. The 11 (9%) MAL-PDT lesions recurring at 1 year comprised 4/15 (27%) face/scalp; 3/69 (4%) trunk/neck; 4/34 (12%) extremities.
Er:YAG laser/PDT)       response at 12 months via dermoscopic images and histological examination of a shave biopsy sample.       PDT 86% RR 1.01 95%CI 0.94-75% RR 1.04 95%CI 0.94-1.14, p = 0.81         0.49	Jansen 2017 <sup>22</sup> (Imiquimod or	Treatment failures histologically confirmed via 3mm punch biopsy.	0.95 95%Cl 0.87–1.04, p = 0.26 MAL-PDT 82% FU 87% RR	95%Cl 0.83–0.99, p = 0.03 MAL- PDT 82% vs FU 89% RR 0.92 95%Cl	70% vs IMQ 84% RR 0.84 95%Cl 0.74– 0.94, p = 0.03: MAL-PDT 70% vs FU 79% RR 0.89 95%Cl 0.78–1.00, p = 0.06 Sustained clearance at 5 years MAL-PDT 59% vs IMQ 73% RR 0.81 95%Cl 0.70– 0.95, p = 0.01 : MAL-PDT 59% vs FU 67%	No data meeting extraction criteria
28		response at 12 months via dermoscopic images and histological	PDT 86% RR 1.01 95%CI 0.94-	75% RR 1.04 95%Cl 0.94–1.14, p =	No data meeting extraction criteria	No data meeting extraction criteria
			28			

, 						
8	Study (Comparator)	Assessment of clearance and recurrence	Clearance at 3 months	Sustained clearance at 1 year	Sustained clearance at 5 years	Recurrence rate ≥ 1 year
€ 10 11 12	Haak 2015 <sup>27</sup> (CO <sub>2</sub> -AFL/MAL-PDT)	At 3, 6, 9 and 12 months treatment response and recurrence assessed by photography (blinded). If noncomplete or uncertain response biopsy performed. Recurrent lesions excluded and treated according to national guidelines. At 12 months biopsies from the centre of treated areas histologically assessed.	AFL-MAL-PDT 100% vs MAL-PDT 88% RR 1.14 95%Cl 0.92–1.41, p = 0.24	Per patient AFL-MAL-PDT 81% vs MAL-PDT 64% RR 1.26 95%Cl 0.80–1.99, p = 0.31 Per lesion AFL-MAL-PDT 63% vs MAL-PDT 64% RR 0.97 95%Cl 0.56– 1.68, p = 0.92	Study terminated at 1 year	No data meeting extraction criteria
13 14 15	Choi 2016 <sup>28</sup> (Er:YAG-AFL/ALA-PDT)	Patients photographed at baseline, 1 week, 3 months and 12 months. Efficacy assessed based on inspection, dermoscopy, photography, palpation and histologic findings. Biopsies performed if clinical doubt. All cases of complete response reviewed at 12 months.	AFL/ALA-PDT 76% vs MAL-PDT 43% RR 1.78 95%Cl 1.03-3.08, p = 0.04	-	No data meeting extraction criteria	AFL/ALA-PDT 6% vs MAL-PDT 56% RR 0.11 95%Cl 0.02–0.82, p = 0.03
16 17 18	Osiecka 2012 <sup>44</sup> (PDT/imiquimod)	Clinical examination and photodynamic diagnosis (PDD). PDD repeated for 6 weeks, then 2 monthly to 14 months.	No data meeting extraction criteria	No data meeting extraction criteria	No data meeting extraction criteria	Per patient > 1-year ALA-PDT/IMQ 25% vs ALA-PDT 40% RR 0.63 95%Cl 0.22–1.75, p = 0.37
10	De Haas 2006 <sup>23</sup> De Vijlder 2012 <sup>24</sup> (Fractionated PDT)	Clinical response assessed by staff. Patients reviewed four times in year 1, then twice yearly until year 5.	No data meeting extraction criteria	ALA-PDT (fractionated) 96% vs ALA-PDT (single) 87% RR 1.11 95%Cl 1.05–1.17, p = 0.0002	ALA-PDT (fractionated) 80% vs ALA-PDT (single) 60% RR 1.33 95%Cl 1.19–1.47, p < 0.00001	No data meeting extraction criteria
21 22	Kessels 2017 <sup>25</sup> (Fractionated ALA-PDT)	Clinical response assessed by two investigators (blinded). Patients assessed at baseline, 3 and 12 months post-treatment.	Frac-ALA-PDT 93% vs MAL-PDT 94% RR 0.99 95%Cl 0.91–1.07, p = 0.79	Frac-ALA-PDT 96% vs MAL-PDT 87% RR 1.11 95%Cl 1.00-1.22, p = 0.05	No data meeting extraction criteria	No data meeting extraction criteria

Abbreviations: MAL, methyl aminolaevulinate; ALA, 5-aminolaevulinic acid; PDT, photodynamic therapy; BCC, basal cell carcinoma; Cl, confidence interval; RR, risk ratio; FU, 5-fluorouracil; IMQ, imiquimod; AFL, Ablative Fractional Laser; Er:YAG, Erbium-doped Yttrium-Aluminium-Garnet; CO<sub>2</sub>-AFL, carbon dioxide Ablative Fractional Laser; Frac, Fractionated.

# Table 5 Cosmetic outcome

,				
0	Study (Comparator)	Assessment method	Investigator assessed cosmetic outcome	Patient assessed cosmetic outcome
1 2	Foley 2009 <sup>15</sup> (Placebo-PDT)	Investigator: 4-point scale*	6 months, good-excellent, MAL-PDT 56% vs Placebo 19% RR 3.00: 95%Cl 1.80– 5.01, p < 0.0001	No data meeting extraction criteria
3 4 5 6 7	2008 <sup>17</sup> (Cryosurgery)	induration, no/slight erythema/dyspigmentation), 'good' (no scarring, atrophy, induration, moderate redness/pigmentation change), 'fair' (slight/moderate scarring, atrophy/induration), 'poor' (extensive scarring, atrophy, induration). Patient: assessed as, excellent, good, fair, poor.	0.004 1 year, excellent, MAL-PDT 32% vs Cryo 12% RR 2.67: 95%Cl 1.22–5.85 2 years, excellent, MAL-PDT 40% vs Cryo 7% RR 5.85: 95%Cl 2.17–15.78, p =	3 months, excellent, MAL-PDT 40% vs Cryo 19% RR 2.13: 95%Cl 1.15–3.92, p = 0.02 1 year, excellent, MAL-PDT 35% vs Cryo 24% RR 1.47: 95%Cl 0.83– 2.59, p = 0.18 2 years, excellent, MAL-PDT 37% vs Cryosurgery 26% RR 1.43: 95%Cl 0.83–2.47, p = 0.19
9	(Cryosurgery)	Physician and 2 scientists (blinded) assessed photographs and video for overall impression (excellent, good, acceptable, blemished) based on dyspigmentation and scarring (none, slight, obvious).	Excellent, 1 year, MAL-PDT 45% vs Cryo 7% RR 6.11: 95%Cl 1.96–19.00	No data meeting extraction criteria
0 1 2		Independent nonmedical assessors (10 men, 10 women) evaluation of clinical photographs. Scar severity 4 point scale (excellent/none to very poor) at 3 , 6, 12 months after last treatment.	No data meeting extraction criteria. Reports (male/female assessors) mean scar severity: surgery, 2.07/2.53; PDT, 1.94/2.23.	No data meeting extraction criteria
3	Mosterd 2008 <sup>30</sup> Roozeboom 2013 <sup>32</sup> (Surgery)	Cosmetic outcome not assessed	No data meeting extraction criteria	No data meeting extraction criteria
5 6 7 8 9	Rhodes 2004 <sup>19</sup> Rhodes 2007 <sup>31</sup> (Surgery)	assessment: 3, 12, 24 months, 4-point scale: excellent, good, fair, poor.	3 months, good-excellent, MAL-PDT 72% vs Surgery 32% RR 2.26: 95%Cl 1.44– 3.54, p = 0.0004 1 year, good-excellent, MAL-PDT 66% vs Surgery 36% RR 1.82: 95%Cl 1.19–2.80, p = 0.006 2 years, good-excellent, MAL-PDT 48% vs Surgery 34% RR 1.41: 95%Cl 0.86–2.31, p = 0.17 5 years, good-excellent, MAL-PDT 54% vs Surgery 40% RR 1.34: 95%Cl 0.87–2.06, p = 0.19	95%Cl 0.87–1.31, p = 0.51
0 1 2	(Surgery)		3 months, good-excellent, MAL-PDT 77% vs Surgery 58% 6 months, good-excellent, MAL-PDT 92% vs Surgery 59% 1 year, good-excellent, MAL-PDT 77% vs Surgery 46% RR 1.68: 95%Cl 1.32–2.14, p < 0.0001	3 months, good-excellent, MAL-PDT 94% vs Surgery 81% 6 months, good-excellent, MAL-PDT 98% vs Surgery 83% 1 year, good-excellent, MAL-PDT 98% vs Surgery 8%3
3 4 5 6	Arits 2013 <sup>20</sup> Roozeboom 2016 <sup>21</sup> Jansen 2017 <sup>22</sup> (IMQ, FU)	At 12 months observer (blinded) assessment, four-point scale (excellent, good, fair, poor). Treatment failures defined poor as re-treated surgically.	1 year, good-excellent, MAL-PDT 57% vs IMQ 57% RR 1.01: 95%CI 0.85–1.19, p = 0.94 1 year, good-excellent, MAL-PDT 57% vs FU 55% RR 1.04: 95%CI 0.88–1.24, p = 0.66	No data meeting extraction criteria

8 9	Study (Comparator)	Assessment method	Investigator assessed cosmetic outcome	Patient assessed cosmetic outcome
10 11 12 13 14 15	(Er:YAG laser, Er:YAG laser/PDT)	12 months observer (blinded) assessed, 4-point scale (1) no damage (2) slight pigmentation changes/palpable healing (3) minor changes in relief/erythema, minor residues of necrotic tissue, minor recurrence (4) fundamental relief damage, scarring, extensive residues of necrotic tissue, ulcer, full recurrence.	3 months, aesthetic result, mean $\pm$ SD: Er:YAG-laser-PDT, 2.00 $\pm$ 0.57; Er:YAG-laser, 1.62 $\pm$ 0.76; p < 0.00001: Er:YAG-laser-PDT, 2 $\pm$ 0.57; MAL-PDT, 3.17 $\pm$ 0.57; p < 0.00001. 6 months, aesthetic result, mean $\pm$ SD: Er:YAG-laser-PDT, 1.17 $\pm$ 0.24; Er:YAG-laser, 1.50 $\pm$ 0.70; p < 0.00001: Er:YAG-laser-PDT, 1.17 $\pm$ 0.24; MAL-PDT, 1.50 $\pm$ 0.43; p < 0.00001. 9 months, aesthetic result, mean $\pm$ SD: Er:YAG-laser-PDT, 1.23 $\pm$ 0.44; Er:YAG-laser, 1.83 $\pm$ 0.95; p < 0.00001: Er:YAG-laser-PDT, 1.23 $\pm$ 0.44; MAL-PDT, 1.67 $\pm$ 0.76; p < 0.00001.	No data meeting extraction criteria
16 17 18 19 20 21	(CO <sub>2</sub> -AFL/PDT)	Dermatologist (blinded) assessment, 3, 6, 9 and 12 months (scarring, hypopigmentation, hyperpigmentation, overall cosmetic outcome referred to clinical photographs and baseline template). Patients evaluation: each visit.	0.71–2.11, p = 0.47	Per patient, 3 months, excellent: AFL-PDT 81% vs MAL-PDT 50% RR 1.63: 95%Cl 0.94–2.80, p = 0.08 Per patient, 6 months, excellent: AFL-PDT 75% vs MAL-PDT 50% RR 1.50: 95%Cl 0.85–2.64, p = 0.16 Per patient, 9 months, excellent: AFL-PDT 63% vs MAL-PDT 50% RR 1.25: 95%Cl 0.67–2.32, p = 0.48 Per patient, 1 year, excellent: AFL-PDT 56% vs MAL-PDT 44% RR 1.29: 95%Cl 0.64–2.60, p = 0.48
22	Choi 2016 <sup>28</sup> (Er:YAG-AFL/PDT)	Investigator assessed complete responses, 3 or 12 months, 4-point scale*.	Per lesion, excellent, 12 months: AFL-PDT 57% vs MAL-PDT 57% RR 1.00: 95%Cl 0.59–1.69, p = 1.00	No data meeting extraction criteria
23 24	Osiecka 2012 <sup>44</sup> (PDT/IMQ)	No formal assessment of cosmesis	No data meeting extraction criteria	No data meeting extraction criteria
25 26	De Haas 2006 <sup>23</sup> De Vijlder 2012 <sup>24</sup> (Fractionated PDT)	No formal assessment of cosmesis	No data meeting extraction criteria	No data meeting extraction criteria
28		2 independent investigators (blinded), four-point scale (poor, fair, good or excellent).Treatment failures scored poor, as excised.	Good-excellent, Frac ALA-PDT 71% vs MAL-PDT 77% vs Surgery 60% RR 1.18 95%CI 0.94–1.48, p = .0.15	No data meeting extraction criteria
29				

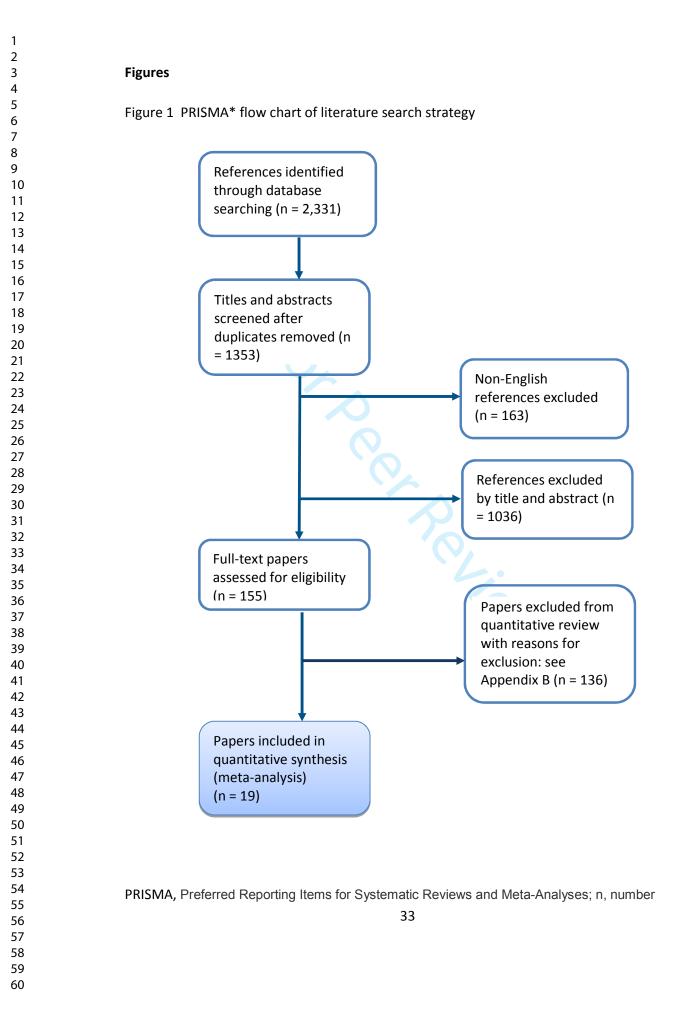
\*scale as in Basset-Seguin<sup>17</sup>; Abbreviations: MAL, methyl aminolaevulinate; ALA, 5-aminolaevulinic acid; PDT, photodynamic therapy; Cl, confidence interval; RR, risk ratio; FU, 5-fluorouracil; IMQ, imiquimod; AFL, Ablative Fractional Laser; Er:YAG, Erbium-doped Yttrium-Aluminium-Garnet; CO<sub>2</sub>-AFL, carbon dioxide Ablative Fractional Laser; Frac, Fractionated. SD, standard deviation

# Table 6 Pain

Study (Comparator)	Analgesia	Assessment of pain	Severe pain*	Low or manageable pain
Foley 2009 <sup>15</sup> (Placebo-PDT)	None stated	During treatment and follow-up, nurse (blinded) noted severity, duration, analgesia.	MAL-PDT 0% vs Placebo 0%	MAL-PDT 90% vs Placebo 66% RR 1.37: 95%Cl 1.14–1.66, p < 0.001
Basset-Seguin 2008 <sup>17</sup> (Cryo)	None stated	Severity and cause recorded at each follow-up, until 3 months after final treatment.	MAL-PDT 5% vs Cryo 2% RR 2.81: 95%Cl 0.30–26.22	MAL-PDT 75% vs Cryo 72% RR 1.02: 95%Cl 0.83–1.27, p < 0.83
Wang 2001 <sup>16</sup> (Cryo)	PDT: water sprayed if pain. Single lesion in PDT group sprayed with LA.	In first week after treatment patient completed a VAS.	MAL-PDT 2% vs Cryo 0% RR 2.63: 95%Cl 0.11–62.73	No data meeting extraction criteria
Berroeta 2007 <sup>29</sup> (Surgery)	Surgery under infiltrative LA. No anaesthesia stated in PDT.	Patients assessed (VAS) during, immediately after, 3, 6, 24, and 48 hours and 1 week later.	No data meeting extraction criteria.	No data meeting extraction criteria
Mosterd 2008 <sup>30</sup> Roozeboom 2013 <sup>32</sup> (Surgery)	Surgery under infiltrative LA.	Documented at review	No data meeting extraction criteria	No data meeting extraction criteria
Rhodes 2004 <sup>19</sup> Rhodes 2007 <sup>31</sup> (Surgery)	Surgery under infiltrative LA. No LA used in PDT.	Severity, duration, and pain relief documented after illumination.	One MAL-PDT patient discontinued treatment due to severe burning sensation; resolved later in day without medical intervention. Otherwise mild to moderate intensity; all resolved < 1 day.	MAL-PDT 54% vs Surgery 30% RR 1.81: 95%Cl 1.09–3.01, p = 0.02
Szeimies 2008 <sup>18</sup> (Surgery)	Mini desk fans available during irradiation.	Severity, duration, and need for pain relief documented at each visit.	3% of the patients needed illumination pausing due to pain at second session of each cycle, but none at start of first cycle.	
Arits 2013 <sup>20</sup> Roozeboom 2016 <sup>21</sup> Jansen 2017 <sup>22</sup> (IMQ or FU)			MAL-PDT 9% vs IMQ 7% ; RR 0.93: 95% Cl 0.61–1.41, p = 0.72: MAL-PDT 9% vs FU 4% ;: RR 1.93: 95% Cl 1.13–3.30, p = 0.02. MAL-PDT severe pain mostly during illumination.	MAL-PDT 85% vs IMQ 85% ; RR 1.00: 95%Cl 0.92–1.08, p = 0.96 : MAL-PDT 85% vs FU 88% RR 0.97: 95%Cl 0.89–1.05, p = 0.40
Smucler 2008 <sup>26</sup> (Er:YAG laser, Er:YAG laser /PDT)	Prior to laser, topical LA and, as needed, infiltrative LA.	None described	No data meeting extraction criteria	No data meeting extraction criteria
Haak 2015 <sup>27</sup> (CO <sub>2-</sub> AFL/PDT)	Prior to AFL, infiltrative LA used.	During illumination and at assessments, patients scored pain on numerical scale.	No data meeting extraction criteria	No data meeting extraction criteria
Choi 2016 <sup>28</sup> (Er:YAG-AFL/PDT)	Prior to AFL, topical anaesthetic applied.	During illumination, patients evaluated pain on a VAS. Reports spontaneous or at visits at 1 week, 3 months, and 1 year.	No severe pain reported; no patients discontinued the study because of pain.	Pain mild to moderate during illumination, after immediately lessened, resolving in a few hours. VAS scores during illumination were similar in each arm.
Osiecka 201244 (PDT/IMQ)	None described	None described	None described	None described
De Haas 2006 <sup>23</sup> De Vijlder 2012 <sup>24</sup> (Fractionated PDT)	ALA with 2% lidocaine. If required paracetamol, lidocaine, or bupivacaine.		ALA-PDT (fractionated) 15% vs ALA-PDT (single) 3% RR 4.85: 95%Cl 1.34–17.53, p = 0.02	
Kessels 2017 <sup>25</sup> (Fractionated ALA-PDT)			No patient discontinued treatment because of pain.	Pain score, mean NRS ± SD: MAL-PDT vs ALA-PDT 2-fold: $1^{st}$ session; 2.25 ± 2.54 vs 1.88 ± 2.36, p = 0.369; $2^{nd}$ session; 2.48 ± 2.57 vs 3.36 ± 2.57, p = 0.039. <sup>25</sup> 16.4% in the ALA-PDT versus 5.8% in the MAL-PDT group reported the use of pain medication post-treatment.

\*Severe pain is defined as pain leading to break in treatment and/or the use of local analgesia.

Abbreviations: MAL, methyl aminolaevulinate; ALA, 5-aminolaevulinic acid; PDT, photodynamic therapy; Cl, confidence interval; RR, risk ratio; LA, local anaesthetic; VAS, visual analogue scale; FU, 5-fluorouracil; IMQ, imiquimod; AFL, Ablative Fractional Laser; Er:YAG, Erbium-doped Yttrium-Aluminium-Garnet; CO<sub>2</sub>-AFL, carbon dioxide Ablative Fractional Laser; NRS, numeric rating scale (score 0-10); SD: standard deviation



# Figure 2 Cosmetic outcome (excellent) patient (superficial and nodular): PDT versus cryosurgery (1 year) assessed by investigator

	PDT		Cryotherapy		<b>Risk Ratio</b>	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Basset-Seguin, EJD 2008 (s)	20	62	7	58	69.3%	2.67 [1.22, 5.85]	
Wang, BJD 2001 (n & s)	21	47	3	41	30.7%	6.11 [1.96, 19.00]	<b>_</b>
Total (95% CI)		109		99	100.0%	3.73 [1.96, 7.07]	•
Total events	41		10				
Heterogeneity: Chi <sup>2</sup> = 1.42, df = 1 (P = 0.23); l <sup>2</sup> = 30%							
Test for overall effect: Z = 4.03 (P < 0.0001)							Favours cryotherapy Favours PDT

PDT, photodynamic therapy; nBCC, nodular basal cell carcinoma; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom. NB: Wang (2001) treated one lesion per patient (ALA-PDT); Basset-Seguin (2008) treated all lesions for each patient (MAL-PDT)

for per peries

### Figure 3 PDT vs surgical excision (nBCC): 3-month initial clearance

	PDT	Г	Surgical ex	cision		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Mosterd, BJD 2008 (n)	79	85	86	88	62.1%	0.95 [0.89, 1.02]	
Rhodes, AD 2004 (n)	48	53	51	52	37.9%	0.92 [0.84, 1.02]	-
Total (95% CI)		138		140	100.0%	0.94 [0.89, 0.99]	•
Total events	127		137				
Heterogeneity: Chi <sup>2</sup> = 0.2	25, df = 1 (	P = 0.6	2); I² = 0%				
Test for overall effect: Z =	= 2.19 (P =	: 0.03)					Favours surgical excision Favours PDT

PDT, photodynamic therapy; nBCC, nodular basal cell carcinoma; M-H, Mantel-Haenszel; Cl, confidence interval; df, degrees of freedom.

to peer period

#### Figure 4 PDT vs surgical excision (nBCC): 1-year sustained clearance

	PDT	Г	Surgical ex	cision		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Berroeta, BJD 2007 (n)	13	21	15	19	11.0%	0.78 [0.52, 1.18]	
Mosterd, BJD 2008 (n)	69	79	83	86	55.3%	0.90 [0.82, 0.99]	-
Rhodes, AD 2004 (n)	44	48	50	51	33.7%	0.94 [0.85, 1.03]	-
Total (95% CI)		148		156	100.0%	0.90 [0.84, 0.97]	◆
Total events	126		148				
Heterogeneity: Chi <sup>2</sup> = 1.0	3, df = 2 (	P = 0.6	0); I <sup>2</sup> = 0%				
Test for overall effect: Z =	2.75 (P =	0.006)					Favours surgical excision Favours PDT

PDT, photodynamic therapy; nBCC, nodular basal cell carcinoma; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

to per period

### Figure 5 PDT vs surgical excision (nBCC): Recurrence rate (>1 year)

	PDT	Г	Surgical ex	cision		<b>Risk Ratio</b>		Risk F	latio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed	1, 95% CI	
Rhodes, AD 2004	5	48	1	51	68.1%	5.31 [0.64, 43.84]				
Roozeboom, JAAD 2013	12	69	0	83	31.9%	30.00 [1.81, 497.72]				<b>_</b>
Total (95% CI)		117		134	100.0%	13.19 [2.58, 67.37]				
Total events	17		1							
Heterogeneity: Chi <sup>2</sup> = 1.04	df = 1 (P	= 0.31)	; l <sup>2</sup> = 4%				0.01		10	100
Test for overall effect: Z = 3	8.10 (P = 0	1.002)					0.01	Favours ALA-PDT	Favours surgica	

PDT, photodynamic therapy; nBCC, nodular basal cell carcinoma; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

for per period

### Conventional and combination topical photodynamic therapy for basal cell carcinoma:

systematic review and meta-analysis

#### **Supporting Information**

#### Table S1 Search strategy

Search no.	Keywords	CENTRAL	MEDLINE and EMBASE	PubMed
1	PubMed carcinoma, basal cell [MeSH Terms] OR basal cell carcinoma OR basal cell neoplasms OR basal cell cancer MEDLINE and EMBASE (basal ADJ0 cell ADJ0 carcinoma\$1) OR (basal ADJ0 cell ADJ0 neoplasm\$1) OR (basal ADJ0 cell ADJ0 cancer\$1) Cochrane (basal cell carcinoma*) OR (basal cell	1112	37778	38167
	neoplasm*) OR (basal cell cancer*) PubMed photodynamic therapy [MeSH Terms]			
2	OR photodynamic therapy OR PDT) MEDLINE and EMBASE (photodynamic ADJ0 therapy) OR PDT	1547	41500	21718
	Cochrane (photodynamic therapy) OR PDT	0		
3	PubMed skin[MeSH Terms] OR cutaneous OR skin)	49701	1718477	778174
	MEDLINE and EMBASE Cutaneous OR skin Cochrane Cutaneous OR skin			
4	1 AND 2 AND 3	101(a)	1572(b)	658(c)
	a (101) + b (1572) + c(658) reference automatic and manual de-duplicatio			

cell carcinoma; sBCC, superficial basal cell carcinoma.

1	
2	
3	
4 5	
5 6	
0 7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20 21	
21	
22	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36 37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50 51	
51	
52 53	
55 54	
55	
56	
57	
58	

Table S2 Papers excluded from quantitation	tive analysis
--	---------------

	References	Reason for exclusion from extraction
1.	Alberdi, E. (2011)	Conference abstract and no comparator arm
	Photodiagnosis Photodyn Ther	
2.	Allen, J. (2011) Photodiagnosis	Conference abstract and no comparator arm
	Photodyn Ther	
3.	Al-Niaimi, F. (2015) J Cutan	Outcomes not pertinent to this guideline
	Aesthet Surg	
4.	Annemans, L. (2008) Eur J	No comparator arm
	Dermatol	
5.	Anolik, R. (2011) Lasers Surg	Conference abstract and no comparator arm
	Med	
6.	Arits, A. (2015) Br J Dermatol	Letter no extractable data
7.	Attili, S. K. (2012)	No comparator arm – case series review
	Photodermatol Photoimmunol	
	Photomed	
8.	Attili, SK (2009) Br J Dermatol	No comparator arm
9.	Baron, E. D. (2010) Lasers Surg	Outcomes not pertinent to this guideline
	Med	
10.	Basset-Seguin, N. (2003) BAD	Conference abstract- Insufficient data to extract
	abstract	
11.	Basset-Seguin, N. (2005) BAD	Conference abstract- Insufficient data to extract
	abstract	
12.	Basset-Seguin, N. (2006) EADO	Conference abstract- Insufficient data to extract
	abstract	
13.	Bath-Hextall, F. J. (2004) BMJ	Review
14.	Bath-Hextall, F. J. (2007)	Review
	Cochrane Database Syst Rev	
15.	Brown, S. B. (2009) BMJ (Online)	Review
16.	Burón Álvarez, I. (2014) Piel	Unavailable

1 2 3 4 5 6	
1 1	0 1 2
1 1 1 1 1	3 4 5 6 7 8 9
2 2 2 2 2	0 1 2 3 4 5 6
2 2 3 3 3	7 8 9 0 1 2
3 3 3 3 3	4 5 7 8 9
4 4 4 4	
4 4 5 5 5	7 8 9 0 1 2
5 5 5 5 5	4 5 6

	References	Reason for exclusion from extraction
17.	Caekelbergh, K. (2009) J Drugs	Unavailable
	Dermatol	
18.	Cai, M. (2009) J Clin Dermatol	Unavailable in English language
19.	Campbell, S. M. (2007) J Environ	Unavailable
	Pathol Toxicol Oncol	
20.	Campbell, S. M. (2008) Br J	Outcomes not pertinent to this guideline
	Dermatol	
21.	Carija, A. (2016) Photodiagnosis	Not randomised clinical trial
	Photodyn Ther	
22.	Chia, H. Y. (2015) Indian J	Case series
	Dermatol Venereol Leprol	
23.	Christensen, E. (2009) J Eur	No comparator arm
	Acad Dermatol Venereol	
24.	Christensen, E. (2011) Acta	Outcomes not pertinent to this guideline
	Derm Venereol	
25.	Christensen, E. (2011) J Skin	No comparator arm
	Cancer	
26.	Christensen, E. (2012) Br J	No comparator arm
	Dermatol	
27.	Clark, C. 2003 (Photodermatol	Not randomised clinical trial
	Photoimmunol Photomed)	
28.	Clayton, T.H 2006 (Euro J Derm)	Outcomes not pertinent to this guideline
29.	Collier, N. J. (2015) Lasers Med	No comparator arm
	Sci	
30.	Cosgarea, R. (2013) J Eur Acad	Not randomised clinical trial
	Dermatol Venereol	
31.	Cottrell, W. J. (2008) Clin Cancer	Outcomes not pertinent to this guideline
	Res	
32.	Curnow, A. (2010) Br J Dermatol	No comparator arm

1	
2	
3 4	
4 5	
5 6	
7	
8	
8 9	
10	
11	
12	
13	
14	
15	
16	
17	
18 19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32 33	
33 34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45 46	
46 47	
47 48	
40 49	
49 50	
51	
52	
53	
54	
55	
56	
57	
58	

	References	Reason for exclusion from extraction
33.	de Haas, E. R. (2008) Acta Derm	Outcomes not pertinent to this guideline
	Venereol	
34.	de Haas, E. R. (2008) J Eur Acad	No comparator arm
	Dermatol Venereol	
35.	Desai, S. (2010) Lasers Surg Med	No comparator arm
36.	Fai, D. (2009) G Ital Dermatol	No comparator arm
	Venereol	
37.	Fantini, F. (2011) J Eur Acad	No comparator arm
	Dermatol Venereol	
38.	Farhadi, M. (2010) J Drugs	Unavailable
	Dermatol	
39.	Fernandez-Guarino, M. (2014) J	No comparator arm
	Skin Cancer	
40.	Fiechter, S. (2012) Dermatology	No comparator arm
41.	Fink-Puches, R (1998) Arch	No comparator arm
	Dermatol	2
42.	Gilchrest, B. A. (2009) Dermatol	Case series
	Surg	L.
43.	Gracia-Cazana, T. (2017)	No comparator arm
	Photodiagnosis Photodyn Ther	4
44.	Griskjans, Z. (2013)	No comparator arm
	Stomatologija	
45.	Grose, D. (2014) Dermatol Surg	Letter
46.	Haak, C. S. (2013) Lasers Surg	Abstract
	Med	
47.	Haedersdal, M. (2012) Lasers	Case series
	Med Sci	
48.	Halldin, C.B (2011) Acta Derm	Not randomised clinical trial
	Venereol	
49.	Haller, J.C (2000) Br J Dermatol	No comparator arm

1 2 3	
4	
5 6	
7 8	
9 10	
11	
12 13	
14 15	
16	
12 13 14 15 16 17 18	
19 20	
21 22	
23 24	
24 25 26	
27	
28 29	
30 31	
32 33	
34	
35 36	
37 38	
39 40	
41 42	
43	
44 45	
46 47	
48 49	
50 51	
52	
53 54	
55 56	
57 58	
59 60	
00	

	References	Reason for exclusion from extraction
50.	Hamdoon, Z. (2011) Br J Oral	Abstract- no comparator arm
	Maxillofac Surg	
51.	Hamdoon, Z. (2011)	Abstract- no comparator arm
	Photodiagnosis Photodyn Ther	
52.	Holmes, M V (2004) Br J	Outcomes not pertinent to this guideline
	Dermatol	
53.	Horn, M (2003) Br J Dermatol	Not randomised clinical trial
54.	Itoh, (2000) Y J Dermatol	No comparator arm
55.	Kauvar, A. N. B. (2015) Dermatol	Review
	Surg	
56.	Kessels, J.P. (2017) Acta Derm	Not randomised clinical trial
	Venereol	
57.	Kuijpers, D.I. (2006) J Drugs	No comparator arm besides PDT
	Dermatol	
58.	Kulakov, E. (2015) J Am Acad	Meeting abstract – no comparator arm
	Dermatol	P
59.	Lecluse, L. L. (2015) Br J	Letter - discussing Arits (2013) Lancet Oncol.
	Dermatol	which is included
60.	Li, Q. (2011) Photomed Laser	Case series No comparator arm
	Surg	4
61.	Lindberg-Larsen, R. (2012) Acta	No comparator arm
	Derm Venereol	
62.	Lippert, J. (2013) Dermatol Surg	Not randomised clinical trial
63.	Loncaster, J. (2009) Clin Oncol	No comparator arm – review of cases
	(R Coll Radiol)	
64.	Longo, C. (2012) Dermatology	Not an end point evaluated in these guideline
65.	Lu, Y. G. (2014) Photodiagnosis	No comparator arm
	Photodyn Ther	
66.	Malik, Z. (2015) Photonics	Review
	Lasers Med	

1 2	
2 3 4	
5	
6 7	
8 9	
9 10 11	
12 13	
12 13 14 15 16	
16 17	
18 19	
20	
21 22	
23 24	
25 26	
27 28	
29 30	
31 32	
33 34 35 36	
35 36	
37 38	
39 40	
41 42	
43 44	
45 46	
47 48	
49 50	
51	
53	
54 55	
56 57	
58 59	

	References	Reason for exclusion from extraction
67.	Mangano, A. (2009) Br J	No comparator arm
	Dermatol	
68.	Maresso, K. C. (2015) CA Cancer	Review
	J Clin	
69.	Meijnders, P.J.N (1996) Lasers	Not randomised clinical trial
	Med Sci	
70.	Metterle, L. (2015) Curr Probl	Review
	Cancer	
71.	Morton, C. A. (2013) J Eur Acad	PDT guidelines - review
	Dermatol Venereol	
72.	Mosterd, K. (2013) J Eur Acad	No comparator arm
	Dermatol Venereol	
73.	Mougel, F. (2009) Dermatology	No comparator arm
74.	Naidenov, N (2004) Acta	No comparator arm
	Dermatovenrol Croat	
75.	Neves, D. R. (2010) An Bras	Case report
	Dermatol	
76.	Nijsten, T. (2015) Br J Dermatol	Letter – no extractable data
77.	Oh, C. C. (2014) Br J Dermatol	Conference abstract – no comparator arm
78.	Ong, M. W. S. (2015) J Am Acad	Conference abstract –no comparator arm
	Dermatol	
79.	Pauwels, C. (2011) J Eur Acad	No comparator arm
	Dermatol Venereol	
80.	Payne, K. F. B. (2013) Br J Oral	Conference abstract – no comparator arm
	Maxillofac Surg	
81.	Pereyra-Rodriguez, J. J. (2009)	Case study
	Indian J Dermatol Venereol	
	Leprol	
82.	Puccioni, M. (2009) Ophthal	No comparator arm
	Plast Reconstr Surg	
L		

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
22	
36	
37 38	
38	
39	
40	
41	
42	
43	
44	
44	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

	References	Reason for exclusion from extraction
83.	Pye, A. (2008) J Cancer Res Clin	Outcomes not pertinent to this guideline
	Oncol	
84.	Ramirez, D. P. (2014)	No comparator arm
	Photodiagnosis Photodyn Ther	
85.	Reddy, K. K. (2010) J Drugs	Unavailable
	Dermatol	
86.	Requena, C. (2012) Int J	Case study
	Dermatol	
87.	Rhodes, L. E. (2007) BAD	Conference abstract- Insufficient data to extra
	conference abstract	
88.	Rhodes, L. E. (2007) EADV	Conference abstract- Insufficient data to extra
	conference abstract	
89.	Rkein, A. M. (2014) Dermatol	Review
	Clin	
90.	Roberts, G. (2015) Br J Dermat	Conference abstract
91.	Rodriguez-Prieto, M. A. (2012) J	No comparator arm
	Am Acad Dermatol.	(O)
92.	Roozeboom, M. H. (2012) Br J	Review
	Dermatol.	
93.	Roozeboom, M. H. (2015) J Am	Case controlled study
	Acad Dermatol.	
94.	Ruiz, E. S. (2015) J Drugs	Review
	Dermatol.	
95.	Saager, R. B. (2011) Lasers Surg	No comparator arm and outcomes not
	Med	pertinent to this guideline
96.	Salavastru, C. (2014) J Am Acad	Conference abstract - no comparator arm
	Dermatol	
97.	Samy, N. A. (2015) Lasers Med	Outcomes not pertinent to this guideline
	Sci	

1	
2	
3	
4	
5	
6	
7	
8	
8 9	
10	
11	
12	
13	
11 12 13 14 15 16 17	
15	
16	
17	
18	
19	
20	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
50	
52	
53	
54	
55	
56	
57	
58	
59	
60	

	References	Reason for exclusion from extraction
98.	Sandberg, C. (2008) Br J	Outcomes not pertinent to this guideline
	Dermatol	
99.	Schweiger, E. S. (2010) J Drugs	Unable to access this reference: case report
	Dermatol; 9: 167–8	
100	Sebaratnam, D. F. (2010)	Conference abstract, full paper Sebaratnam
	Australas J Dermatol	(2011) which has been included
101	Sebaratnam, D. F. (2011) J Eur	Insufficient data to extract
	Acad Dermatol Venereol	
102	Segura, S. (2011) J Eur Acad	No comparator arm
	Dermatol Venereol	
103	Serra-Guillén, C. (2012) Actas	Review
	Dermosifiliogr	
104	Shokrollahi, K. (2009) Cases J	Case report
105	Shokrollahi, K. (2014) Ann Plast	No comparator arm
	Surg	
106	Shumack, S. (2009) Australas J	Conference abstract – no extractable data
	Dermatol	
107	Sidoroff, A. (2010)	Review
	Photodiagnosis Photodyn Ther	
108	Smucler, R. (2011) Lasers Surg	Conference abstract- Insufficient data to extr
	Med.	
109	Smucler, R. (2012) Photomed	Not randomised clinical trial
	Laser Surg	
110	Soler, A.M. (2000)	No comparator arm besides PDT
	Photodiagnosis Photodyn Ther	
111	Soler, A.M. (2000) Brit J	Not randomised clinical trial
	Dermatol	
112	Soler, A.M. (1999) Acta Derm	Not randomised clinical trial
	Venereol	

	References	Reason for exclusion from extraction		
113	Sotiriou, E. (2013) J Dtsch	Conference abstract - no comparator arm		
	Dermatol Ges; 22–3			
114	Sotiriou, E. (2013) J Dtsch	Conference abstract – insufficient data to		
	Dermatol Ges; 110	extract		
115	Souza, C. S. (2009)	No comparator arm		
	Photodiagnosis Photodyn Ther			
116	Spada, J. (2012) J Am Acad	Conference abstract – case study		
	Dermatol			
117	Star, W.M. (2006) Acta Derm	Not randomised clinical trial		
	Venereol			
118	Sunar, U. (2013) Lasers Surg	Conference abstract – outcomes not pertinent		
	Med	to this guideline		
119	Sunar, U. (2013) Biomed Opt	Outcomes not pertinent to this guideline		
	Express			
120	Surrenti, T. (2007) Eur J	From abstract no comparator arm		
	Dermatol			
121	Szeimies, R. M. (2007) Dermatol	Review		
	Clin	· L.		
122	Taborda, V (2016) J Eur Acad	Not randomised clinical trial		
	Dermatol	4		
123	Tehranchinia, Z. (2013) Indian J	No comparator arm		
	Dermatol			
124	Themstrup, L. (2014)	No comparator arm		
	Photodiagnosis Photodyn Ther			
125	Thissen, M.R. (2000) Brit J	No comparator arm		
	Dermatol			
126	Tierney, E. (2010) Lasers Surg	No comparator arm		
	Med; 7			
127	Tierney, E. P. (2010) Lasers Surg	Conference abstract - no comparator arm. case		
	Med; 37	series		

1 2 3	
4 5 6 7	
	0
1 1 1	3 4
1 1 1 1	6 7
2 2 2	3 4 5
2 2 2	8 9
3	4 5 6 7
3 3 4 4	0
4 4 4	2 3 4
4 4 4 4	6 7
4 5 5 5	0 1
5 5 5 5 5	3 4 5
5	

	References	Reason for exclusion from extraction
128	Toll, A. (2008) Dermatol Surg	Case report
129	Torres, T. (2010) J Am Acad	Conference abstract – no comparator arm. Case
	Dermatol	study
130	Valentine, R. (2011) Lasers Med	Conference abstract – insufficient data to
	Sci	extract
131	Venturini, M. (2013) Br J	No comparator arm
	Dermatol	
132	Vinviullo, C (2005) Brit J	No comparator arm
	Dermatol	
133	Wang, K. K. (2009) Lasers Surg	Outcomes not pertinent to this guideline
	Med	
134	Wang, Y. (2009) Chin Ger J Clin	No comparator arm
	Oncol	
135	Whitaker, I. S. (2007) Ann Plast	No comparator arm
	Surg	
136	Zeitouni, N.C. (2014) Dermatol	No comparator arm besides PDT
	Surg	

# Table S3 Cochrane risk of bias

		BIAS						
Publication	Outcome	Overall	Selection	Performance	Attrition	Detection	Outcome	Other
Wang Br J Dermatol. 2001	Recurrence rate (> 1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Wang Br J Dermatol. 2001	Cosmetic outcome	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wang Br J Dermatol. 2001	Severe pain	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes. Arch Dermatol. 2004	Initial clearance of BCC (3 months)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes. Arch Dermatol. 2004	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes. Arch Dermatol. 2004	Recurrence rate (> 1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes. Arch Dermatol. 2004	Treatment tolerability	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes. Arch Dermatol. 2004	Cosmetic outcome	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes Arch Dermatol, 2007	Sustained clearance of BCC (5 years)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes Arch Dermatol, 2007	Cosmetic outcome	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rhodes Arch Dermatol, 2007	Severe pain	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
de Haas J. Invest. Dermatol. 2006	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
de Haas. J. Invest Dermatol. 2006	Severe pain	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
de Vijlder. Acta. Derm. Venereol. 2012	Sustained clearance of BCC (5 years)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kessels Br J Dermatol. 2017	Initial clearance of BCC (3 months)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kessels Br J Dermatol. 2017	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kessels Br J Dermatol. 2017	Cosmetic outcome	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
L. Berroeta Br J Dermatol. 2007	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
L. Berroeta Br J Dermatol. 2007	Treatment tolerability	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Smucler. Lasers Surg. Med. 2008	Initial clearance of BCC (3 months)	Very High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Smucler. Lasers Surg. Med. 2008	Sustained clearance of BCC (1 year)	Very High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Smucler Lasers Surg. Med. 2008	Cosmetic outcome	Very High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Szeimies J Eur Acad Dermatol Venereol. 2008	Initial clearance of BCC (3 months)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Szeimies J Eur Acad Dermatol Venereol. 2008	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

1	
2	
3	
4	
5	
6	
7	
8	
9	
1	0
1	1
1	2
1	3
1	
1	5
1	6
1	7
1	8
	9
	0
2	
2	2
2	
	4
	5
2	6
2	7
2	8
	9
	0
3	
3	
3	
	4
	5
	6
3	
3	8
	9
	0
4	
4	2
4	
4	
4	
4	
4	
4	
	9
	0
5	
5	1 2
	2 3
	5 4
5	
э 5	
5 5	
5	
С	0

#### British Journal of Dermatology

Szeimies J Eur Acad Dermatol Venereol. 2008	Cosmetic outcome	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Mosterd Br J Dermatol. 2008	Initial clearance of BCC (3 months)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Mosterd Br J Dermatol. 2008	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Roozeboom, J. Am Acad Dermatol. 2013	Sustained clearance of BCC (5 years)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Roozeboom, J. Am Acad Dermatol. 2013	Recurrence rate (> 1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Basset-Seguin, Eur. J. Dermatol. 2008	Initial clearance of BCC (3 months)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Basset-Seguin, Eur. J. Dermatol. 2008	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Basset-Seguin. Eur. J. Dermatol. 2008	Sustained clearance of BCC (5 years)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Basset-Seguin, Eur. J. Dermatol. 2008	Recurrence rate (> 1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Basset-Seguin, Eur. J. Dermatol. 2008	Cosmetic outcome	Very High risk	High risk	High risk	Low risk	Low risk	Low risk	
Basset-Seguin, Eur. J. Dermatol. 2008	Treatment tolerability	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Basset-Seguin, Eur. J. Dermatol. 2008	Severe pain	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Foley, Int. J. Dermatol. 2009	Initial clearance of BCC (3 months)	High risk	Low risk	Low risk	Low risk	Low risk	High risk	
Foley, Int. J. Dermatol. 2009	Cosmetic outcome	Very High risk	Low risk	Low risk	Very High risk	Low risk	High risk	
Foley, Int. J. Dermatol. 2009	Treatment tolerability	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Foley, Int. J. Dermatol. 2009	Severe pain	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Osiecka, Med. Sci. Monit. 2012	Recurrence rate (> 1 year)	Very High risk	Low risk	High risk	Low risk	Low risk	High risk	
Arits, Lancet Oncol. 2013	Initial clearance of BCC (3 months)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Arits, Lancet Oncol. 2013	Sustained clearance of BCC (1 year)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Arits, Lancet Oncol. 2013	Treatment tolerability	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Arits, Lancet Oncol. 2013	Severe pain	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Arits, Lancet Oncol. 2013	Cosmetic outcome	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Jansen, J Invest Dermatol. 2017.	Sustained clearance of BCC (5 years)	High risk	Low risk	High risk	Low risk	Low risk	Low risk	
Haak, Br. J. Dermatol. 2015	Initial clearance of BCC (3 months)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Haak, Br. J. Dermatol. 2015	Sustained clearance of BCC (1 year)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Haak, Br. J. Dermatol. 2015	Sustained clearance of BCC (1 year)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Haak, Br. J. Dermatol. 2015	Cosmetic outcome	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	

Low risk

Low

risk

Low

risk

Low

risk

Low risk

Low

risk

| Haak, Br. J.<br>Dermatol. 2015 | Other adverse effects               | Low risk | Low r |
|--------------------------------|-------------------------------------|----------|----------|----------|----------|----------|-------|
| Choi, JEADV.<br>2016           | Initial clearance of BCC (3 months) | Low risk | Low r |
| Choi, JEADV.<br>2016           | Sustained clearance of BCC (1 year) | Low risk | Low r |
| Choi, JEADV.<br>2016           | Recurrence rate (> 1<br>year)       | Low risk | Low r |
| Choi, JEADV.<br>2016           | Cosmetic outcome                    | Low risk | Low r |
| Choi, JEADV.<br>2016           | Other adverse effects               | Low risk | Low r |

S13

#### Table S4 GRADE evidence

PDT vs placebo-PDT

			Quality as	sessment			No of	patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT	Placebo- PDT	Relative (95% Cl)	Absolute	•	
Clearance	of treated B	CC (3 mon	ths initial lesion cl	earance) lesion:	MAL-PDT vs pla	icebo			I	L		
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/75 (73.3%)		RR 2.75 (1.84 to 4.1)	467 more per 1000 (from 224 more to 828 more)		CRITICAL
Severe pa	in (leading to	break in t	reatment/use of lo	cal analgesia) pa	atient: MAL-PDT	vs placebo			•		•	1
	1	1										
1	randomised trials	serious <sup>1</sup>	2	no serious indirectness	2	none	0/66 (0%)	0%	not pooled	not pooled	2	CRITICAL
1 Cosmetic	trials		good) lesion: MAL	indirectness	2	none		0%	not pooled	not pooled	2	CRITICAL
1 Cosmetic 1	trials		good) lesion: MAL	indirectness	no serious imprecision	none		0%	not pooled RR 3 (1.8 to 5.01)	not pooled 374 more per 1000 (from 150 more to 750 more)	2 ⊕⊕OO LOW	CRITICAL
1	trials outcome (exe randomised trials	very serious <sup>1</sup>	no serious	indirectness -PDT vs placebo no serious indirectness	no serious imprecision	84.	(0%)		RR 3 (1.8 to	374 more per 1000 (from		

<sup>1</sup>Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

<sup>2</sup> Unable to assess inconsistency, imprecision or outcome due to lack of events in either arm

<sup>3</sup> Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

# PDT vs cryosurgery

			Quality ass	essment			No c	of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT	Cryosurgery	Relative (95% Cl)	Absolute		
Clearance	e of treated B	CC (3 month	s initial lesion cle	arance) lesion: F	PDT vs cryosurg	gery						
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	56/62 (90.3%)	89.7%	RR 1.01 (0.89 to 1.14)	9 more per 1000 (from 99 fewer to 126 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustaine	d clearance o	f treated BCC	C (1 year) patient:	MAL-PDT vs Cry	yosurgery		•					
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	51/56 (91.1%)	92.3%		9 fewer per 1000 (from 111 fewer to 102 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustaine	d clearance o	f treated BCC	C (5 years) patient	: MAL-PDT vs C	ryosurgery		1		I			
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	32/56 (57.1%)	78.9%	RR 0.72 (0.55 to 0.95)	221 fewer per 1000 (from 39 fewer to 355 fewer)	⊕⊕OO LOW	CRITICAL
Recurren	ce rate (1 yea	r) patient (su	perficial): PDT vs	cryosurgery								
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	8/22 (36.4%)	5.9%	RR 6.18 (0.85 to 44.78)	306 more per 1000 (from 9 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Recurren	ce rate (1 yea	r) patient (no	odular): PDT vs cr	yosurgery			1					
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	3/25 (12%)	20.8%	RR 0.58 (0.15 to 2.15)	87 fewer per 1000 (from 177 fewer to 239 more)	⊕OOO VERY LOW	CRITICAL
Recurren	ce rate (>1 ye	ar <2 years)	patient: PDT vs c	ryosurgery	<u>I</u>	L						
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	7/51 (13.7%)	6.3%	RR 2.2 (0.6 to 8.01)	76 more per 1000 (from 25 fewer to 442	⊕000 VERY LOW	CRITICAL

	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	11/51 (21.6%)	6.3%	RR 3.45 (1.02 to 11.62)	154 more per 1000 (from 1 more to 669 more)	⊕⊕OO LOW	CRITICA
Recur	rence rate (>1 ye	ear <4 years)	patient: PDT vs	cryosurgery			<u> </u>					L
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	11/51 (21.6%)	6.3%	RR 3.45 (1.02 to 11.62)	154 more per 1000 (from 1 more to 669 more)	⊕OOO VERY LOW	CRITICA
Recur	rence rate (>1 ye	ear <5 years)	patient: PDT vs	cryosurgery					1			<u> </u>
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	11/51 (21.6%)	8.3%	RR 2.59 (0.88 to 7.58)	132 more per 1000 (from 10 fewer to 546 more)	⊕000 VERY LOW	CRITICA
Severe	e pain (leading to	o break in tre	atment/use of lo	ocal analgesia) pa	atient: PDT vs cr	yosurgery	<u> </u>					
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	4/109 (3.7%)	0.9%	RR 2.74 (0.44 to 17.06)	16 more per 1000 (from 5 fewer to 145 more)	⊕OOO VERY LOW	CRITICA
Cosm	etic outcome (ex	cellent) patie	ent: PDT vs cryo	surgery (3 month	is) assessed by	investigator						
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/62 (27.4%)	3.5%	RR 7.95 (1.92 to 32.92)	243 more per 1000 (from 32 more to 1000 more)	⊕⊕OO LOW	IMPORTA
Cosm	etic outcome (ex	cellent) patie	ent: PDT vs cryo	surgery (3 month	is) assessed by	patient	<u> </u>		1.			
	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	25/62 (40.3%)	19%	RR 2.13 (1.15 to 3.92)	215 more per 1000 (from 28 more to 555 more)	⊕000 VERY LOW	IMPORTA
1			ent: PDT vs crvo	surgery (1 year) a	assessed by inv	estigator						<u> </u>
1 Cosmo	etic outcome (ex	cellent) patie							DD 0 70	265 mars par 1000	⊕⊕00	IMPORTA
	randomised	very serious <sup>1</sup>		no serious indirectness	no serious imprecision	none	41/109 (37.6%)	9.7%	RR 3.73 (1.96 to 7.07)	265 more per 1000 (from 93 more to 589 more)	LOW	
2	randomised trials	very serious <sup>1</sup>	no serious inconsistency		imprecision			9.7%		(from 93 more to 589		

1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	22/62 (35.5%)	24.1%	RR 1.47 (0.83 to 2.59)	113 more per 1000 (from 41 fewer to 383 more)		IMPORTAN
Cosme	etic outcome (ex	cellent) patie	nt: PDT vs cryo	surgery (2 years	) assessed by ir	vestigator	- <b>1</b> - <b>1</b>				•	
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/62 (40.3%)	6.9%	RR 5.85 (2.17 to 15.78)	335 more per 1000 (from 81 more to 1000 more)		IMPORTAN
Cosme	etic outcome (ex	cellent) patie	ent: PDT vs cryo	surgery (2 years	) assessed by p	atient				I		
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	23/62 (37.1%)	25.9%	RR 1.43 (0.83 to 2.47)	111 more per 1000 (from 44 fewer to 381 more)	⊕OOO VERY LOW	IMPORTAN
Cosme	etic outcome (ex	cellent) patie	ent: PDT vs cryo	surgery (3 years	) assessed by ir	vestigator				L		
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/62 (30.6%)	8.6%	RR 3.55 (1.42 to 8.9)	219 more per 1000 (from 36 more to 679 more)	⊕⊕OO LOW	IMPORTAN
Cosme	etic outcome (ex	cellent) patie	ent: PDT vs cryo	surgery (4 years	) assessed by ir	vestigator			•			
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/62 (30.6%)	8.6%	RR 3.55 (1.42 to 8.9)	219 more per 1000 (from 36 more to 679 more)	⊕⊕OO LOW	IMPORTAN
	otic outcome (or	cellent) patie	ent: PDT vs cryo	surgery (5 years	) assessed by in	vestigator			•		<u> </u>	
Cosme	elic outcome (ex	oononi, pune										
Cosme	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/62 (30.6%)	12.1%	RR 2.54 (1.15 to 5.59)	186 more per 1000 (from 18 more to 555 more)	⊕⊕OO LOW	IMPORTAI
1	randomised	very serious <sup>1</sup>	inconsistency	indirectness	imprecision	none		12.1%		(from 18 more to 555		IMPORTAI

S17

2 No clinical important difference - between MIDs

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

# PDT vs surgical excision

			Quality as	ssessment			No of I	oatients		Effect	Quality	Importanc
No of studies	Deeran	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT	Surgical	Relative (95% Cl)	Absolute		
Clearand	ce of treated sl	BCC (3 mo	nths initial lesion	clearance) lesion	: PDT vs surgica	l excision	<b></b>					
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	118/135 (87.4%)	88.6%	RR 0.99 (0.9 to 1.08)	9 fewer per 1000 (from 89 fewer to 71 more)	⊕⊕⊕O MODERATE	CRITICAL
Clearand	ce of treated nl	BCC (3 mo	nths initial lesion	clearance) lesion	: PDT vs surgica	I excision						
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	48/53 (90.6%)	98.1%	RR 0.92 (0.84 to 1.02)	78 fewer per 1000 (from 157 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustaine	ed clearance of	treated sl	BCC (1 year) lesion	n: PDT vs surgica	al excision							
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	107/118 (90.7%)	100%	RR 0.91 (0.85 to 0.96)	90 fewer per 1000 (from 40 fewer to 150 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Sustaine	ed clearance of	treated n	BCC (1 year) lesio	n: PDT vs surgica	al excision							
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	57/69 (82.6%)	88.5%	RR 0.9 (0.8 to 1.01)		⊕⊕⊕O MODERATE	CRITICA
Sustaine	ed clearance of	treated B	CC (5 years) patie	nt: PDT vs surgic	al excision							
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	31/52 (59.6%)	71.4%	RR 0.83 (0.63 to 1.11)	121 fewer per 1000 (from 264 fewer to 79 more)	⊕OOO VERY LOW	CRITICA
							1					
Recurre	nce rate (>1 ye	ar <2 year	s) lesion: PDT vs s	angiour excision								
Recurrer	randomised	ar <2 years	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	3/44 (6.8%)	2%	RR 3.41 (0.37 to 31.6)	48 more per 1000 (from 13 fewer to 612 more)	⊕OOO VERY LOW	CRITICA
1	randomised trials	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>3</sup>	none	-	2%	· · ·			CRITICA

S18

	trials	serious <sup>1</sup>	inconsistency	indirectness			(10.2%)		to 13.05)	18 fewer to 470 more)	VERY LOW	
Cosme	etic outcome (ex	cellent or	good) patient: PD	)T vs surgical ex	cision (3 months)	) assessed by i	nvestigator				I	1
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/50 (72%)	31.9%	RR 2.26 (1.44 to 3.54)	402 more per 1000 (from 140 more to 810 more)	⊕⊕⊕O MODERATE	IMPORTAN
Cosme	etic outcome (ex	cellent or	good) patient: PD	)T vs surgical ex	cision (3 months)	) assessed by	patient				I	
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	39/50 (78%)	78.7%	RR 0.99 (0.8 to 1.22)	8 fewer per 1000 (from 157 fewer to 173 more)	⊕⊕⊕O MODERATE	IMPORTAN
Cosme	etic outcome (ex	cellent or	good) sBCC patie	ent: PDT vs surgi	cal excision (1 y	ear) assessed	oy investigato	r			I	
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	77/100 (77%)	45.8%	RR 1.68 (1.32 to 2.14)	311 more per 1000 (from 147 more to 522 more)		IMPORTAN
Cosme	etic outcome (ex	cellent or	good) nBCC patio	ent: PDT vs surgi	ical excision (1 y	ear) assessed	oy investigato	or				I
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	33/50 (66%)	36.2%	RR 1.82 (1.19 to 2.8)	297 more per 1000 (from 69 more to 652 more)	⊕⊕OO LOW	IMPORTAN
Cosme	etic outcome (ex	cellent or	good) nBCC patio	ent: PDT vs surgi	ical excision (1 y	ear) assessed	by patient				L	
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	41/50 (82%)	76.6%	RR 1.07 (0.87 to 1.31)	54 more per 1000 (from 100 fewer to 237 more)	⊕⊕OO LOW	IMPORTAN
Cosme	etic outcome (ex	cellent or	good) nBCC patio	ent: PDT vs surgi	ical excision (2 y	ears) assessed	by investigat	or				I
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	24/50 (48%)	34%	RR 1.41 (0.86 to 2.31)	139 more per 1000 (from 48 fewer to 445 more)	⊕000 VERY LOW	IMPORTAN
Cosme	etic outcome (ex	cellent or	good) nBCC pation	ent: PDT vs surgi	ical excision (2 y	ears) assessed	by patient				I	
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	28/50 (56%)	57.5%	RR 0.97 (0.69 to 1.38)	17 fewer per 1000 (from 178 fewer to 218 more)	⊕OOO VERY LOW	IMPORTAN
Cosme	etic outcome (ex	cellent or	good) nBCC patio	ent: PDT vs surgi	ical excision (5 y	ears) assessed	by investigat	or			L	
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	27/50 (54%)	40.4%	RR 1.34 (0.87 to 2.06)	137 more per 1000 (from 53 fewer to 428 more)	⊕OOO VERY LOW	IMPORTAN
Treatm	ent tolerability -	low or ma	anageable pain P	DT vs Surgical ex	cision						<u> </u>	
						S19						

1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	27/50 (54%)	29.8%	RR 1.81 (1.09 to 3.01)	241 more per 1000 (from 27 more to 599 more)	⊕⊕OO LOW	IMPORTAN
Treatmo	ent tolerability -	low or ma	anageable pain P	DT vs Surgical e	cision (during tr	eatment) (Better	indicated by	y lower v	values)			
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	11	-	MD 3.57 higher (1.7 to 5.44 higher)	⊕⊕⊕O MODERATE	IMPORTA
Treatmo	ent tolerability -	low or ma	anageable pain P	DT vs Surgical ex	ccision (immediat	ely after treatme	ent) (Better i	ndicated	l by lower value	es)		
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	11	-	MD 3.57 higher (1.7 to 5.44 higher)	⊕⊕⊕O MODERATE	IMPORTA
Treatmo	ent tolerability -	low or ma	anageable pain P	DT vs Surgical ex	cision (3 hours a	ifter treatment) (	Better indica	ated by I	ower values)			
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	15	11	-	MD 1.06 higher (0.41 lower to 2.53 higher)	⊕OOO VERY LOW	IMPORTA
Treatmo	ent tolerability -	low or ma	anageable pain P	DT vs Surgical ex	cision (6 hours a	ifter treatment) (l	Better indica	ated by I	ower values)			1
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	15	11	-	MD 0.66 lower (2.3 lower to 0.98 higher)	⊕000 VERY LOW	IMPORTA
Treatmo	ent tolerability -	low or ma	anageable pain P	DT vs Surgical e	cision (24 hours	after treatment)	(Better indi	cated by	lower values)			
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	15	11	-	MD 0.4 lower (1.7 lower to 0.9 higher)	⊕000 VERY LOW	IMPORTA
Treatmo	ent tolerability -	low or ma	anageable pain P	DT vs Surgical ex	cision (48 hours	after treatment)	(Better indi	cated by	lower values)			<u> </u>
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	15	11	V	MD 0.6 lower (1.72 lower to 0.52 higher)	⊕⊕OO LOW	IMPORTA
Treatmo	ent tolerability -	low or ma	anageable pain P	DT vs Surgical e	cision (1 week a	fter treatment) (E	Better indica	ted by lo	ower values)			1
1	randomised trials	serious <sup>1</sup>	4	no serious indirectness	4	none	15	11	-	not pooled	4	IMPORTA

2 No clinical important difference - between MIDs

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

4 Unable to assess inconsistency, imprecision or outcome due to mean/SD of 0

# PDT vs topicals

PDT vs	topicals											
			Quality as	sessment			No of	patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT	Topicals	Relative (95% CI)	Absolute		
Clearance	e of treated B	CC (3 mont	ths initial lesion cl	earance) patient:	PDT vs topicals	(imiquimod)						
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	165/202 (81.7%)		RR 0.95 (0.87 to 1.04)	43 fewer per 1000 (from 112 fewer to 34 more)	⊕⊕OO LOW	CRITICAL
Clearance	of treated B	CC (3 mont	ths initial lesion cl	earance) patient:	PDT vs topicals	(fluorouracil)	•	•				
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	165/202 (81.7%)		RR 0.94 (0.87 to 1.03)	52 fewer per 1000 (from 113 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
Sustained	d clearance of	treated B0	CC (1 year) patient	: PDT vs topicals	(imiquimod)		1	1				
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	135/165 (81.8%)		RR 0.91 (0.83 to 0.99)	81 fewer per 1000 (from 9 fewer to 153 fewer)	⊕⊕OO LOW	CRITICAL
Sustained	l clearance of	treated B0	CC (1 year) patient	: PDT vs topicals	(fluorouracil)							
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	135/165 (81.8%)		RR 0.92 (0.85 to 1.01)	71 fewer per 1000 (from 133 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
Sustained	d clearance of	treated B0	CC (3 years) patier	nt: PDT vs topical	ls (imiquimod)							
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	116/165 (70.3%)		RR 0.84 (0.74 to 0.94)	135 fewer per 1000 (from 50 fewer to 219 fewer)	⊕OOO VERY LOW	CRITICAL
Sustained	d clearance of	treated BO	CC (3 years) patier	nt: PDT vs topical	ls (fluorouracil)		<u> </u>	<u> </u>			ı	
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	116/165 (70.3%)		RR 0.89 (0.78 to 1)	87 fewer per 1000 (from 174 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Severe pa	ain patient: M/	AL-PDT vs	topical (imiquimo	d)	I	<u> </u>	1	1	I		I	
1	randomised	serious <sup>1</sup>	no serious	no serious	very serious <sup>3</sup>	none	35/202	18.7%	RR 0.93 (0.61	13 fewer per 1000 (from	⊕000	CRITICAL

	trials		inconsistency	indirectness			(17.3%)		to 1.41)	73 fewer to 77 more)	VERY LOW	
Severe	pain patient: M	AL-PDT vs	topical (fluorou	racil)					I		<u>I</u>	<u> </u>
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	35/202 (17.3%)	9%	RR 1.93 (1.13 to 3.3)	84 more per 1000 (from 12 more to 207 more)	⊕⊕OO LOW	CRITICAL
Cosme	etic outcome (ex	cellent or	good) patient: PD	OT vs topicals (im	iquimod)						<u> </u>	I
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	116/202 (57.4%)	57.1%	RR 1.01 (0.85 to 1.19)	6 more per 1000 (from 86 fewer to 108 more)	⊕⊕⊕O MODERATE	IMPORTAN
Cosme	etic outcome (ex	cellent or	good) patient: PD	)T vs topicals (flu	orouracil)	-						<u>I</u>
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	116/202 (57.4%)	55.2%	RR 1.04 (0.88 to 1.24)	22 more per 1000 (from 66 fewer to 132 more)	⊕⊕⊕O MODERATE	IMPORTAI
Other a	adverse effects (	serious ar	nd unexpected re	actions): PDT vs	topicals (imiquim	iod)					<u> </u>	L
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3,4</sup>	none	0/202 (0%)	4.8%	RR 0.05 (0 to 0.84)	46 fewer per 1000 (from 8 fewer to 48 fewer)	⊕⊕OO LOW	IMPORTAN
Other a	adverse effects (	serious ar	nd unexpected re	actions): PDT vs	topicals (fluorou	acil)			I		<u>I</u>	<u> </u>
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3,4</sup>	none	0/202 (0%)	2%	RR 0.11 (0.01 to 2.04)	18 fewer per 1000 (from 20 fewer to 21 more)	⊕000 VERY LOW	IMPORTAN
							i í		,	,	-	

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

4 No events on one arm

# Combination PDT vs PDT

			Quality asses	ssment			No of patie	nts		Effect	Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination PDT	PDT	Relative (95% Cl)	Absolute		
learanc	e of treated B	CC (3 months	initial lesion clea	arance) patient: A	ALA-PDT + in	niquimod vs ALA-F	PDT	<u> </u>	<u> </u>		II	
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	18/24 (75%)	60%	OR 2 (0.42 to 9.58)	150 more per 1000 (from 213 fewer to 335 more)	⊕000 VERY LOW	CRITICA
Recurren	ice rate (>1 ye	ar) patient: A	LA-PDT + imiquin	nod vs ALA-PDT	.1	1 1		1	1			
	randomised trials		no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/24 (4.2%)	0%	RR 1.32 (0.06 to 29.92)	-	⊕⊕OO LOW	CRITICA
Clearanc	e of treated B	CC (3 months	initial lesion clea	arance) patient: A	AFXL-MAL-PI	DT vs MAL-PDT						
learanc	randomised trials	-	no serious inconsistency	no serious indirectness	Serious <sup>2</sup>	DT vs MAL-PDT	16/16 (100%)	87.5%	RR 1.14 (0.92 to 1.41)	122 more per 1000 (from 70 fewer to 359 more)	⊕⊕⊕O MODERATE	CRITICA
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>			87.5%		(from 70 fewer to 359		CRITICA
	randomised trials	no serious risk of bias CC (3 months	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none				(from 70 fewer to 359 more) 335 more per 1000		CRITICA
Clearanc	randomised trials e of treated B randomised trials	no serious risk of bias CC (3 months no serious risk of bias	no serious inconsistency s initial lesion clea no serious	no serious indirectness arance) lesion: A no serious indirectness	serious <sup>2</sup> FL-PDT (Er:Y	none (AG) vs MAL-PDT	(100%)		to 1.41) RR 1.78 (1.03	(from 70 fewer to 359 more) 335 more per 1000 (from 13 more to 892	MODERATE ⊕⊕⊕O	
Clearanc	randomised trials e of treated B randomised trials	no serious risk of bias CC (3 months no serious risk of bias f treated BCC	no serious inconsistency initial lesion clea no serious inconsistency	no serious indirectness arance) lesion: A no serious indirectness	serious <sup>2</sup> FL-PDT (Er:Y	none (AG) vs MAL-PDT	(100%)	42.9%	to 1.41) RR 1.78 (1.03	(from 70 fewer to 359 more) 335 more per 1000 (from 13 more to 892	MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O	CRITICA
Clearanc	randomised trials e of treated B randomised trials d clearance of randomised trials	no serious risk of bias CC (3 months no serious risk of bias f treated BCC no serious risk of bias	no serious inconsistency initial lesion clea no serious inconsistency (1 year) patient: a no serious	no serious indirectness arance) lesion: A no serious indirectness AFXL-MAL-PDT no serious indirectness	serious <sup>2</sup> FL-PDT (Er:Y serious <sup>2</sup> vs MAL-PDT serious <sup>2</sup>	none <b>'AG) vs MAL-PDT</b> none	(100%) 16/21 (76.2%) 13/16	42.9%	to 1.41) RR 1.78 (1.03 to 3.08) RR 1.26 (0.8	(from 70 fewer to 359 more) 335 more per 1000 (from 13 more to 892 more) 167 more per 1000 (from 129 fewer to 637	MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O	

										more)		
Recurre	ence rate (1 yea	r) lesion: AF	XL-MAL-PDT vs	MAL-PDT				_			I	
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	3/16 (18.8%)	43.8%	RR 0.43 (0.13 to 1.37)	250 fewer per 1000 (from 381 fewer to 162 more)	⊕⊕⊕O MODERATE	CRITIC
Cosmeti	ic outcome (ex	cellent) patie	ent: AFXL-MAL-P	DT vs MAL-PDT	(3 months) a	ssessed by inves	tigator		•		•	
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	11/16 (68.8%)	56.3%	RR 1.22 (0.71 to 2.11)	124 more per 1000 (from 163 fewer to 625 more)	⊕⊕OO LOW	IMPORTA
Cosmeti	ic outcome (ex	cellent) patie	ent: AFXL-MAL-P	DT vs MAL-PDT	(3 months) a	ssessed by patier	nt		L		1	1
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	13/16 (81.3%)	50%	RR 1.62 (0.94 to 2.8)	310 more per 1000 (from 30 fewer to 900 more)	⊕⊕⊕O MODERATE	IMPORTA
Cosmeti	ic outcome (ex	cellent) patie	ent: AFXL-MAL-P	DT vs MAL-PDT	(6 months) a	ssessed by inves	tigator	<u> </u>			1	
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	12/16 (75%)	37.5%	RR 2 (1 to 4)	375 more per 1000 (from 0 more to 1000 more)	⊕⊕⊕O MODERATE	IMPORTA
Cosmeti	ic outcome (ex	cellent) patie	ent: AFXL-MAL-P	DT vs MAL-PDT	(6 months) a	ssessed by patier	nt		<u> </u>		I	<b>I</b>
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	12/16 (75%)	50%	RR 1.5 (0.85 to 2.64)	250 more per 1000 (from 75 fewer to 820 more)	⊕⊕⊕O MODERATE	IMPORTA
Cosmeti	ic outcome (ex	cellent) patie	ent: AFXL-MAL-P	DT vs MAL-PDT	(9 months) a	ssessed by inves	tigator					
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	8/16 (50%)	43.8%	RR 1.14 (0.54 to 2.4)	61 more per 1000 (from 201 fewer to 613 more)	⊕⊕OO LOW	IMPORTA
Cosmeti	ic outcome (ex	cellent) patie	ent: AFXL-MAL-P	DT vs MAL-PDT	(9 months) a	ssessed by patier	nt					
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	10/16 (62.5%)	50%	RR 1.25 (0.67 to 2.32)	125 more per 1000 (from 165 fewer to 660 more)	⊕⊕OO LOW	IMPORT/

Page	52 of	97
------	-------	----

sed no seriou risk of bia e (excellent) le sed no seriou risk of bia ects (hyperpig sed no seriou risk of bia	s inconsistency sion: AFL-PDT (Er no serious inconsistency mentation) patient: no serious inconsistency mentation) patient: a 3	no serious indirectness :YAG) vs MAL-PE no serious indirectness : AFL-PDT (Er:YA no serious indirectness	very serious <sup>2</sup> DT assessed very serious <sup>2</sup> G) vs MAL-P very serious <sup>2</sup>	none by investigato none PDT none	9/16 (56.3%)	57.1%	1.69) RR 1.19 (0.69 to 2.04)	(from 158 fewer to 701 more) 0 fewer per 1000 (from 234 fewer to 394 more)	LOW ⊕⊕OO LOW	IMPORTAN
risk of bia e (excellent) le sed no seriou risk of bia ects (hyperpig sed no seriou risk of bia ects (hyperpig sed no seriou	s inconsistency sion: AFL-PDT (Er no serious inconsistency mentation) patient: no serious inconsistency mentation) patient: a 3	indirectness :YAG) vs MAL-PE no serious indirectness : AFL-PDT (Er:YA no serious indirectness : AFXL-MAL-PDT no serious	serious <sup>2</sup> DT assessed very serious <sup>2</sup> G) vs MAL-P very serious <sup>2</sup>	by investigato none PDT none (3 months)	(56.3%) or 12/21 (57.1%) 12/18 (66.7%)	57.1%	to 2.6) RR 1 (0.59 to 1.69) RR 1.19 (0.69 to 2.04)	(from 158 fewer to 701 more) 0 fewer per 1000 (from 234 fewer to 394 more) 107 more per 1000 (from 175 fewer to 586	LOW ⊕⊕OO LOW	IMPORTAN
sed no seriou risk of bia ects (hyperpig sed no seriou risk of bia ects (hyperpig sed no seriou	no serious inconsistency nentation) patient: no serious inconsistency nentation) patient:	no serious indirectness AFL-PDT (Er:YA no serious indirectness AFXL-MAL-PDT no serious	very serious <sup>2</sup> G) vs MAL-P very serious <sup>2</sup>	none PDT none (3 months)	12/21 (57.1%) 12/18 (66.7%)	56.3%	1.69) RR 1.19 (0.69 to 2.04)	234 fewer to 394 more) 107 more per 1000 (from 175 fewer to 586	LOW ⊕⊕OO	
risk of bia ects (hyperpig sed no seriou risk of bia ects (hyperpig sed no seriou	s inconsistency mentation) patient: s no serious inconsistency mentation) patient:	indirectness AFL-PDT (Er:YA no serious indirectness AFXL-MAL-PDT no serious	serious <sup>2</sup> G) vs MAL-P very serious <sup>2</sup>	PDT none (3 months)	(57.1%) 12/18 (66.7%)	56.3%	1.69) RR 1.19 (0.69 to 2.04)	234 fewer to 394 more) 107 more per 1000 (from 175 fewer to 586	LOW ⊕⊕OO	
sed no seriou risk of bia ects (hyperpig	no serious sinconsistency nentation) patient:	no serious indirectness AFXL-MAL-PDT no serious	very serious <sup>2</sup>	none (3 months)	(66.7%)		to 2.04)	(from 175 fewer to 586		IMPORTAN
risk of bia ects (hyperpig sed no seriou	s inconsistency nentation) patient:	indirectness AFXL-MAL-PDT no serious	serious <sup>2</sup>	(3 months)	(66.7%)		to 2.04)	(from 175 fewer to 586		IMPORTAN
sed no seriou	<b>3</b>	no serious	vs MAL-PDT		0/16	0%				
			3	none	0/16	0%				
				YN.	(0%)	070	not pooled	not pooled		IMPORTAN
ects (hyperpig	nentation) patient:	AFXL-MAL-PDT	vs MAL-PDT	(6 months)						1
		no serious indirectness	very serious <sup>2</sup>	none	0/16 (0%)	6.3%	RR 0.33 (0.01 to 7.62)	42 fewer per 1000 (from 62 fewer to 417 more)	⊕⊕OO LOW	IMPORTAN
ects (hyperpig	mentation) patient:	AFXL-MAL-PDT	vs MAL-PDT	(9 months)					1	1
		no serious indirectness	very serious <sup>2</sup>	none	0/16 (0%)	6.3%	RR 0.33 (0.01 to 7.62)	42 fewer per 1000 (from 62 fewer to 417 more)	⊕⊕OO LOW	IMPORTAN
ects (hyperpig	nentation) patient:	AFXL-MAL-PDT	vs MAL-PDT	(1 year)					1	1
		no serious indirectness	very serious <sup>2</sup>	none	0/16 (0%)	12.5%	RR 0.2 (0.01 to 3.86)	100 fewer per 1000 (from 124 fewer to 357 more)	⊕⊕OO LOW	IMPORTAI
	risk of bia ects (hyperpigr sed no serious risk of bia ects (hyperpigr sed no serious risk of bia	risk of bias       inconsistency         ects (hyperpigmentation) patient:         sed       no serious risk of bias       no serious inconsistency         ects (hyperpigmentation) patient:         sed       no serious risk of bias       no serious no serious risk of bias	risk of biasinconsistencyindirectnessacts (hyperpigmentation) patient:AFXL-MAL-PDTsedno seriousno seriousno seriousrisk of biasno seriousno seriousno seriousacts (hyperpigmentation) patient:AFXL-MAL-PDTsedno seriousno seriousno seriousrisk of biasno seriousno seriousno seriousinconsistencyno seriousno seriousrisk of biasinconsistencyindirectness	risk of bias       inconsistency       indirectness       serious <sup>2</sup> acts (hyperpigmentation) patient:       AFXL-MAL-PDT vs       MAL-PDT         sed       no serious       no serious       no serious <sup>2</sup> acts (hyperpigmentation) patient:       AFXL-MAL-PDT vs       MAL-PDT         sed       no serious       no serious <sup>2</sup> serious <sup>2</sup> acts (hyperpigmentation) patient:       AFXL-MAL-PDT vs       MAL-PDT         sed       no serious       no serious       no serious         risk of bias       no serious       no serious       very         inconsistency       indirectness       very         sed       no serious       no serious       very         set       no serious       no serious       very         inconsistency       indirectness       very	risk of bias       inconsistency       indirectness       serious <sup>2</sup> acts (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (9 months)         sed       no serious       no serious       no serious         risk of bias       inconsistency       indirectness       very         acts (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (1 year)         sed       no serious       no serious       no serious         no serious       no serious       no serious       very	risk of bias       inconsistency       indirectness       serious <sup>2</sup> (0%)         acts (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (9 months)         sed       no serious       no serious       no serious       no serious         risk of bias       no serious       no serious       no serious       none       0/16         acts (hyperpigmentation) patient: AFXL-MAL-PDT vs       MAL-PDT (1 year)       serious <sup>2</sup> none       0/16         acts (hyperpigmentation) patient: AFXL-MAL-PDT vs       MAL-PDT (1 year)       sed       no serious       no serious       no serious         sed       no serious       no serious       no serious       serious <sup>2</sup> none       0/16         (0%)       inconsistency       indirectness       very       serious <sup>2</sup> none       0/16	risk of bias       inconsistency       indirectness       serious <sup>2</sup> (0%)         ects (hyperpigmentation) patient: AFXL-MAL-PDT vs       MAL-PDT (9 months)         sed       no serious       no serious       no serious         inconsistency       indirectness       very       none       0/16         ects (hyperpigmentation) patient: AFXL-MAL-PDT vs       MAL-PDT (9 months)         ects (hyperpigmentation) patient: AFXL-MAL-PDT vs       MAL-PDT (1 year)         sed       no serious       no serious       no serious         inconsistency       no serious       very       none         of bias       no serious       no serious       12.5%         indirectness       very       none       0/16       12.5%	risk of biasinconsistencyindirectnessserious2(0%)to 7.62)ects (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (9 months)sedno serious inconsistencyno serious indirectnessno serious2none0/16 (0%)6.3% to 7.62)ects (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (1 year)sedno serious inconsistencyno serious indirectnessvery serious2none0/16 (0%)6.3% to 7.62)sedno serious inconsistencyno serious indirectnessvery serious2none0/16 (0%)12.5% to 3.86)	risk of biasinconsistencyindirectnessserious²(0%)to 7.62)62 fewer to 417 more)acts (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (9 months)sedno serious inconsistencyno serious indirectnessno serious²none0/16 (0%)6.3% to 7.62)RR 0.33 (0.01 42 fewer per 1000 (from 62 fewer to 417 more)acts (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (1 year)serious²none0/16 (0%)6.3% to 7.62)RR 0.2 (0.01 to 3.86)100 fewer per 1000 (from 124 fewer to 357 more)	risk of bias       inconsistency       indirectness       serious <sup>2</sup> (0%)       to 7.62)       62 fewer to 417 more)       LOW         acts (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (9 months)         sed       no serious risk of bias       no serious inconsistency       no serious indirectness       very serious <sup>2</sup> none       0/16 (0%)       6.3% (0%)       RR 0.33 (0.01 42 fewer per 1000 (from to 7.62)       ⊕⊕OO 26 fewer to 417 more)       DOW         acts (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (1 year)       none       0/16 (0%)       12.5% (0%)       RR 0.2 (0.01 to 3.86)       100 fewer per 1000 (from 124 fewer to 357 more)       ⊕⊕OO LOW

# British Journal of Dermatology

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	12/20 (60%)	47.4%	RR 1.27 (0.7 to 2.29)	128 more per 1000 (from 142 fewer to 611 more)	⊕⊕OO LOW	IMPORTAN
owngraded	by 1 increment if the confi	dence interval crossed	is at high risk of bias, and downgr one MID or by 2 increments if th lack of events in either arm			vas at very high risk of bias		•				
						S26						

# Combination PDT vs surgical excision

			Quality as	sessment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination PDT	Surgical	Relative (95% Cl)	Absolute		
Clearance of treated BCC (3 months initial lesion clearance) nodular lesion: Combination PDT vs surgical excision												
	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	79/85 (92.9%)	97.7%	RR 0.95 (0.89 to 1.02)	49 fewer per 1000 (from 107 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Sustained	I clearance of	f treated B	SCC (1 year) nodul	ar lesion: Combi	nation PDT vs s	urgical excision	L					
	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	69/79 (87.3%)	96.5%	RR 0.9 (0.82 to 0.99)	97 fewer per 1000 (from 10 fewer to 174 fewer)	⊕⊕OO LOW	CRITICAL
Sustained	I clearance of	f treated B	SCC (5 years) lesio	n: Combination I	PDT vs surgical	excision	•					
	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	42/79 (53.2%)	74.4%	RR 0.71 (0.56 to 0.91)	216 fewer per 1000 (from 67 fewer to 327 fewer)	⊕OOO VERY LOW	CRITICAL
Recurren	ce rate (>1 ye	ar <2 year	s) lesion: Combin	ation PDT vs sur	gical excision			•				•
	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3,4</sup>	none	5/69 (7.2%)	0%	RR 13.2 (0.74 to 234.59)	-	⊕OOO VERY LOW	CRITICAL
Recurren	ce rate (>1 ye	ar <5 year	s) lesion: Combin	ation PDT vs sur	gical excision							
1	randomised	very	no serious	no serious	serious <sup>3,4</sup>	none	12/69	0%	RR 30 (1.81 to	-	⊕000	CRITICAL
	trials	serious <sup>1</sup>	inconsistency was at high risk of bias, and dow	indirectness			(17.4%)		497.72)		VERY LOW	

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 No clinical important difference - between MIDs

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

4 No events on one arm

#### Fractionated PDT vs PDT

			Quality as	sessment			No of patie	nts		Effect	Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractionated PDT	PDT	Relative (95% Cl)	Absolute		
Sustained clearance of treated BCC (1 year) lesion: ALA-PDT (2-fold) vs ALA-PDT (single)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none	252/262 (96.2%)	86.8%	RR 1.11 (1.05 to 1.17)	95 more per 1000 (from 43 more to 148 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustained	d clearance o	f treated B	CC (5 years) lesio	n: PDT (2-fold) v	s PDT (single)							
1	randomised trials		no serious inconsistency	no serious Vindirectness	serious <sup>3</sup>	none	376/471 (79.8%)	60.2%	RR 1.33 (1.19 to 1.47)	199 more per 1000 (from 114 more to 283 more)	⊕⊕OO LOW	CRITICAL
Severe pa	ain (leading to	break in	treatment/use of l	ocal analgesia) p	atient: ALA-PD1	۲ (2-fold) vs ALA-P	DT (single)	<u> </u>			I	
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/55 (16.4%)	3%	RR 5.45 (1.54 to 19.32)	133 more per 1000 (from 16 more to 550 more)	⊕⊕⊕O MODERATE	CRITICA
2 No clinical impo	rtant difference - betwe	en MIDs	was at high risk of bias, and dow	•		at very high risk of bias	er.	2	2		I	

Table S5 Non-pain	adverse	events	(AE)
-------------------	---------	--------	------

Study (Comparator)	Assessment of adverse effects*	Notes on adverse effects other than pain*
Foley 2009 <sup>1</sup> (Placebo-PDT)	A study nurse (blinded) monitored adverse events during treatment sessions and at follow-up. Severity, duration and need for additional therapy was recorded.	MAL-PDT, total adverse effects 74% (erythema 21%, crusting 8%, bleeding 6%) Placebo-PDT, total adverse effects 46% (erythema 6%, crusting 5%) All local adverse events were of mild to moderate intensity resolving within 1 day except bleeding, crusting, and erythema persisting for 3, 5 and 32 days respectively.
Basset-Seguin 2008 <sup>2</sup> (Cryosurgery)	Enquiry of adverse effects occurred at each follow-up visit, up to 3 months after the final treatment. Effect severity and causal relationship was recorded. Additionally a safety follow-up telephone call was performed fortnightly after treatments.	MAL-PDT total adverse effects 73% (crusting 35%, erythema 30%) Severity mild 80%, moderate 13%, severe 5% Cryo total adverse effects 79% (crusting 47%, erythema 21%, blisters 21%) Severity mild 73%, moderate 25%, severe 1% All local adverse events were transient, resolving within 5 days with the exception of crusting, erythema and itching with both treatments and suppuration in the cryosurgery group.
Wang 2001 <sup>3</sup> (Cryosurgery)	Visual analogue scale (VAS) completed by patient in first week after treatment.	Significantly shorter healing time after ALA-PDT as compared with cryosurgery. Leakage, oedema and erythema assessed at 1 week. MAL-PDT: Leakage (none 57%, mild 9%, moderate 9%, severe 0%), oedema (none 61%, mild 11%, moderate 0%, severe 0%), erythema (none 5%, mild 45%, moderate 20%, sever 0%). Cryosurgery: Leakage (none 16%, mild 18%, moderate 27%, severe 11%), oedema (none 25%, mild 36%, moderate 9%, severe 2%), erythema (none 2%, mild 41%, moderate 27%, severe 4%)
Berroeta 2007 <sup>4</sup> (Surgery)		Not stated
Mosterd 2008 <sup>5</sup> Roozeboom 2013 <sup>6</sup> (Surgery)	Adverse events of the two treatment modalities were documented at review	Secondary wound infection was observed once after ALA–PDT treatment
Rhodes 2004 <sup>7</sup> Rhodes 2007 <sup>8</sup> (Surgery)	Skin reactions from MAL application and illumination documented with adverse event severity, duration, and any additional therapy.	Adverse effects more common with MAL-PDT (52%) than surgery (29%) p = 0.03 PDT: erythema:14%, skin infection 0%, crusting 4%, itching 2% Surgery: erythema:2%, skin infection 6%, crusting 0%, itching 0% Local adverse events were of mild to moderate intensity, and all resolved in < 1 day.
Szeimies 2008 <sup>9</sup> (Surgery)	Adverse events (AEs), were recorded at each visit together with their severity, duration and need for additional therapy.	MAL-PDT adverse events: photosensitivity (31%), milia (2%). Surgery adverse events: wound infection (5.2%), erythema (3.1%), wound dehiscence (2.1%).
Arits 2013 <sup>10</sup> Roozeboom 2016 <sup>11</sup> Jansen 2017 <sup>12</sup> (IMQ or FU)	Local adverse reactions (redness, swelling, erosion, crusts, vesicles, squamae, and itching) were reported on a scale of 1–4. Serious adverse reactions were also recorded by the treating physician.	Suspected unexpected serious adverse reactions: MAL-PDT 0%, IMQ 4.8%, FU 2.1%. Symptoms during treatment (moderate/severe) and signs (moderate/severe) during treatment weeks: MAL-PDT treatment weeks (1,2) Redness (37%), swelling (3%, 4%), erosions (5%, 8%), crusts (8%, 11%), blistering (6%, 8%) squamae (6%, 5%), itching (9%, 12%). IMQ treatment weeks (1,2,3,4,5,6) Redness (36%, 52%, 56%, 56%, 56%, 55%, 49%), swelling (14%, 21%, 19%, 20%, 19%, 19%, erosions (5%, 16%, 24%, 30%, 28%, 26%), crusts (5%, 23%, 29%, 34%, 34%, 36%), blisterin (5%, 14%, 11%, 14%, 12%, 13%), squamae (1%, 3%, 4%, 5%, 8%, 7%), itching (19%, 28%, 27%, 30%, 31%, 28%,), tingling (4%, 4%, 3%, 4%, 4%, 4%). FU treatment weeks (1,2,3,4) Redness (31%, 51%, 61%, 59%), swelling (3%, 7%, 16%, 19%), erosions (5%, 17%, 31%, 31%), crusts (3%, 11%, 20%, 27%), blistering (4%, 10%, 18%, 17%), squamae (2%, 6%, 6%, 7%), itching (10%, 21%, 33%, 35%).
Smucler 2008 <sup>13</sup> (Er:YAG-laser, Er:YAG-laser/PDT)	None described	Not described
Haak 2015 <sup>14</sup> (CO <sub>2</sub> -AFL/PDT)	At the clinical assessments, adverse reactions were graded on a 4-point scale of severity.	Per patient other adverse effects (hyperpigmentation) at 3 months AFL-MAL-PDT 0% vs MAL-PDT 0% Per patient other adverse effects (hyperpigmentation) at 6 months AFL-MAL-PDT 0% vs MAL-PDT 6% : RR 0.33: 95%CI 0.01–7.62, p = 0.49 Per patient other adverse effects (hyperpigmentation) at 9 months AFL-MAL-PDT 0% vs MAL-PDT 6% : RR 0.33: 95%CI 0.01–7.62, p = 0.49 Per patient other adverse effects (hyperpigmentation) at 1 year AFL-MAL-PDT 0% vs MAL-PDT 13% : RR 0.20: 95%CI 0.01–3.86, p = 0.29
Choi 2016 <sup>15</sup> (Er:YAG-AFL/PDT)		Although no patient discontinued the study because of adverse events, all patients in bot groups experienced some adverse events, most commonly crusting. No patients discontinued the study because of adverse events but all patients reported ≥ adverse events. Frequently reported adverse events (AFL-PDT/MAL-PDT) Crusting (94%/88%), erythema (94%/88%), hyperpigmentation (67%/56%), itching (22%/18%), scale (17%/13%), blistering (17%/13%), oozing (11%/6%), bleeding (11%/6%)
Osiecka 2012 <sup>16</sup> (PDT/IMQ)	None described	Most patients during and after PDT complained of erythema and oedema that persisted for several days. Patients complained of increasing symptoms such as itching, large oedema, and strong irritation of skin, with erosions, after each application of IMQ.

Study	Assessment of adverse effects*	Notes on adverse effects other than pain*
(Comparator) De Haas 2006 <sup>17</sup>	Assessment of adverse enects	Notes on adverse enects other than pain
De Vijlder 2012 <sup>18</sup> (Fractionated PDT)		
DT) essels 2017 <sup>19</sup> Fractionated LA-PDT)		Erythema %: MAL-PDT vs ALA-PDT 2-fold: absent/mild 50.7% vs 16.3%; moderate/severe 38.4% vs 73.8%, p < 0.001; not available 11% vs 10%. Swelling %: MAL-PDT vs ALA-PDT 2-fold: absent/mild 83.6% vs 78.8%; moderate/severe 6.8% vs 11.3%, p = 0.406; not available 9.6% vs 10%. Wounds %: MAL-PDT vs ALA-PDT 2-fold: absent/mild 82.2% vs 70%; moderate/severe 5.5% vs 20%, p = 0.014; not available 12.3% vs 10%. Crusts %: MAL-PDT vs ALA-PDT 2-fold: absent/mild 82.2% vs 71.3%; moderate/severe 8.2% vs 18.8%, p = 0.062; not available 9.6% vs 10%. Vesicles %: MAL-PDT vs ALA-PDT 2-fold: absent/mild 83.6% vs 67.5%; moderate/severe 6.8% vs 22.5%, p = 0.011; not available 9.6% vs 10%. Scaling %: MAL-PDT vs ALA-PDT 2-fold: absent/mild 80.8% vs 71.3%; moderate/severe 9.6% vs 17.5%, p = 0.160; not available 9.6% vs 11.3%. Pruritus %: MAL-PDT vs ALA-PDT 2-fold: absent/mild 72.6% vs 70%; moderate/severe
*These are adverse	events other than pain, therefore exc	17.8% vs 20%, p = 0.835; not available 9.6% vs 10%. duding reference to pain, burning sensation, stinging, tingling etc.
VAS, visual analogu	laevulinate; ALA, 5-aminolaevulinic ac e scale; FU, 5-fluorouracil; IMQ, imiqu	:id; PDT, photodynamic therapy; CI, confidence interval; RR, risk ratio; LA, local anaesthetic; imod; AFL, Ablative Fractional Laser; Er:YAG, Erbium-doped Yttrium-Aluminium-Garnet;
CO2-AFL, carbon di	oxide Ablative Fractional Laser.	
		17.8% vs 20%, p = 0.835; not available 9.6% vs 10%. Juding reference to pain, burning sensation, stinging, tingling etc. id; PDT, photodynamic therapy; Cl, confidence interval; RR, risk ratio; LA, local anaesthetic; imod; AFL, Ablative Fractional Laser; Er:YAG, Erbium-doped Yttrium-Aluminium-Garnet;
		S30
		330

# Appendix S1 Forest plots

Basal Cell Carcinoma (BCC) (n) - nodular, (s) - superficial

NB: If the outcome being measured is positive i.e. clearance the intervention will

appear on the righthand axis of the forest plots. If negative i.e. severe pain, the

intervention will appear on the left hand axis of the forest plots.

PDT vs. Placebo-PDT

Clearance of treated nBCC (3 months initial lesion clearance) lesion: MAL-PDT vs

placebo PDT (vehicle cream)

	MAL-P	DT	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup					Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Foley, IJD 2009 (n)	55	75			100.0%	2.75 [1.84, 4.10]	
Total (95% CI)		75		75	100.0%	2.75 [1.84, 4.10]	•
Total events	55		20			2110 [110 1] 1110]	
Heterogeneity: Not ap							
Test for overall effect		(P < 0.0	00001)				0.05 0.2 1 5 : Favours placebo Favours MAL-PDT
							Favours placebo Favours MAL-PDT
					S	31	
					5		

	-PDT (veh					
Study or Subgroup	MAL-PDT Events Tot	Placel al Events		Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
Foley, IJD 2009 (n)	06	6 0	65		Not estimable	
Total (95% CI) Total events Heterogeneity: Not ap	0	6 0	65		Not estimable	H
Test for overall effect:	Not applicabl	е				Favours MAL-PDT Favours pl
(NB.	The risk ratio	o cannot be	e estir	nated w	nen there are no e	vents on either arm)
Cosmetic outco	me (exce	llent or	good	l) nBC	Clesion: MAL-	PDT vs placebo-PDT (vehi
cream)						
Study or Subgroup	MAL-PDT Events Tot	Placel al Events		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
Foley, IJD 2009 (n)	42 7	5 14	75	100.0%	3.00 [1.80, 5.01]	
Total (95% CI) Total events Heterogeneity: Not ap	42	75 14	75	100.0%	3.00 [1.80, 5.01]	
Test for overall effect:		0.0001)				0.05 0.2 1 Favours placebo Favours M/
PDT (vehicle cre						
Study or Subgroup	MAL-PDT Events Tot	Placel al Events		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
		6 43		100.0%	1.37 [1.14, 1.66]	
Foley, IJD 2009 (n)		i6 43	65	100.0%	1.37 [1.14, 1.66]	•
Total (95% CI)						ı
	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl
Total (95% CI) Total events Heterogeneity: Not ap	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl
Total (95% CI) Total events Heterogeneity: Not ap	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl
Total (95% CI) Total events Heterogeneity: Not ap	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl
Total (95% CI) Total events Heterogeneity: Not ap	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl
Total (95% CI) Total events Heterogeneity: Not ap	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl
Total (95% CI) Total events Heterogeneity: Not ap	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl
Total (95% CI) Total events Heterogeneity: Not ap	60 plicable					0.05 0.2 1 Favours MAL-PDT Favours pl

# PDT vs. Cryosurgery

# Clearance of treated sBCC (3 months initial lesion clearance) patient: MAL-PDT vs

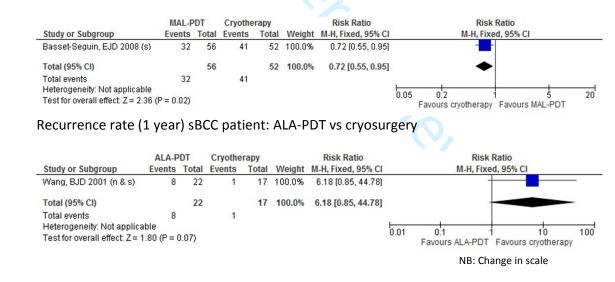
# cryosurgery

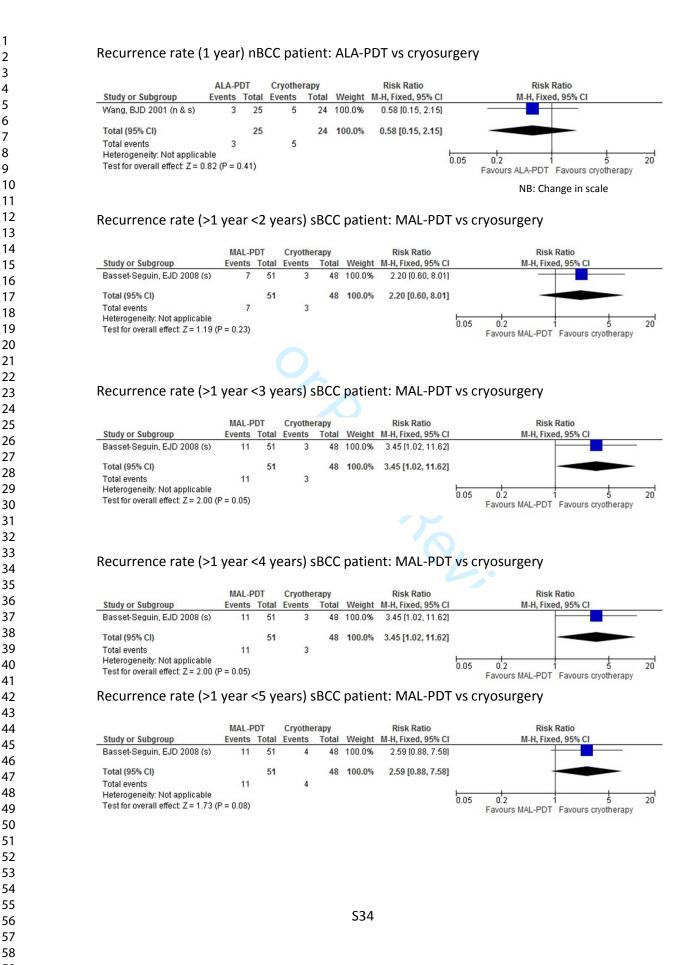
	MAL-P	DT	Cryothe	rapy		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Basset-Seguin, EJD 2008 (s)	56	62	52	58	100.0%	1.01 [0.89, 1.14]	-
Total (95% CI)		62		58	100.0%	1.01 [0.89, 1.14]	<b>•</b>
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.12 (	56 P = 0.90)		52				0.05 0.2 1 5 20 Favours cryotherapy Favours MAL-PDT

# Sustained clearance of treated sBCC (1 year) patient: MAL-PDT vs cryosurgery

Study or Subgroup	MAL-PDT		Cryotherapy		Risk Ratio		Risk Ratio	
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Basset-Seguin, EJD 2008 (s)	51	56	48	52	100.0%	0.99 [0.88, 1.11]	-	
Total (95% CI)		56		52	100.0%	0.99 [0.88, 1.11]	•	
Total events Heterogeneity: Not applicable	51		48					
Test for overall effect: Z = 0.23 (P = 0.82)							0.05 0.2 1 5 20 Favours cryotherapy Favours MAL-PDT	

# Sustained clearance of treated sBCC (5 years) patient: MAL-PDT vs cryosurgery





# Severe pain (leading to break in treatment/use of local analgesia) BCC patient: PDT vs

# cryosurgery

	PDT	Г	Cryothe	rapy		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Basset-Seguin, EJD 2008 (s)	3	62	1	58	66.9%	2.81 [0.30, 26.22]	
Wang, BJD 2001 (n & s)	1	47	0	41	33.1%	2.63 [0.11, 62.73]	
Total (95% CI)		109		99	100.0%	2.74 [0.44, 17.06]	
Total events	4		1				
Heterogeneity: Chi <sup>2</sup> = 0.00, df =	1 (P = 0.9)	7); 12 =	0%				0.01 0.1 1 10 100
Test for overall effect: Z = 1.08 (	P = 0.28)						0.01 0.1 1 10 100 Favours PDT Favours cryotherapy
							NB: Change in scale

# Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (3 months)

### assessed by investigator

	MAL-P	DT	Cryothe	rapy		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Basset-Seguin, EJD 2008 (s)	17	62	2	58	100.0%	7.95 [1.92, 32.92]	
Total (95% CI)		62		58	100.0%	7.95 [1.92, 32.92]	
Total events	17		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.86 (F	P = 0.004)	)					Favours cryotherapy Favours MAL-PDT

# Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (3 months)

#### assessed by patient

	MAL-P	DT	Cryothe	erapy		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Basset-Seguin, EJD 2008 (s)	25	62	11	58	100.0%	2.13 [1.15, 3.92]	
Total (95% CI)		62		58	100.0%	2.13 [1.15, 3.92]	◆
Total events	25		11				
Heterogeneity: Not applicable							0.01 0.1 1 10 100
Test for overall effect: Z = 2.42 (	P = 0.02)						Favours cryotherapy Favours MAL-PDT

### Cosmetic outcome (excellent) BCC patient: PDT vs cryosurgery (1 year) assessed by

#### investigator

	PDT	Г	Cryothe	rapy		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Basset-Seguin, EJD 2008 (s)	20	62	7	58	69.3%	2.67 [1.22, 5.85]	
Wang, BJD 2001 (n & s)	21	47	3	41	30.7%	6.11 [1.96, 19.00]	
Total (95% CI)		109		99	100.0%	3.73 [1.96, 7.07]	•
Total events	41		10				
Heterogeneity: Chi2 = 1.42, df =	1 (P = 0.2)	3);  2 =	30%				0.01 0.1 1 10 100
Test for overall effect: Z = 4.03 (	P < 0.000	1)					0.01 0.1 1 10 100 Favours cryotherapy Favours PDT

NB: Wang (2001) treated one lesion per patient (ALA-PDT); Basset-Seguin (2008) treated all lesions for each patient (MAL-PDT)

100

100

100

#### Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (1 year) assessed by patient PDT **Risk Ratio Risk Ratio** Cryotherapy Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Study or Subgroup Basset-Seguin, EJD 2008 (s) 100.0% 1.47 [0.83, 2.59] 22 62 14 58 Total (95% CI) 58 100.0% 1.47 [0.83, 2.59] 62 Total events 22 14 Heterogeneity: Not applicable 0.01 0.1 10 Test for overall effect: Z = 1.33 (P = 0.18) Favours cryotherapy Favours PDT Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (2 years) assessed by investigator MAL-PDT Cryotherapy **Risk Ratio Risk Ratio** Study or Subgroup **Events Total** Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI Basset-Seguin, EJD 2008 (s) 62 58 100.0% 5.85 [2.17, 15.78] 25 4 Total (95% CI) 100.0% 5.85 [2.17, 15.78] 62 58 25 Total events Δ Heterogeneity: Not applicable 0.01 0.1 10 Test for overall effect: Z = 3.49 (P = 0.0005) Favours cryotherapy Favours MAL-PDT Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (2 years) assessed by patient MAL-PDT Cryotherapy **Risk Ratio Risk Ratio** Study or Subgroup **Events Total** Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI Basset-Seguin, EJD 2008 (s) 23 62 15 58 100.0% 1.43 [0.83, 2.47] Total (95% CI) 62 58 100.0% 1.43 [0.83, 2.47] Total events 23 15 Heterogeneity: Not applicable 0.01 0.1 10 Test for overall effect: Z = 1.30 (P = 0.19) Favours cryotherapy Favours MAL-PDT Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (3 years) assessed by investigator MAL-PDT Cryotherapy **Risk Ratio Risk Ratio** Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Study or Subgroup **Events Total Events** Basset-Seguin, EJD 2008 (s) 19 62 5 58 100.0% 3.55 [1.42, 8.90] 58 100.0% 3.55 [1.42, 8.90] Total (95% CI) 62 Total events 19 5 Heterogeneity: Not applicable 0.01 0.1 10 Test for overall effect: Z = 2.71 (P = 0.007) Favours cryotherapy Favours MAL-PDT

# Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (4 years) assessed

# by investigator

	MAL-P	DT	Cryothe	rapy		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Basset-Seguin, EJD 2008 (s)	19	62	5	58	100.0%	3.55 [1.42, 8.90]	
Total (95% CI)		62		58	100.0%	3.55 [1.42, 8.90]	-
Total events	19		5				
Heterogeneity: Not applicable Test for overall effect: Z = 2.71 (	P = 0.007	)					0.01 0.1 1 10 100 Favours cryotherapy Favours MAL-PDT

# Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (5 years) assessed

# by investigator

	MAL-P	DT	Cryothe	rapy		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Basset-Seguin, EJD 2008 (s)	19	62	7	58	100.0%	2.54 [1.15, 5.59]	
Total (95% CI)		62		58	100.0%	2.54 [1.15, 5.59]	-
Total events Heterogeneity: Not applicable	19		7				
Test for overall effect: Z = 2.31 (I	P = 0.02)						Favours cryotherapy Favours MAL-PDT

# Treatment tolerability - low or manageable pain sBCC: MAL-PDT vs cryosurgery

	MAL-F	DT	Cryothe	rapy		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Basset-Seguin, EJD 2008 (s)	46	62	42	58	100.0%	1.02 [0.83, 1.27]	
Total (95% CI)		62		58	100.0%	1.02 [0.83, 1.27]	+
Total events	46		42				
Heterogeneity: Not applicable							0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 0.22 (	(P = 0.83)						Favours MAL-PDT Favours cryotherapy
							NB: Change in scale

### PDT vs. Surgical excision

### Clearance of treated sBCC (3 months initial lesion clearance) lesion: MAL-PDT vs

#### surgical excision

	MAL-P	DT	Surgical ex	cision		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Szeimies, JEADV 2008 (s)	118	135	117	132	100.0%	0.99 [0.90, 1.08]	<b>—</b>
Total (95% CI)		135		132	100.0%	0.99 [0.90, 1.08]	•
Total events Heterogeneity: Not applicabl	118 e		117				
Test for overall effect: Z = 0.3		6)					0.1 0.2 0.5 1 2 5 Favours surgical excision Favours MAL-PDT
					S37	7	
					55	/	

Clearance of treated nBCC (3 months initial lesion clearance) lesion: PDT vs surgical

# excision

	PD	Г	Surgical ex	cision		<b>Risk Ratio</b>			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95% CI		
Rhodes, AD 2004 (n)	48	53	51	52	100.0%	0.92 [0.84, 1.02]						
Total (95% CI)		53		52	100.0%	0.92 [0.84, 1.02]			•			
Total events	48		51									
Heterogeneity: Not app	licable							02	0.5	1 1	-	10
Test for overall effect: Z	z = 1.65 (P	= 0.10	)				Favo	·	urgical excision	Favours PDT	5	10

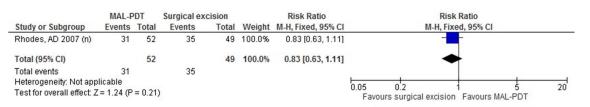
# Sustained clearance of treated sBCC (1 year) lesion: MAL-PDT vs surgical excision

	MAL-P		Surgical ex			Risk Ratio			<b>Risk Ratio</b>			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	Fixed, 95	6 CI		
Szeimies, JEADV 2008 (s)	107	118	117	117	100.0%	0.91 [0.85, 0.96]						
Total (95% CI)		118		117	100.0%	0.91 [0.85, 0.96]			•			
Total events	107		117									
Heterogeneity: Not applicabl	le						01 0	2 0.5		1	1	10
Test for overall effect: Z = 3.1	8 (P = 0.0	01)						urs surgical exci	sion Eavo	urs MAL-P	DT	10

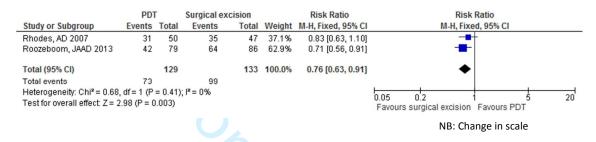
# Sustained clearance of treated nBCC (1 year) lesion: PDT vs surgical excision

	PDT	Г	Surgical exe	cision		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Berroeta, BJD 2007 (n)	13	21	15	19	24.5%	0.78 [0.52, 1.18]	
Rhodes, AD 2004 (n)	44	48	50	51	75.5%	0.94 [0.85, 1.03]	-
Total (95% CI)		69		70	100.0%	0.90 [0.80, 1.01]	•
Total events	57		65				
Heterogeneity: Chi <sup>2</sup> = 1.1	4, df = 1 (	P = 0.2	9); I <sup>2</sup> = 12%				0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z =	= 1.79 (P =	0.07)					Favours surgical excision Favours PDT

# Sustained clearance of treated nBCC (5 years) patient: MAL-PDT vs surgical excision



### Sustained clearance of treated NMSC (5 years) lesion: PDT vs surgical excision



# Recurrence rate (>1 year <2 years) nBCC lesion: PDT vs surgical excision

	PDT	Г	Surgical exc	ision		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Rhodes, AD 2004 (n)	3	44	1	50	100.0%	3.41 [0.37, 31.60]	
Total (95% CI)		44		50	100.0%	3.41 [0.37, 31.60]	
Total events	3		1				
Heterogeneity: Not app	licable						
Test for overall effect: Z	(P	= 0.28)	)				Favours PDT Favours surgical excision
							NB: Change in scale

# Recurrence rate (>1 year <5 years) nBCC lesion: PDT vs surgical excision

	PD	Г	Surgical ex	cision		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Rhodes, AD 2007 (n)	5	49	2	52	100.0%	2.65 [0.54, 13.05]		
Total (95% CI)		49		52	100.0%	2.65 [0.54, 13.05]		
Total events	5		2					
Heterogeneity: Not app	licable						0.01 0.1 1 10	100
Test for overall effect: Z	.= 1.20 (P	= 0.23	)				Favours PDT Favours surgical	

Study or Subgroup Rhodes, AD 2004 (n) Total (95% CI) Total events Heterogeneity: Not app Test for overall effect 2	MAL-PD Events T 1) 36	Total	Surgical exc	noisi		Risk Ratio	Risk Ratio
Total (95% CI) Total events Heterogeneity: Not app	1) 50	50	Events 15	Total	Weight 100.0%	M-H, Fixed, 95% CI 2.26 [1.44, 3.54]	M-H, Fixed, 95% Cl
Testion overall effect. 2	36 applicable :t: Z = 3.53 (P =	50	15		100.0%	2.26 [1.44, 3.54]	0.05 0.2 Favours surgical excision Favours MAL-F
Cosmetic outc months) asses				good	) nBCC	patient: M	AL-PDT vs surgical excision (
	MAL-PD		Surgical exc			Risk Ratio	Risk Ratio
Study or Subgroup Rhodes, AD 2004 (n)	Events T n) 39	Total 50	Events 37		Weight 100.0%	M-H, Fixed, 95% Cl 0.99 [0.80, 1.22]	M-H, Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Not app Test for overall effect: 2		50 = 0.93)	37	47	100.0%	0.99 [0.80, 1.22]	0.05 0.2 1 1
Cosmetic outc year) assessed	ed by inve	estig	ator			1	AL-PDT vs surgical excision (2
	And by invertised by invertise	<b>estig</b> L-PDT t <u>s Tota</u> 77 100 <b>10</b> 0 77	Surgical Surgical Events 0 44 0 44	excision Tol	1	Risk Ratio t M-H, Fixed, 95% ( 5 1.68 (1.32, 2.1	AL-PDT vs surgical excision (2 Risk Ratio CI M-H, Fixed, 95% CI
year) assessed <u>Study or Subgroup</u> Szeimies, JEADV 2008 Total (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z	ed by inve MAL Event 08 (s) 7 7 pplicable t Z = 4.19 (P < 0 tcome (e)	estiga L-PDT ts Tota 77 100 100 77 0.0001) •xcella estiga	ator Surgical Events 0 44 0 44 ent or g ator	excision Tot	1 <u>tal Weigh</u> 96 100.0% 96 100.0%	Risk Ratio t M-H, Fixed, 95% ( 5 1.68 (1.32, 2.1 6 1.68 [1.32, 2.1	AL-PDT vs surgical excision (2 Risk Ratio CI M-H, Fixed, 95% CI 41 41 41 41 41 41 41 41 41 41
year) assessed <u>Study or Subgroup</u> Szeimies, JEADV 2008 Total (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z Cosmetic outco	ed by inve MAL Event 08 (s) 7 7 pplicable t Z = 4.19 (P < 0 t come (e) ed by inve MAL-PD Events T	estiga <u>ts Tota</u> 77 100 100 77 0.0001) excelle estiga 0.001 s	Surgical Surgical Events 0 44 0 44 ent or §	excision Tot good	n <u>tal Weigh</u> 96 100.09 96 100.09	Risk Ratio t M-H, Fixed, 95% ( 5 1.68 (1.32, 2.1 6 1.68 [1.32, 2.1	AL-PDT vs surgical excision (2 Risk Ratio CI M-H, Fixed, 95% CI 41 4] 0.05 Favours surgical excision Favours MAL-F AL-PDT vs surgical excision ( Risk Ratio

# Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (1

# year) assessed by patient

	MAL-F	DT	Surgical ex	cision		<b>Risk Ratio</b>	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% Cl	
Rhodes, AD 2004 (n)	41	50	36	47	100.0%	1.07 [0.87, 1.31]			
Total (95% CI)		50		47	100.0%	1.07 [0.87, 1.31]		•	
Total events	41		36						
Heterogeneity: Not app	licable						0.05 0.2		20
Test for overall effect: Z	C= 0.65 (P	= 0.51	)				Favours surgical excision	Favours MAL-PDT	20

# Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (2

### years) assessed by investigator

	MAL-P	DT	Surgical ex	cision		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Rhodes, AD 2004 (n)	24	50	16	47	100.0%	1.41 [0.86, 2.31]	
Total (95% CI)		50		47	100.0%	1.41 [0.86, 2.31]	-
Total events	24		16				
Heterogeneity: Not app	licable						0.05 0.2 1 5 20
Test for overall effect: Z	:= 1.37 (P	= 0.17)					Favours surgical excision Favours MAL-PDT

# Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (2

# years) assessed by patient

	MAL-P	DT	Surgical ex	cision		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Rhodes, AD 2004 (n)	28	50	27	47	100.0%	0.97 [0.69, 1.38]	-
Total (95% CI)		50		47	100.0%	0.97 [0.69, 1.38]	+
Total events	28		27				
Heterogeneity: Not app	licable						0.05 0.2 1 5 20
Test for overall effect: Z	Z = 0.14 (P	= 0.89)	)				Favours surgical excision Favours MAL-PDT

# Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (5

# years) assessed by investigator

	MAL-F	DT	Surgical ex	cision		<b>Risk Ratio</b>	Risk Rati	D	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95	5% CI	
Rhodes, AD 2007 (n)	27	50	19	47	100.0%	1.34 [0.87, 2.06]		_	
Total (95% CI)		50		47	100.0%	1.34 [0.87, 2.06]	-		
Total events	27		19						
Heterogeneity: Not app Test for overall effect: 2		= 0.19)	)				0.05 0.2 1 Favours surgical excision Fav	ours MAL-PDT	20

Rhodes, AD 2004 (n)         27         50         14         47         100.0%         1.81 [1.09, 3.01]           Total (95% CI)         50         47         100.0%         1.81 [1.09, 3.01]	Bindes, AD 2004 (n)         27         50         14         47         100.0%         1.81 (1.09, 3.01)           Total (95% C)         50         47         100.0%         1.81 (1.09, 3.01)           Total events         27         14           Helerogeneity, Not applicable         Testfor overall effect Z = 2.30 (P = 0.02)         14           Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment)         Mean Difference         Mean Difference           Study of Subgroup         ALA-PDT manageable         Strigical excision         Mean Difference         Mean Difference           Helerogeneity, Not applicable         Sto Total         Weight         Nr, Fixed, 95% CI         Vr, Fixed, 95% CI           Peroversal effect Z = 3.74 (P = 0.002)         15         11         100.0%         3.57 (1.70, 5.44]           Helerogeneity, Not applicable         Mean 5D         Total Mean         SD         Total Mean         SD         Total Mean         SD         Total Veight W, Fixed, 95% CI         Vr, Fixed, 95% CI         NB and Difference         NB and Difference         Mean Difference         Mean Difference         NB and Difference         NB and Difference         NB and Difference         NB and Difference         NF and gas		MAL-PDT		ical excisio				isk Ratio		Risk Ratio
Total (95% CI)         50         47         100.0%         1.81 [1.09, 3.01]           Total events         27         14           Heterogenety, Not applicable         14         0.05         0.2         5           Treatment tolerability - low or manageable pain PDT vs Surgical excision (during           treatment)         ALA-PDT         Surgical excision         Mean Difference         Mean Difference           Study or Subgroup         ALA-PDT         Surgical excision         Mean SD         Total         Weight         V, Fixed, 95% CI         N, Fixed, 95% CI           Total (95% CI)         14         10.0.9%         3.57 [1.70, 5.44]         10         -5         0         -5           Berroeta, BJD 2007 (n)         48         201         15         11         100.0%         3.57 [1.70, 5.44]         -0         -5         -0         -5           Total (95% CI         N, Fixed, 95% CI	Total (95% CI) 50 47 100.0% 1.81 [1.09, 3.01] Total events 27 14 Heterogenety Not applicable Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment) $\frac{ALA-PDT}{Mean SD Total Mean SD Total Mean SD Total Weight W, Fixed, 95% CI V, Fixed,$	Study or Subgroup	Events Total	Eve							M-H, Fixed, 95% CI
Total events 27 14 Heterogenetic Not applicable Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment) $\frac{ALA-PDT}{Mean SD Total Mean SD Total Mean SD Total Mean SD Total (SK-C)}{15 11 100.0\% 3.57 [1.70, 5.44]}$ Heterogenetic Not applicable Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately Mean SD Total Mean SD Total Mean SD Total Mean SD Total Mean SD Total Weight N, Fixed, 95% Cl N, Fixed, 95%	Total events       27       14         Helerogeneity: Not applicable       23.00 (P = 0.02)         Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment)         Study or Subgroup       ALA-PDT Alego and the set of the set o	10 A.			14						
Testfor overall effect Z = 2.30 (P = 0.02)       UUS	Testfor overall effect Z = 2.30 (P = 0.02)       0.05       <				14	4/ 1	00.0%	6 1.	81 [1.09, 3.01]		
Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment) Study or Subgroup Mean SD Total Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 9	Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment)          Study or Subgroup       ALA-PDT Surgical excision       Mean Difference       Mean Difference         Berroeta, BJD 2007 (n)       4.8       2.01       15       11       100.0%       3.57 [1.70, 5.44]         Test for overall effect Z = 3.74 (P = 0.0002)       15       11       100.0%       3.57 [1.70, 5.44]         Heterogeneity. Not applicable       15       11       100.0%       3.57 [1.70, 5.44]         Study or Subgroup       Mean SD Total       Mean SD Total       Mean Difference         NB: Change in scale       NB: Change in scale         Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment)       Mean SD Total       Mean SD									0.05	
treatment) $\frac{ALA-PDT}{Berroeta, BJD 2007 (n)} \text{Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95%$	Mean SD Total Mean SD Total Mean SD Total Weight W, Fixed, 95% CI       Mean Difference         Berroeta, BJD 2007 (r)       ALA-PDT       Surgical excision       Mean Difference       Mean Difference         Derroeta, BJD 2007 (r)       ALA-PDT       15       11       10.00%       3.57 [1.70, 5.44]         Total (95% CI)       15       11       10.00%       3.57 [1.70, 5.44]         Heterogenity. Not applicable         Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment)         Mean Difference       Mean Difference       Mean Difference         Surgical excision       Mean Difference       Mean Difference         Surgical excision       Mean Difference       Nean Difference         Surgical excision       Mean Difference       Nean Difference         Surgical excision       Mean Difference       N.Fixed, 95% CI         Not subgroup       ALA-PDT       Surgical excision         Mean Difference       N.Fixed, 95% CI<										Favours MAL-PDT Favours surgical excis
$\frac{ALA-PDT}{Berroeta, BJD 2007 (n)} \underbrace{ALA-PDT}_{4.8 \ 2.01 \ 15 \ 15 \ 11 \ 100.0\% \ 3.57 [1.70, 5.44]}_{10 \ 5 \ 100.0\% \ 3.57 [1.70, 5.44]}$ $\frac{ALA-PDT}{Favours ALA-PDT \ Favours aurgical excision \ Mean Difference \ NB: Change in scale}$ Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) $ALA-PDT \ Surgical excision \ Mean Difference \ NF, Fixed, 95\% Cl \ Favours ALA-PDT \ Favours aurgical excision \ Mean Difference \ NF, Fixed, 95\% Cl \ Favours ALA-PDT \ Favours aurgical excision \ Mean Difference \ NF, Fixed, 95\% Cl \ NF, Fixed, 95\% Cl \ NF, Fixed, 95\% Cl \ Favours aurgical excision \ Subgroup \ Mean SD \ Total \ Mean \ SD \ Total \ Mean $	$\frac{\text{ALA-PDT}}{\text{Bernote}, \text{BUD} 2007 (n)} \xrightarrow{\text{ALA}-PDT}_{\text{4.8} 2.01} \xrightarrow{\text{SUrgical} excision}}_{\text{15} 1.23} \xrightarrow{\text{SUrgical} excision}_{\text{5.6} 11 100.0\%} \xrightarrow{\text{SUF} (170, 5.44]}_{10} $	Treatment tole	rability - l	ow	or man	agea	able	e pai	n PDT vs	Surgic	al excision (during
$\frac{ALA-PDT}{Berroeta, BJD 2007 (n)} \underbrace{ALA-PDT}_{4.8 \ 2.01 \ 15 \ 15 \ 11 \ 100.0\% \ 3.57 [1.70, 5.44]}_{10 \ 5 \ 100.0\% \ 3.57 [1.70, 5.44]}$ $\frac{ALA-PDT}{Favours ALA-PDT \ Favours aurgical excision \ Mean Difference \ NB: Change in scale}$ Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) $ALA-PDT \ Surgical excision \ Mean Difference \ NF, Fixed, 95\% Cl \ Favours ALA-PDT \ Favours aurgical excision \ Mean Difference \ NF, Fixed, 95\% Cl \ Favours ALA-PDT \ Favours aurgical excision \ Mean Difference \ NF, Fixed, 95\% Cl \ NF, Fixed, 95\% Cl \ NF, Fixed, 95\% Cl \ Favours aurgical excision \ Subgroup \ Mean SD \ Total \ Mean \ SD \ Total \ Mean $	$\frac{\text{ALA-PDT}}{\text{Bernota, BJD 2007 (n)}} \underbrace{\frac{\text{ALA}}{13} \underbrace{\text{Bean}}{\text{SD}} \underbrace{\text{Total}}{\text{Total}} \underbrace{\text{Mean}}{\text{SD}} \underbrace{\frac{\text{SD}}{\text{Total}} \underbrace{\text{Total}}{\text{Total}} \underbrace{\text{Mean}}{\text{SD}} \underbrace{\frac{\text{SD}}{\text{Total}} \underbrace{\text{Weight}}{\text{IV}, \text{Fixed, 95% CI}} \underbrace{\text{Mean Difference}}{\text{IV}, \text{Fixed, 95% CI}} \underbrace{\text{N}, \text{Fixed, 95% CI}}{\text{Favours ALA-PDT} \underbrace{\text{Favours surgical}}{\text{SD}} \underbrace{\frac{1}{10} \frac{1$										
Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (r)         4.8         2.01         15         1.1         100.0%         3.57 (1.70, 5.44)         IV	Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BUD 2007 (n)         4.8         2.01         15         11         100.0%         3.57 [1.70, 5.44]         10<	treatment)									
Berroeta, BJD 2007 (n)         4.8         2.01         15         1.1         100.0%         3.57 [1.70, 5.44]           Total (95% CI)         15         11         100.0%         3.57 [1.70, 5.44]           Heterogeneity: Not applicable         5         11         100.0%         3.57 [1.70, 5.44]           Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately         NB: Change in scale           Study or Subgroup         ALA-PDT Mean         Surgical excision         Mean Difference         Mean Difference           Study or Subgroup         ALA-PDT Heterogeneity: Not applicable         15         11         100.0%         3.57 [1.70, 5.44]           Heterogeneity: Not applicable         SD         Total         Mean         SD         Total         Mean 0ifference           Study or Subgroup         ALA-PDT Heterogeneity: Not applicable         SD         Total         Veight         V, Fixed, 95% CI         IV, Fixed, 95% CI           Total (95% CI)         15         11         100.0%         3.57 [1.70, 5.44]	Berroeta, BJD 2007 (n)         4.8         2.01         15         1.23         2.66         11         100.0%         3.57 [1.70, 5.44]           Total (95% Cl)         15         11         100.0%         3.57 [1.70, 5.44]         -5         0         5           Test for overall effect Z = 3.74 (P = 0.0002)         15         11         100.0%         3.57 [1.70, 5.44]         -6         -6           Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment)         NB: Change in scale         NB: Change in scale           Study or Subgroup         ALA-PDT Mean SD Total Mean SD Total Mean SD Total Mean SD Total (V, Fixed, 95% Cl)         V, Fixed, 95% Cl         V, Fixed, 95% Cl         V, Fixed, 95% Cl           Heterogeneity: Not applicable         15         11         100.0%         3.57 [1.70, 5.44]         -10         -5         -5           Total (95% Cl)         4.8         2.01         15         11         100.0%         3.57 [1.70, 5.44]         -10         -5         -5         -5           Total (95% Cl)         15         11         100.0%         3.57 [1.70, 5.44]         -10         -5         -5         -6         -5         -6         -7         -7         -7         -7         -7         -7         -7		ALA-PDT		Surgical ex	cision			Mean Difference	B	Mean Difference
Total (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 3.74 (P = 0.0002) Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) Study or Subgroup ALA-PDT Surgical excision Mean Difference Berroeta, BJD 2007 (n) 4.8 2.01 15 1.23 2.66 11 100.0% 3.57 (1.70, 5.44] Heterogeneity: Not applicable Test for overall effect: Z = 3.74 (P = 0.0002) Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) Total (95% CI) 15 11 100.0% 3.57 (1.70, 5.44] Total (95% CI) 15 11 100.0% 3.57 (1.70, 5.44] Test for overall effect: Z = 3.74 (P = 0.0002) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Study or Subgroup ALA-PDT Surgical excision Mean Difference treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Study or Subgroup ALA-PDT Surgical excision Mean Difference treatment) Study or Subgroup ALA-PDT Surgical excision Mean Difference treatment) Study or Subgroup ALA-PDT Surgical excision Mean Difference treatment) Study or Subgroup ALA-PDT Surgical excision SD Total Mean SD Total Mean SD Total Mean SD Total Mean Difference N, Fixed, 95% CI N, Fixed	Total (95% CI) Heterogenetly: Not applicable Test for overall effect: $Z = 3.74$ (P = 0.0002) Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) Study or Subgroup Mean SD Total Mean SD Total Mean Difference Berroeta, BJD 2007 (n) 4.8 2.01 15 1.23 2.66 11 100.0% 3.57 (1.70, 5.44) Heterogenetly: Not applicable Test for overall effect: $Z = 3.74$ (P = 0.0002) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Sudy or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Berroeta, BJD 2007 (n) 1.78 2.26 15 0.73 1.56 11 100.0% 1.06 [-0.41, 2.53] Total (95% CI) 1.78 2.28 15 0.73 1.56 11 100.0% 1.06 [-0.41, 2.53] Heterogenetify Mot applicable Favours Surgical excision (3 hours after IV, Fixed, 95% CI Heterogenetify Mot applicable Favours Surgical excision (3 hours after IV, Fixed, 95% CI Heterogenetify Mot applicable Favours Surgical PDT VS I I 100.0% 1.06 [-0.41, 2.53] Heterogenetify Mot applicable Favours Surgical PDT VS I I 100.0% 1.06 [-0.41, 2.53] Heterogenetify Mot Z = 0.100 ZI Heterogenetify Mot										IV, Fixed, 95% CI
Heterogeneity: Not applicable Test for overall effect Z = 3.74 (P = 0.0002) Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) <u>ALA-PDT</u> Surgical excision Mean Difference <u>Berroeta, BJD 2007 (n)</u> 4.8 2.01 15 1.23 2.66 11 100.0% 3.57 (1.70, 5.44) Heterogeneity: Not applicable Treatment tolerability - low or manageable pain PDT vs Surgical excision (January Subgroup Mean Difference) <u>ALA-PDT</u> Surgical excision Mean Difference <u>Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI</u> IV, Fixed, 95% CI Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) <u>ALA-PDT</u> Surgical excision Mean Difference <u>Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after</u> treatment) <u>ALA-PDT</u> Surgical excision Mean Difference <u>Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after</u> <u>Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI</u> IV, Fixed, 95% CI <u>Favours ALA-PDT</u> Favours surgical excision (3 hours after <u>Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI</u> <u>Berroeta, BJD 2007 (n) 1.79 2.26 15 0.73 1.56 11 100.0% 1.06 [0.41, 2.53]</u> <u>Total (95% CI)</u> 15 11 100.0% 1.06 [0.41, 2.53]	Heterogeneily: Not applicable Test for overall effect Z = 3.74 (P = 0.0002) ALA-PDT Surgical excision Mean Difference Mean Difference Mean Difference Mean Difference N, Fixed, 95% CI Heterogeneily: Not applicable Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) ALA-PDT Surgical excision Mean Difference N, Fixed, 95% CI Favours ALA-PDT Favours surgical + Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) ALA-PDT Surgical excision Mean Difference N, Fixed, 95% CI Nean Difference N, Fixed, 95% CI Nean Difference N, Fixed, 95% CI Nean Difference N, Fixed, 95% CI Heterogeneily: Not applicable Total (95% CI) 15 11 100.0% 1.06 [-0.41, 2.53] -10 -5 0 5		4.8 2.01		1.23 2.0						
Test for overall effect: Z = 3.74 (P = 0.0002) Favours ALA-PDT Favours surgical exc NB: Change in scale Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) <u>ALA-PDT Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixe</u>	Test for overall effect: Z = 3.74 (P = 0.0002)       Total (P = 0.0002)       Total PDT vs Surgical excision (immediately NB: Change in scale         Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment)       ALA-PDT Surgical excision Nean Difference (V, Fixed, 95% CI (V, F		able	15		1	11 1	00.0%	3.57 [1.70, 5.44		<u> </u>
Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) <u>Study or Subgroup</u> <u>Mean SD Total Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% C</u>	Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) $\frac{ALA-PDT}{Berroeta, BJD 2007 (n)} \xrightarrow{ALA-PDT} \underbrace{Surgical excision}_{Ala = 2.01 \ 15} SD \ Total \ Mean \ SD \ Total \ $			:)						-10	-5 U 5 Favours ALA-PDT Favours surgical excis
ALA-PDT Surgical excision Mean Difference Mean Difference W, Fixed, 95% Cl W, Fixed, 95\% Cl	after treatment) $\frac{ALA-PDT}{Berroeta, BJD 2007 (n)} \xrightarrow{ALA-PDT} Surgical excision} SD Total Mean Difference} W, Fixed, 95% Cl Heterogeneity: Not applicable Test for overall effect. Z = 3.74 (P = 0.0002) Favours surgical excision (3 hours after treatment) Study or Subgroup ALA-PDT Surgical excision Mean Difference Mean Difference W, Fixed, 95% Cl Heterogeneity: Not applicable Test for overall effect. Z = 3.74 (P = 0.0002) Favours all effect. Z = 3.7$										NB: Change in scale
ALA-PDT Surgical excision Mean Difference Mean Difference W, Fixed, 95% Cl W, Fixed, 95\% Cl	after treatment) $\frac{ALA-PDT}{Berroeta, BJD 2007 (n)} \xrightarrow{ALA-PDT} Surgical excision} SD Total Mean Difference} W, Fixed, 95% Cl Heterogeneity: Not applicable Test for overall effect. Z = 3.74 (P = 0.0002) Favours surgical excision (3 hours after treatment) Study or Subgroup ALA-PDT Surgical excision Mean Difference Mean Difference W, Fixed, 95% Cl Heterogeneity: Not applicable Test for overall effect. Z = 3.74 (P = 0.0002) Favours all effect. Z = 3.7$										
Heterogeneily: Not applicable Test for overall effect: Z = 3.74 (P = 0.0002)       Image: Constraint of the provided and the provided an	Heterogeneity: Not applicable Test for overall effect: Z = 3.74 (P = 0.0002)       Image: Constraint of the product		Mean SD T		Mean S	D Tot		Veight	IV, Fixed, 95% (	CI	
Heterogeneily: Not applicable Test for overall effect: Z = 3.74 (P = 0.0002)       Image: Constraint of the provided and the provided an	Heterogeneity: Not applicable       10       -5       0       5         Trest for overall effect: Z = 3.74 (P = 0.0002)       Favours ALA-PDT       Favours surgical         Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment)         Study or Subgroup       ALA-PDT       Surgical excision       Mean Difference       Mean Difference         Berroeta, BJD 2007 (n)       1.79       2.26       15       0.73       1.56       11       100.0%       1.06 [-0.41, 2.53]         Heterogeneity: Not applicable       15       11       100.0%       1.06 [-0.41, 2.53]       10       -5       0       5		4.8 2.01		1.23 2.0					-	
Test for overall effect: Z = 3.74 (P = 0.0002)       Favours ALA-PDT       Favours ALA-PDT       Favours augical excision (3 hours after treatment)         Study or Subgroup       ALA-PDT       Surgical excision       Mean Difference       Mean Difference         Study or Subgroup       ALA-PDT       Surgical excision       Mean Difference       IV, Fixed, 95% CI         Berroeta, BJD 2007 (n)       1.79       2.26       15       0.73       1.56       11       100.0%       1.06 [-0.41, 2.53]         Total (95% CI)       15       11       100.0%       1.06 [-0.41, 2.53]       10       5       10       5	Test for overall effect: Z = 3.74 (P = 0.0002)         Favours ALA-PDT Favours surgical excision         Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment)         Mean SD Total Mean SD Total Mean SD Total Weight IV, Fixed, 95% Cl IV, Fixe	Heterogeneity: Not applic				2		00.0%	5.57 [1.10, 5.44	L	-5 0 5
ALA-PDT         Surgical excision         Mean Difference         Mean Difference           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Veight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% CI)         15         11         100.0%         1.06 [-0.41, 2.53]         10         5         10         5	ALA-PDT Surgical excision       Mean Difference         Study or Subgroup       ALA-PDT Total       Surgical excision       Mean Difference       Mean Difference         Study or Subgroup       Mean       SD       Total       Weight       NV, Fixed, 95% CI       NV, Fixed, 95% CI         Berroeta, BJD 2007 (n)       1.79       2.26       15       0.73       1.56       11       100.0%       1.06 [-0.41, 2.53]       Image: Colspan="5">Image: Colspan="5" Colspan="5	Test for overall effect: Z =	3.74 (P = 0.0002	!)						10	Favours ALA-PDT Favours surgical excis
ALA-PDT         Surgical excision         Mean Difference         Mean Difference           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Veight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% CI)         15         11         100.0%         1.06 [-0.41, 2.53]         10         5         10         5	ALA-PDT Surgical excision       Mean Difference         Study or Subgroup       ALA-PDT Total       Surgical excision       Mean Difference       Mean Difference         Study or Subgroup       Mean       SD       Total       Weight       NV, Fixed, 95% CI       NV, Fixed, 95% CI         Berroeta, BJD 2007 (n)       1.79       2.26       15       0.73       1.56       11       100.0%       1.06 [-0.41, 2.53]       Image: Colspan="5">Image: Colspan="5" Colspan="5										
ALA-PDT         Surgical excision         Mean Difference         Mean Difference           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Veight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% CI)         15         11         100.0%         1.06 [-0.41, 2.53]         10         5         10         5	ALA-PDT Surgical excision         Mean Difference           Study or Subgroup         ALA-PDT Total         Surgical excision         Mean Difference         Mean Difference           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% Cl)         15         11         100.0%         1.06 [-0.41, 2.53]         10         10         1.06 [-0.41, 2.53]         10         10         1.06 [-0.41, 2.53]         10         10         -5         0         5										
ALA-PDT         Surgical excision         Mean Difference         Mean Difference           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% CI)         15         11         100.0%         1.06 [-0.41, 2.53]         10         5         0         5	Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Fixed, 95% CI         Mean Difference         Mean Difference         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]         Image: Comparison of the comp	Treatment tole	erability - I	ow	or mar	nage	abl	e pa	in PDT vs	Surgio	cal excision (3 hours after
ALA-PDT         Surgical excision         Mean Difference         Mean Difference           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% CI)         15         11         100.0%         1.06 [-0.41, 2.53]         10         5         0         5	Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Fixed, 95% CI         Mean Difference         Mean Difference         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]         Image: Comparison of the comp	troatmont)									
Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% CI)         15         11         100.0%         1.06 [-0.41, 2.53]         10         5         10         5	Study or Subgroup         Mean         SD         Total         Weight         IV, Fixed, 95% CI         IV, Fixed, 95% CI           Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% CI)         15         11         100.0%         1.06 [-0.41, 2.53]         Image: Comparison of the state of the st	treatment)									
Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% Cl)         15         11         100.0%         1.06 [-0.41, 2.53]         Image: the second se	Berroeta, BJD 2007 (n)         1.79         2.26         15         0.73         1.56         11         100.0%         1.06 [-0.41, 2.53]           Total (95% Cl)         15         11         100.0%         1.06 [-0.41, 2.53]         Image: the second se				-						
Total (95% CI) 15 11 100.0% 1.06 [-0.41, 2.53]	Total (95% Cl) 15 11 100.0% 1.06 [-0.41, 2.53]										IV, Fixed, 95% CI
Heterogeneity: Not applicable	Heterogeneity: Not applicable $-10$ $-5$ $0$ $5$		1.75 2.20		0.75 1.5						
-10 -2 0 2			cable	15		1	11 1	00.0%	1.00 [-0.41, 2.5.		į
		Test for overall effect: 7 -	1.41 (P = 0.16)							-10	-5 U 5 Favours ALA-PDT Favours surgical excis
	Tect for overall effect 7 = 1.41 (P = 0.16) -10 -5 U 5	Study or Subgroup Berroeta, BJD 2007 (n) Total (95% CI)	ALA-PDT <u>Mean SD T</u> 1.79 2.26	otal	Surgical ex Mean S	cision D Tot	tal M	Veight 00.0%	Mean Difference IV, Fixed, 95% ( 1.06 (-0.41, 2.5)	e CI 3] 3]	Mean Difference IV, Fixed, 95% CI

S42



# Treatment tolerability - low or manageable pain PDT vs Surgical excision (6 hours after

# treatment)

	AL	A-PD1	Г	Surgio	al exci	sion		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Berroeta, BJD 2007 (n)	1.25	1.65	15	1.91	2.39	11	100.0%	-0.66 [-2.30, 0.98]	
Total (95% CI)			15			11	100.0%	-0.66 [-2.30, 0.98]	-
Heterogeneity: Not applic Test for overall effect: Z =		= 0.43	)						-10 -5 0 5 10 Favours ALA-PDT Favours surgical excision

### Treatment tolerability - low or manageable pain PDT vs Surgical excision (24 hours

### after treatment)

	AL	A-PD	т	Surgic	alexci	sion		Mean Difference		M	ean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV	, Fixed, 95% CI		
Berroeta, BJD 2007 (n)	0.6	1.3	15	1	1.9	11	100.0%	-0.40 [-1.70, 0.90]			-		
Total (95% CI)			15			11	100.0%	-0.40 [-1.70, 0.90]			-		
Heterogeneity: Not applic Test for overall effect: Z =		= 0.5	5)						-10	-5 Favours ALA	0 0 -PDT Favours	5 surgical exc	10 cision

### Treatment tolerability - low or manageable pain PDT vs Surgical excision (48 hours

### after treatment)

	AL	A-PDT	Г <sup>.1</sup>	Surgio	alexci	sion		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Berroeta, BJD 2007 (n)	0.13	0.52	15	0.73	1.85	11	100.0%	-0.60 [-1.72, 0.52]	
Total (95% CI)			15			11	100.0%	-0.60 [-1.72, 0.52]	-
Heterogeneity: Not applic	able								-10 -5 0 5 11
Test for overall effect: Z =	1.05 (P	= 0.30	)						Favours ALA-PDT Favours surgical excision

### Treatment tolerability - low or manageable pain PDT vs Surgical excision (1 week after

#### treatment)

	ALA	A-PD	Т	Surgio	al exci	sion		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Berroeta, BJD 2007 (n)	0	0	15	0.1	0.32	11		Not estimable	e
Total (95% CI)			15			11		Not estimable	e
Heterogeneity: Not applic Test for overall effect: No		ble							-10 -5 0 5 10 Favours ALA-PDT Favours surgical excision

(NB. The risk ratio cannot be estimated when the mean is zero)

2 3

4 5 6

7 8

9

10 11

12

13

14

15 16

17 18

19 20

21

22

23

24

25

26

27 28 29

30 31

32

33

34

35

36

41 42

43

44

45

46

47

#### PDT vs. Topicals Clearance of treated sBCC (3 months initial lesion clearance) patient: MAL-PDT vs imiquimod MAL-PDT Imiguimod **Risk Ratio Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Arits, Lancet Oncol 2013 (s) 202 198 100.0% 0.95 [0.87, 1.04] 165 170 Total (95% CI) 202 198 100.0% 0.95 [0.87, 1.04] Total events 165 170 Heterogeneity: Not applicable 0.1 0.2 0.5 10 Test for overall effect: Z = 1.13 (P = 0.26) Favours imiguimod Favours MAL-PDT NB: Change in scale Clearance of treated sBCC (3 months initial lesion clearance) patient: MAL-PDT vs fluorouracil MAL-PDT Fluorouracil **Risk Ratio Risk Ratio** Total Weight M-H, Fixed, 95% Cl Study or Subgroup **Events Total Events** M-H, Fixed, 95% CI 201 100.0% 0.94 [0.87, 1.03] Arits, Lancet Oncol 2013 (s) 165 202 174 Total (95% CI) 202 201 100.0% 0.94 [0.87, 1.03] Total events 165 174 Heterogeneity: Not applicable 01 10 0'2 0'5 Ż Test for overall effect: Z = 1.34 (P = 0.18) Favours fluorouracil Favours MAL-PDT Sustained clearance of treated sBCC (1 year) patient: MAL-PDT vs imiguimod MAL-PDT Imiquimod **Risk Ratio Risk Ratio** Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI Study or Subgroup Arits, Lancet Oncol 2013 (s) 135 165 153 170 100.0% 0.91 [0.83, 0.99] 0.91 [0.83, 0.99] Total (95% CI) 165 170 100.0% Total events 135 153 Heterogeneity: Not applicable 0.1 0.5 0.2 10 Ż Ś Test for overall effect: Z = 2.13 (P = 0.03) Favours imiquimod Favours MAL-PDT Sustained clearance of treated sBCC (1 year) patient: MAL-PDT vs fluorouracil MAL-PDT **Risk Ratio** Fluorouracil **Risk Ratio** Study or Subgroup **Events Total Events** Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Arits, Lancet Oncol 2013 (s) 135 165 154 174 100.0% 0.92 [0.85, 1.01] Total (95% CI) 174 100.0% 0.92 [0.85, 1.01] 165 Total events 135 154 Heterogeneity: Not applicable 0.1 n'2 0'5 ż 10 Test for overall effect: Z = 1.72 (P = 0.09) Favours fluorouracil Favours MAL-PDT

# Sustained clearance of treated sBCC (3 years) patient: MAL-PDT vs imiquimod

	MAL-P	DT	Imiquir	nod		<b>Risk Ratio</b>		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
Roozeboom, JID 2016 (s)	116	165	143	170	100.0%	0.84 [0.74, 0.94]					
Total (95% CI)		165		170	100.0%	0.84 [0.74, 0.94]		•	•		
Total events	116		143								
Heterogeneity: Not applicab Test for overall effect: Z = 2.4		003)					↓ 0.1	0.2 0.5 Favours imiquimod	1 2 I Favours MA	5 L-PDT	10

### Sustained clearance of treated sBCC (3 years) patient: MAL-PDT vs fluorouracil

	MAL-P	DT	Fluorou	racil		<b>Risk Ratio</b>			Ris	k Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95%	6 CI		
Roozeboom, JID 2016 (s)	116	165	138	174	100.0%	0.89 [0.78, 1.00]							
Total (95% CI)		165		174	100.0%	0.89 [0.78, 1.00]			•				
Total events Heterogeneity: Not applicab	116 Ile		138				H			<u> </u>	1	<u> </u>	
Test for overall effect: Z = 1.	89 (P = 0.	06)					0.1	Favour	0.5 s fluorouraci	1 I Favor	Z Urs MAL-	PDT	10

#### Sustained clearance of treated sBCC (5 years) patient: MAL-PDT vs imiquimod

Study or Subgroup	MAL-P Events		Imiquir Events	nod Total	Woight	Risk Ratio M-H, Fixed, 95% Cl			Ratio ed, 95% Cl		
Study of Subgroup	Evenus	TUtal	Evenus	TUtal	weight	M-H, FIXeu, 95% CI		M-FI, FIA	u, 95% CI		
Jansen, JID 2017 (s)	98	165	124	170	100.0%	0.81 (0.70, 0.95)		_			
Total (95% CI)		165		170	100.0%	0.81 [0.70, 0.95]		•			
Total events	98		124								
Heterogeneity: Not app	licable						<u> </u>			<u> </u>	
Test for overall effect: Z	= 2.58 (P	= 0.01	0)				U.1	0.2 0.5 Favours imiquimod	Favours MAL-P	DT	10

# Sustained clearance of treated sBCC (5 years) patient: MAL-PDT vs fluorouracil

	MAL-P	DT	Fluorou	racil		<b>Risk Ratio</b>			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl			M-H, Fixe	ed, 95% (	CI		
Jansen, JID 2017 (s)	98	165	117	174	100.0%	0.88 [0.75, 1.04]			-				
Total (95% CI)		165		174	100.0%	0.88 [0.75, 1.04]			•				
Total events	98		117										
Heterogeneity: Not app Test for overall effect: Z		= 0.14	)				0.1	0.2 Favou	0.5 Irs fluorouracil	1 Favour	2 5 s MAL-PDT	1	10

#### Severe pain sBCC patient: MAL-PDT vs imiquimod



(2) Pain is measured at treatment and then each week for 2 weeks for PDT and each week for 4 weeks for fluorouracil and for 6 weeks for imiquimod. The events record is the cumulative number of patients that reported pain at each timepoint. This will almost certainly count patients who have experienced severe pain

on multiple occasions multiple times. Though a patient who had severe pain for all 6 weeks is more severely affected than a patient who only experienced severe pain for a single week.

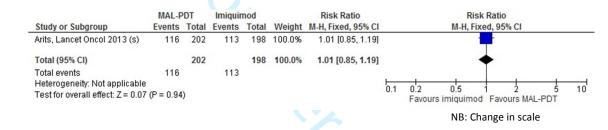
Severe pain (leading to break in treatment/use of local analgesia) sBCC patient: MAL-

#### PDT vs fluorouracil

	MAL-P	DT	Topical (Flour	ouracil)		Risk Ratio		Risk R	latio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed	I, 95% CI	
Arits, Lancet Oncol 2013 (s)	35	202	18	201	100.0%	1.93 [1.13, 3.30]				
Total (95% CI)		202		201	100.0%	1.93 [1.13, 3.30]			•	
Total events	35		18				-			
Heterogeneity: Not applicable Test for overall effect: Z = 2.42		!)						0.2 1 Yours MAL-PDT	5 Favours flourouracil	20

NB: Pain is measured at treatment and then each week for 2 weeks for PDT and each week for 4 weeks for fluorouracil and for 6 weeks for imiquimod. The events record is the cumulative number of patients that reported pain at each timepoint. This will almost certainly count patients who have experienced severe pain on multiple occasions multiple times. Though a patient who had severe pain for all 6 weeks is more severely affected than a patient who only experienced severe pain for a single week

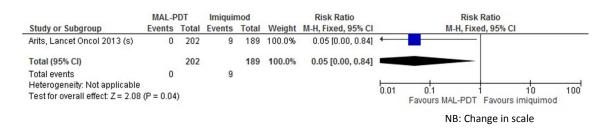
### Cosmetic outcome (excellent or good) sBCC patient: MAL-PDT vs imiquimod



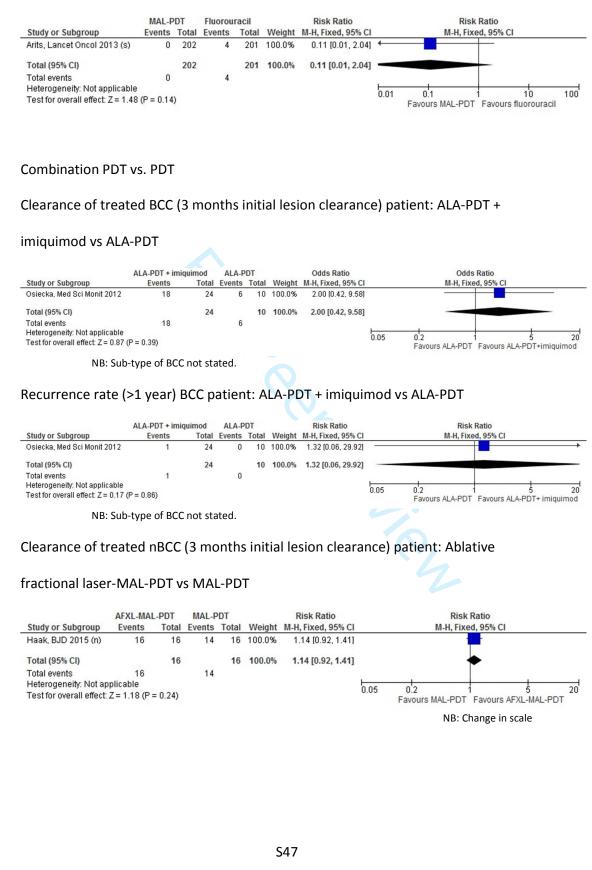
# Cosmetic outcome (excellent or good) sBCC patient: MAL-PDT vs fluorouracil

	MAL-P	DT	Fluorou	racil		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Arits, Lancet Oncol 2013 (s)	116	202	111	201	100.0%	1.04 [0.88, 1.24]	] •
Total (95% CI)		202		201	100.0%	1.04 [0.88, 1.24]	1 +
Total events	116		111				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.45	(P = 0.66	)					0.1 0.2 0.5 1 2 5 10 Favours fluorouracil Favours MAL-PDT

# Other adverse effects (serious and unexpected reactions): PDT vs imiquimod



racil
ri



# Clearance of treated nBCC (3 months initial lesion clearance) lesion: Er:YAG ablative

# fractional laser-PDT vs MAL-PDT

	AFL-PDT (Er:	YAG)	MAL-P	DT		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Choi, JEADV 2016 (n)	16	21	9	21	100.0%	1.78 [1.03, 3.08]	
Total (95% CI)		21		21	100.0%	1.78 [1.03, 3.08]	-
Total events Heterogeneity: Not appl Test for overall effect: Z		4)	9				0.05 0.2 1 5 20 Favours MAL-PDT Favours AFL-PDT (Er: YAG)

# Clearance of treated nBCC (3 months initial lesion clearance) patient: Er:YAG-laser-PDT

#### vs Er:YAG laser

-

	AFL-PDT (E	r:YAG)	Laser (Er	: YAG)		<b>Risk Ratio</b>		Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95% CI			
Smucler, Lasers Surg Med 2008 (n)	248	286	244	286	100.0%	1.02 [0.95, 1.09]						
Total (95% CI)		286		286	100.0%	1.02 [0.95, 1.09]			<b>\</b>			
Total events	248		244									
Heterogeneity: Not applicable Test for overall effect: Z = 0.48 (P = 0.63	3)						0.1	0.2 0.5 Favours Laser (Er: YAG	1 2 Favours AF	5 L-PDT (Er:Y	AG)	10

# Clearance of treated nBCC (3 months initial lesion clearance) patient: Er:YAG-laser-PDT

#### vs MAL-PDT

	AFL-PDT (E	r:YAG)	MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Smucler, Lasers Surg Med 2008 (n)	248	286	246	286	100.0%	1.01 [0.94, 1.08]	
Total (95% CI)		286		286	100.0%	1.01 [0.94, 1.08]	♦
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.24 (P = 0.8	248 1)		246				0.1 0.2 0.5 1 2 5 10 Favours MAL- PDT Favours AFL-PDT (Er:YAG)

# Sustained clearance of treated nBCC (1 year) patient: Ablative fractional laser -MAL-

#### PDT vs MAL-PDT

	XFXL-MAI	-PDT	MAL-P	DT		<b>Risk Ratio</b>		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI	
Haak, BJD 2015 (n)	13	16	9	14	100.0%	1.26 [0.80, 1.99]			
Total (95% CI)		16		14	100.0%	1.26 [0.80, 1.99]		-	
Total events	13		9						
Heterogeneity: Not ap Test for overall effect:		= 0.31)					0.05	0.2 1 5 Favours MAL-PDT Favours AFXL-N	20 MAL-PDT

# Sustained clearance of treated nBCC (1 year) lesion: Er:YAG ablative fractional laser-

# PDT vs MAL-PDT

	AFL-PDT (Er	YAG)	MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Choi, JEADV 2016 (n)	15	16	4	9	100.0%	2.11 [1.01, 4.43]	
Total (95% CI)		16		9	100.0%	2.11 [1.01, 4.43]	-
Total events	15		4				
Heterogeneity: Not app Test for overall effect: Z		5)					0.05 0.2 1 5 20 Favours MAL-PDT Favours AFL-PDT (ER:YAG)

# Sustained clearance of treated nBCC (1 year) lesion: Er:YAG-laser-PDT vs Er:YAG laser

	AFL-PDT (E	r:YAG)	Laser (Er	YAG)		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Smucler, Lasers Surg Med 2008 (n)	192	248	178	244	100.0%	1.06 [0.96, 1.17]	<b>–</b>
Total (95% CI)		248		244	100.0%	1.06 [0.96, 1.17]	+
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.15 (P = 0.2)	192 5)		178				0.1 0.2 0.5 1 2 5 10 Favours Laser (Er: YAG Favours AFL-PDT (Er:YAG)

# Sustained clearance of treated nBCC (1 year) lesion: patient: Er:YAG-laser-PDT vs MAL-

#### PDT

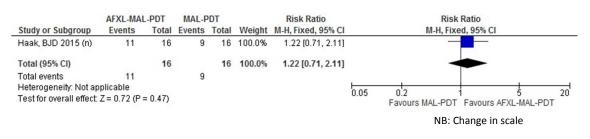
	AFL-PDT (E	r:YAG)	MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Smucler, Lasers Surg Med 2008 (n)	192	248	184	246	100.0%	1.04 [0.94, 1.14]	<b>—</b>
Total (95% CI)		248		246	100.0%	1.04 [0.94, 1.14]	•
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.68 (P = 0.4	192 9)		184				0.1 0.2 0.5 1 2 5 10 Favours MAL- PDT Favours AFL-PDT (Er:YAG)

# Recurrence rate (1 year) nBCC lesion: Ablative fractional laser -MAL-PDT vs MAL-PDT

	AFL-PDT (Er	: YAG)	MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Haak, BJD 2015 (n)	3	16	7	16	100.0%	0.43 [0.13, 1.37]	
Total (95% CI)		16		16	100.0%	0.43 [0.13, 1.37]	
Total events Heterogeneity: Not ap Test for overall effect:	And the second sec	0.15)	7				0.01 0.1 10 100 Favours AFL-PDT (ER:YAG) Favours MAL-PDT
							NB: Change of scale

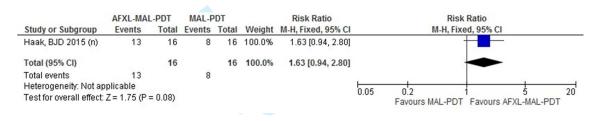
# Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

# PDT (3 months) assessed by investigator



### Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

#### PDT (3 months) assessed by patient



# Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs Er:YAG (3

### months) assessed by evaluator

	AFL-PI	DT (Er:)	(AG)	Lase	r Er:Y	AG		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Smucler, Lasers Surg Med 2008 (n)	2	0.57	246	1.62	0.76	246	100.0%	0.38 [0.26, 0.50]	
Total (95% CI)			246			246	100.0%	0.38 [0.26, 0.50]	
Heterogeneity: Not applicable Test for overall effect: Z = 6.27 (P < 0.00	0001)								-10 -5 0 5 10 Favours AFL-PDT (Er:YAG) Favours Laser Er:YAG

# Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs MAL-PDT (3

#### months) assessed by evaluator

	AFL-PI	DT (Er:Y	AG)	MAL-PDT				Mean Difference	Mean Di	ifference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	d, 95% CI
Smucler, Lasers Surg Med 2008 (n)	2	0.57	246	3.17	0.57	246	100.0%	-1.17 [-1.27, -1.07]		
Total (95% CI)			246			246	100.0%	-1.17 [-1.27, -1.07]	1	
Heterogeneity: Not applicable Test for overall effect: Z = 22.76 (P < 0.	00001)								-10 -5 Favours AFL-PDT (Er:YAG)	I I 0 5 1 Favours MAL-PDT

# Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

# PDT (6 months) assessed by investigator

	AFXL-MAI	L-PDT	MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Haak, BJD 2015 (n)	12	16	6	16	100.0%	2.00 [1.00, 4.00]	
Total (95% CI)		16		16	100.0%	2.00 [1.00, 4.00]	-
Total events	12		6				
Heterogeneity: Not ap	plicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 1.96 (P	= 0.05)					0.05 0.2 1 5 20 Favours MAL-PDT Favours AFXL-MAL-PDT

# Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

# PDT (6 months) assessed by patient

	AFXL-MAL	-PDT	MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Haak, BJD 2015 (n)	12	16	8	16	100.0%	1.50 [0.85, 2.64]	+
Total (95% CI)		16		16	100.0%	1.50 [0.85, 2.64]	-
Total events	12		8				
Heterogeneity: Not ap	plicable						0.05 0.2 1 5 20
Test for overall effect:	Z=1.40 (P:	= 0.16)					Favours MAL-PDT Favours AFXL-MAL-PDT

# Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs Er:YAG (6

### months) assessed by evaluator

	AFL-PI	DT (Er:Y	AG)	Laser	Er:Y/	AG		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Smucler, Lasers Surg Med 2008 (n)	1.17	0.24	208	1.5	0.7	208	100.0%	-0.33 [-0.43, -0.23]	•
Total (95% CI)			208			208	100.0%	-0.33 [-0.43, -0.23]	
Heterogeneity: Not applicable Test for overall effect: Z = 6.43 (P < 0.0	0001)								Favours AFL-PDT (Er.YAG) Favours Laser Er.YAG

# Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs MAL-PDT (6

# months) assessed by evaluator

	AFL-PI	DT (Er:Y	AG)	MA	L-PD1	r		Mean Difference		Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI		
Smucler, Lasers Surg Med 2008 (n)	1.17	0.24	208	1.5	0.43	208	100.0%	-0.33 [-0.40, -0.26]					
Total (95% CI)			208			208	100.0%	-0.33 [-0.40, -0.26]		. 1			
Heterogeneity: Not applicable Test for overall effect: Z = 9.66 (P < 0.0	0001)								-10 Favours AF	-5 ( L-PDT (Er:YAG)	Favours MAI	5 PDT	10

# Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

# PDT (9 months) assessed by investigator

	AFXL-MAL	-PDT	MAL-F	DT		<b>Risk Ratio</b>		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Haak, BJD 2015 (n)	8	16	7	16	100.0%	1.14 [0.54, 2.40]			
Total (95% CI)		16		16	100.0%	1.14 [0.54, 2.40]		-	
Total events	8		7						
Heterogeneity: Not ap Test for overall effect:	•	= 0.72)					0.05	0.2 1 5 Favours MAL-PDT Favours AFXL-MAL-PDT	21

#### Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

### PDT (9 months) assessed by patient

			MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Haak, BJD 2015 (n)	10	16	8	16	100.0%	1.25 [0.67, 2.32]	
Total (95% CI)		16		16	100.0%	1.25 [0.67, 2.32]	-
Total events	10		8				
Heterogeneity: Not ap	plicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.71 (P =	= 0.48)					Favours MAL-PDT Favours AFXL-MAL-PDT

# Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs Er:YAG (9

### months) assessed by evaluator

	AFL-PI	DT (Er:)	'AG)	Lase	FER:Y	AG		Mean Difference	Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fix	ed, 95% CI	
Smucler, Lasers Surg Med 2008 (n)	1.23	0.44	184	1.83	0.95	184	100.0%	-0.60 [-0.75, -0.45]			
Total (95% CI)			184			184	100.0%	-0.60 [-0.75, -0.45]		•	
Heterogeneity: Not applicable Test for overall effect: Z = 7.77 (P < 0.0	0001)								-10 -5 Favours AFL-PDT (Er:YA	0 5 3) Favours Laser E	10 r:YAG

# Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs MAL-PDT (9

# months) assessed by evaluator

	AFL-P	DT (Er:Y	AG)	MA	L-PDT	Г		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Smucler, Lasers Surg Med 2008 (n)	1.23	0.44	184	1.67	0.76	184	100.0%	-0.44 [-0.57, -0.31]	•	
Total (95% CI)			184			184	100.0%	-0.44 [-0.57, -0.31]	•	
Heterogeneity: Not applicable Test for overall effect: Z = 6.80 (P < 0.0	0001)								-10 -5 0 5 Favours AFL-PDT (Er:YAG) Favours MAL-PDT	10

# Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

# PDT (1 year) assessed by investigator

	AFXL-MAL	-PDT	MAL-P	DT		<b>Risk Ratio</b>		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Haak, BJD 2015 (n)	8	16	4	16	100.0%	2.00 [0.75, 5.33]			
Total (95% CI)		16		16	100.0%	2.00 [0.75, 5.33]			
Total events	8		4						
Heterogeneity: Not ap Test for overall effect:		= 0.17)					0.05	0.2 1 5 Favours MAL-PDT Favours AFXL-MAL-PD	20 T

### Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-

### PDT (1 year) assessed by patient

	AFXL-MAL	-PDT	MAL-F	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Haak, BJD 2015 (n)	9	16	7	16	100.0%	1.29 [0.64, 2.60]	
Total (95% CI)		16		16	100.0%	1.29 [0.64, 2.60]	-
Total events	9		7				
Heterogeneity: Not ap	plicable						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.70 (P =	= 0.48)					Favours MAL-PDT Favours AFXL-MAL-PDT

# Cosmetic outcome (excellent) nBCC lesion: Er:YAG ablative fractional laser-PDT vs

# MALPDT assessed by investigator

	AFL-PDT (Er	YAG)	MAL-F	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Choi, JEADV 2016 (n)	12	21	12	21	100.0%	1.00 (0.59, 1.69)	
Total (95% CI)		21		21	100.0%	1.00 [0.59, 1.69]	+
Total events Heterogeneity: Not appl Test for overall effect: Z		)0)	12				0.05 0.2 1 5 20 Favours AFL-PDT (Er:YAG) Favours MAL-PDT

# Treatment tolerability - low or manageable pain: Er:YAG ablative fractional laser-PDT

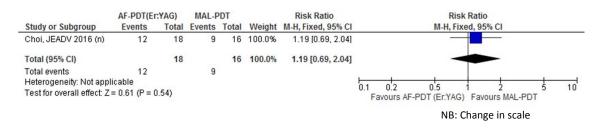
#### vs MAL-PDT

	AFL-PDT (Er	YAG)	MAL-P	DT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Choi, JEADV 2016 (n)	12	20	9	19	100.0%	1.27 [0.70, 2.29]	
Total (95% CI)		20		19	100.0%	1.27 [0.70, 2.29]	-
Total events	12		9				
Heterogeneity: Not appl	icable						0.05 0.2 1 5 20
Test for overall effect: Z	= 0.78 (P = 0.4	4)					Favours AFL-PDT (Er:YAG) Favours MAL-PDT

1 2 3	
4 5 6 7 8	
9 10 11 12	
13 14 15 16	
17 18 19 20 21	
22 23 24 25	
26 27 28 29	
30 31 32 33 34	
35 36 37 38	
39 40 41 42	
43 44 45 46 47	
47 48 49 50 51	
52 53 54 55	
56 57 58 59 60	

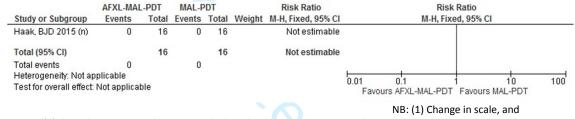
# Other adverse effects (hyperpigmentation) patient: Er:YAG ablative fractional laser-

### PDT vs MAL-PDT



#### Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-

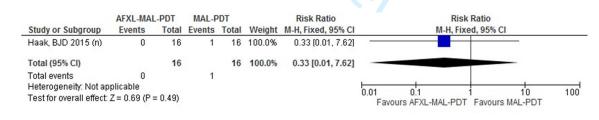
# MAL-PDT vs MAL-PDT (3 months)



(2) the risk ratio cannot be estimated when there are no events on either arm.

#### Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-

#### MAL-PDT vs MAL-PDT (6 months)



# Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-

### MAL-PDT vs MAL-PDT (9 months)

	AFXL-MAL		MAL-P	-		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
łaak, BJD 2015 (n)	0	16	1	16	100.0%	0.33 [0.01, 7.62]	
otal (95% CI)		16		16	100.0%	0.33 [0.01, 7.62]	
otal events	0		1				
leterogeneity: Not ap	plicable						
est for overall effect:	Z = 0.69 (P =	= 0.49)					0.01 0.1 1 10 100 Favours AFXL-MAL-PDT Favours MAL-PDT



# Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-

# MAL-PDT vs MAL-PDT (1 year)

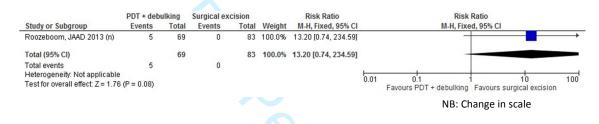
Chudu an Cubanaun	AFXL-MAL-PDT			Mainhé	Risk Ratio	Risk Ratio
Study or Subgroup Haak, BJD 2015 (n)		6 2		00.0%	M-H, Fixed, 95% Cl 0.20 [0.01, 3.86]	M-H, Fixed, 95% CI
Haak, DJD 2013 (II)	0 1	0 2	10 1	00.0%	0.20 (0.01, 3.80)	
Total (95% CI)	1	6	16 1	00.0%	0.20 [0.01, 3.86]	
Total events	0	2				
Heterogeneity: Not ap						0.01 0.1 1 10
Test for overall effect:	Z = 1.07 (P = 0.29	)				Favours AFXL-MAL-PDT Favours MAL-PDT
Combination			icion			
Combination F	PT vs. surg	ical exc				
	_					
Clearance of t	reated NM	SC (3 m	onths	initia	al lesion clea	rance) nodular lesion: ALA-PDT
+ debulking vs	surgical ex	cision				
	PDT + debulking	Surgical e	xcision		Risk Ratio	Risk Ratio
Study or Subgroup	Events Tota				M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Mosterd, BJD 2008 (n)	79 85	86	88	100.0%	0.95 [0.89, 1.02]	-
Total (95% CI)	85		88	100.0%	0.95 [0.89, 1.02]	•
Total events	79	86				
Heterogeneity: Not appli Test for overall effect: Z =						0.1 0.2 0.5 1 2 5
						Favours surgical excision Favours PDT + debulking
						NB: Change in scale
	rance of tr	aatad N		(1 vo	ar) nodular l	esion: ALA-PDT + debulking vs
Suctained clea	i ance or tr	ealeu n	INISC	(туе	ai) nouulai i	esion. ALA-PDT + debuiking vs
Sustained clea						
Sustained clea surgical excisio						
		Surgical e	xcision		Risk Ratio	Risk Ratio
Surgical excisio	ON PDT + debulking Events Tota	Events	Total		M-H, Fixed, 95% Cl	Risk Ratio MH, Fixed, 95% Cl
surgical excision	ON PDT + debulking	Events		Weight 100.0%	M-H, Fixed, 95% Cl	
Surgical excision Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI)	DT + debulking <u>Events Tota</u> 69 75	Events 83	Total 86		M-H, Fixed, 95% Cl 0.90 (0.82, 0.99)	
Surgical excision Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI) Total events	DDT + debulking Events Tota 69 79 75 69	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl
Surgical excision Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI)	DDT + debulking Events Tota 69 75 69 icable	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl
Surgical excisions Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI) Total events Heterogeneity: Not appli	DDT + debulking Events Tota 69 75 69 icable	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl
Surgical excisions Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI) Total events Heterogeneity: Not appli	DDT + debulking Events Tota 69 75 69 icable	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl
Surgical excisions Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI) Total events Heterogeneity: Not appli	DDT + debulking Events Tota 69 75 69 icable	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl
Surgical excisions Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI) Total events Heterogeneity: Not appli	DDT + debulking Events Tota 69 75 69 icable	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl
Surgical excisions Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI) Total events Heterogeneity: Not appli	DDT + debulking Events Tota 69 75 69 icable	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl
Surgical excisions Study or Subgroup Mosterd, BJD 2008 (n) Total (95% CI) Total events Heterogeneity: Not appli	DDT + debulking Events Tota 69 75 69 icable	Events 83	Total 86	100.0%	M-H, Fixed, 95% Cl 0.90 [0.82, 0.99] 0.90 [0.82, 0.99]	M-H, Fixed, 95% Cl

# Sustained clearance of treated NMSC (5 years) lesion: ALA-PDT + debulking vs surgical

#### excision

	PDT + debu	ulking	Surgical ex	cision		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Roozeboom, JAAD 2013 (n)	42	79	64	86	100.0%	0.71 [0.56, 0.91]	
Total (95% CI)		79		86	100.0%	0.71 [0.56, 0.91]	◆
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.73			64				0.05 0.2 1 5 20 Favours surgical excision Favours PDT + debulking
							NB: Change in scale

### Recurrence rate (>1 year <2 years) lesion: ALA-PDT + debulking vs surgical excision

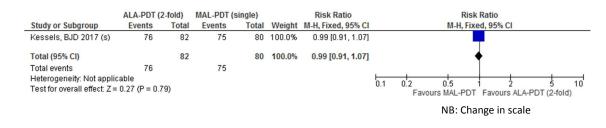


### Recurrence rate (>1 year <5 years) lesion: ALA-PDT + debulking vs surgical excision

	PDT + debu	ulking	Surgical ex	cision		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Roozeboom, JAAD 2013 (n)	12	69	0	83	100.0%	30.00 [1.81, 497.72]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		69		83	100.0%	30.00 [1.81, 497.72]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.37			0				0.01 0.1 1 10 100 Favours PDT + debulking Favours surgical excision
ractionated PD1	r vs. PD	т					

#### Clearance of treated sBCC (3 months initial lesion clearance) patient: Fractionated ALA-

#### PDT vs MAL-PDT

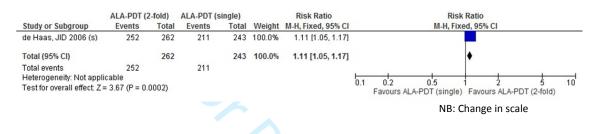


# Sustained clearance of treated sBCC (1 year) patient: Fractionated ALA-PDT vs

### MAL-PDT

	ALA-PDT (2	-fold)	MAL-PDT (	single)		<b>Risk Ratio</b>			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl			M-H, Fixe	ed, 95% C			
Kessels, BJD 2017 (s)	72	75	65	75	100.0%	1.11 [1.00, 1.22]							
Total (95% CI)		75		75	100.0%	1.11 [1.00, 1.22]				•			
Total events	72		65										
Heterogeneity: Not applic Test for overall effect: Z =		5)					0.1	0.2 Favo	0.5 Durs MAL-PDT	1 Favours	2 ALA-PDT	5 (2-fol	10 d)

# Sustained clearance of treated sBCC (1 year) lesion: Fractionated ALA-PDT vs ALA-PDT



# Sustained clearance of treated sBCC (5 years) lesion: Fractionated PDT vs ALA-PDT

	ALA-PDT (	2-fold)	ALA-PDT (S	single)		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
de Vijlder, ADV 2012 (s)	376	471	165	274	100.0%	1.33 [1.19, 1.47]	
Total (95% CI)		471		274	100.0%	1.33 [1.19, 1.47]	•
Total events	376		165				
Heterogeneity: Not applic	able						
Test for overall effect: Z =	5.19 (P < 0.0	0001)					0.1 0.2 0.5 1 2 5 10 Favours ALA-PDT (single) Favours ALA-PDT (2-fold)

# Cosmetic outcome (good or excellent) sBCC patient: Fractionated ALA-PDT vs MAL-PDT

	ALA-PDT (2	2-fold)	MAL-PDT (	single)		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kessels, BJD 2017 (s)	58	82	48	80	100.0%	1.18 [0.94, 1.48]	
Total (95% CI)		82		80	100.0%	1.18 [0.94, 1.48]	◆
Total events	58		48				
Heterogeneity: Not appli							0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z =	= 1.42 (P = 0.1	5)					Favours MAL-PDT Favours ALA-PDT (2-fold)
							· · · · · · · · · · · · · · · · · · ·

S57

Study or Subgroup	ALA-PDT (2 fold) Events Total			Veight	Risk Ratio M-H, Fixed, 95% Cl			Risk Ratio Fixed, 95% Cl
de Haas, JID 2006 (s)	9 55	3	100 1	00.0%	5.45 [1.54, 19.32]		m-n,	
Total (95% CI) Total events	9 9	3	100 1	00.0%	5.45 [1.54, 19.32]			
Heterogeneity: Not appl Test for overall effect: Z						0.05 Favou	0.2 rs ALA-PDT (2-1	old) Favours ALA-P
							Ν	B: Change in sc
				S	58			
				S	58			
				S	58			

# References

1

2 3 4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22 23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42 43

44 45

46

47

48

49

50

51

52

53

54 55

1 Foley P, Freeman M, Menter A et al. Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies. International journal of dermatology 2009; 48: 1236-45. 2 Basset-Seguin N, Ibbotson SH, Emtestam L et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol 2008; 18: 547-53. 3 Wang I, Bendsoe N, Klinteberg CA et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. Br J Dermatol 2001; 144: 832-40. 4 Berroeta L, Clark C, Dawe RS et al. A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma. Br J Dermatol 2007; 157: 401-3. 5 Mosterd K, Thissen MR, Nelemans P et al. Fractionated 5-aminolaevulinic acidphotodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. Br J Dermatol 2008; 159: 864-70. 6 Roozeboom MH, Aardoom MA, Nelemans PJ et al. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. Journal of the American Academy of Dermatology 2013; 69: 280-7. 7 Rhodes LE, de Rie M, Enstrom Y et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol 2004; 140: 17-23. 8 Rhodes LE, de Rie MA, Leifsdottir R et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007; 143: 1131-6. 9 Szeimies RM, Ibbotson S, Murrell DF et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. Journal of the European Academy of Dermatology and Venereology 2008; 22: 1302-11. 10 Arits AH, Mosterd K, Essers BA et al. Photodynamic therapy versus topical imiguimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. The lancet oncology 2013; 14: 647-54. 11 Roozeboom M, Arits A, Mosterd K et al. Three-year follow-up results of photodynamic therapy vs. Imiguimod vs. Fluorouracil for treatment of superficial basal cell carcinoma: a single-blind, noninferiority, randomized controlled trial. In: Journal of investigative dermatology, Vol. 136. 2016; 1568-74. 12 Jansen MHE, Mosterd K, Arits A et al. Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma. J Invest Dermatol 2017. 13 Smucler R, Vlk M. Combination of Er:YAG laser and photodynamic therapy in the treatment of nodular basal cell carcinoma. Lasers in Surgery and Medicine 2008; 40: 153-8. Haak C, Togsverd-Bo K, Thaysen-Petersen D et al. Fractional laser-mediated 14 photodynamic therapy of high-risk basal cell carcinomas--a randomized clinical trial. In: The British journal of dermatology, Vol. 172. 2015; 215-22. 15 Choi SH, Kim KH, Song KH. Er: YAG ablative fractional laser-primed photodynamic therapy with methyl aminolevulinate as an alternative treatment option for patients S59

1		with this nodular bacal call carcinoma, 12 month follow up recults of a randomized
2		with thin nodular basal cell carcinoma: 12-month follow-up results of a randomized,
3		prospective, comparative trial. J Eur Acad Dermatol Venereol 2016; <b>30</b> : 783-8.
4	16	Osiecka B, Jurczyszyn K, Ziolkowski P. The application of Levulan-based photodynamic
5		therapy with imiquimod in the treatment of recurrent basal cell carcinoma. Med Sci
6		Monit 2012; <b>18</b> : PI5-9.
7	17	de Haas ER, Kruijt B, Sterenborg HJ et al. Fractionated illumination significantly
8		improves the response of superficial basal cell carcinoma to aminolevulinic acid
9		photodynamic therapy. J Invest Dermatol 2006; <b>126</b> : 2679-86.
9 10	40	
	18	Vijlder H, Sterenborg H, Neumann H et al. Light fractionation significantly improves the
11		response of superficial basal cell carcinoma to aminolaevulinic acid photodynamic
12		therapy: five-year follow-up of a randomized, prospective trial. In: Acta dermato-
13		<i>venereologica</i> , Vol. 92. 2012; 641-7.
14	19	Kessels J, Kreukels H, Nelemans PJ et al. Treatment of superficial basal cell carcinoma
15		by topical photodynamic therapy with fractionated 5-aminolevulinic acid 20% versus
16		
17		Br J Dermatol 2017.
18		
19		
20		
21		
22		
23		two stage topical methylaminolevulinic acid: results of a randomized controlled trial. Br J Dermatol 2017.
24		
25		
26		
27		
27		
29		
30		
31		
32		
33		
34		
35		
36		
37		
38		
39		
40		
41		
42		
43		
44		
45		
46		
47		
48		
40		
49 50		
51		
52		
53		
54		
55		S60
56		200
57		
58		