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

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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.[1] BCCs form a substantial and growing proportion of a dermatologist's workload and are a large burden to Western health services.[2] 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.[3] 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.[4]

Surgical excision allows unparalleled cure rates but the cosmetic outcome depends on BCC size and location, reconstruction method, and expertise.[4-6] One of several non-surgical treatments available for nBCC and sBCC[7,8] is topical PDT with 5-aminolaevulinic acid (ALA) or methyl aminolaevulinate (MAL).[9] 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.[10] High clearance rate (although lower for nBCC than sBCC), excellent cosmesis and low adverse event (AE) rate are reported.[9]

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.[11,12] 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[13] 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).[14]

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 I^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 follow-up 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.[15] A cycle of two treatments, 1 week apart was performed; at 3 months, partially-responding lesions were re-treated 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).[16,17] 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.[16] The other RCT compared MAL-PDT with cryosurgery (≤20 seconds freeze, repeated 2-3 times; Table 3).[17]

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). [17]

For nBCC there was no difference in 1-year recurrence rates between cryosurgery and ALA-PDT. [16] 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;[18] 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.[18]

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% CI 1.32–2.14; p < 0.0001) and nBCC (RR 1.82; 95% CI 1.19–2.80; p = 0.006; Table 5).[18,19]

Low-to-manageable pain was greater for MAL-PDT than for excision (RR 1.81; 95% CI 1.09–3.01; p = 0.02; Table 6).[19]

PDT vs. Topical Treatments

A single RCT compared MAL-PDT with repeated applications of imiquimod or fluorouracil for sBCC.[20-22] 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).[20]

PDT vs. Fractionated PDT

Two RCTs compared conventional PDT with fractionated ALA-PDT for sBCC (for protocols see Table 3).[23-25] The first involved 195 patients (573 lesions), with single-illumination ALA-PDT as the conventional arm.[23,24] 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% CI 1.05–1.17; p = 0.0002), and at 5 years, 80% vs. 60% (RR 1.33; 95% CI 1.19–1.47; p < 0.00001; Table 4).[23,24] The second RCT, involving 162 patients with one primary sBCC treated per patient, used the one-cycle MAL-PDT protocol without re-treatment 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).[25]

PDT vs. Laser or vs. Laser-enhanced PDT

Three RCTs compared conventional MAL-PDT and MAL-PDT with prior ablative laser treatment.[26-28] The largest (286 patients), a within-patient design, compared treatments in patients with three recurrent nBCCs in three arms: MAL-PDT, erbium-doped yttrium-aluminium-garnet (Er:YAG)-laser ablation, and Er:YAG-laser ablation plus MAL-PDT.[26] The within-patient design precluded meta-analysis with the other RCTs.[27,28] 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

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_2-AFL, the other Er:YAG-AFL.[27,28] The clearance rates at 3 months were, CO_2-AFL–PDT 100% vs. PDT 88% and Er:YAG-AFL–PDT 76% vs. PDT 43% (RR 1.78; 95% CI 1.03–3.08).[27,28] One-year sustained clearance showed no significant difference in the CO_2-AFL trial (CO_2-laser–PDT 81% vs. PDT 64%). The CO_2-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.[27,28]

PDT and placebo cream vs. PDT and imiquimod

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.[26] 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.[18,19,29-32] 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[9,10] 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%).[16]

One RCT compared MAL-PDT with imiquimod or fluorouracil for sBCC.[20-22] 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.[21]

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.[33] 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.[16] Cosmetic differences between therapies were smaller in patient assessments, and diminished with time.[17,19,31] 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.[16] Pain intensified with treatment repetition;[16] 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

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.[20] Recent PDT studies utilising low irradiance protocols (≤35 $mWcm^{-2}$, compared with 50-200 $mWcm^{-2}$ in this review) show reduced pain with apparent preservation of efficacy.[34-38]

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.[18,20,39] Following PDT, effects including weeping, crusting, erosion and ulceration were less severe and resolved more rapidly than with cryosurgery, imiquimod or fluorouracil.[16,17,20] MAL-PDT had fewer reports of moderate-to-severe local swelling, itching, crusting or erosion than either imiquimod or fluorouracil.[20-22] The non-pain-related AEs were largely transient and of mild-to-moderate intensity after PDT and cryosurgery, and were less frequent following PDT.[16,17] 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.[12,40,41] 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.[17,19] 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.[11] 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.[40,41] Cosmesis and AEs need to be taken into account as well as clearance, to reflect patient's views.[11,42,43]

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.[44] 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 meta-analyses 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.[45,46] Non-English language studies were not included. The major limitations reflected those of the reviewed studies, including no systematic reporting of patient concerns.[41,42] 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

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.[33] 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.

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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.

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Table 1 Trials comparator arms

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

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

Study	Population (age in years)	Lesion characteristics	Inclusion and exclusion criteria
Foley 2009[15] Parallel groups 2 RCTs Australia and USA	n = 131 (150 nBCC); **PDT**: 47 M 19 F, mean age 66 (range 28–88), skin type I (41%), II (39%), III and IV (20%); **Placebo-PDT**: 52 M,13 F, mean age 67 (range 39–88) skin type I (29%), II (43%), III and IV (28%)	Primary nBCC: **PDT**: 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): **Placebo-PDT**: 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),
Basset-Seguin 2008[17] Parallel groups RCT 13 European centres	n = 120 (> 219 sBCC); Per protocol: **PDT**: 39 M 19 F, mean age 62 (range 25–86), skin type I 5%, II 57%, III 33% IV 5%: **Cryosurgery**: 30 M, 23 F, mean age 64 (range 38–90) skin type I 5%, II 63%, III 30% IV 2%	Primary sBCC: **PDT**: face/scalp 6%, trunk/neck 72%, extremities 22%, largest diameter (mm) 5–10 43%, 11–19 42%, ≥ 20 16%: **Cryosurgery**: face/scalp 4%, trunk/neck 76%, extremities 20%, largest diameter (mm) 5–10 42%, 11–19 42%, ≥ 20 16%	**Standard, plus the Inclusions:** Patients with ≤ 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).
Wang 2001[16] Parallel groups RCT Sweden	n = 88 (88 lesions: 39 sBCC, 49 nBCC); 44 F: 44 M. Age range 42–88	nBCC and sBCC: **PDT**: 22 sBCC, 25 nBCC: **Cryosurgery**: 17 sBCC, 24 nBCC; **Location**: 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.
Berroeta 2007[29] Parallel groups RCT UK	n = 31 (40 nBCC); 12 F: 19 M; Median age 72 (range 50–83)	nBCC; Largest diameter ≤ 20mm on anatomically noncritical sites	**Standard, plus the exclusions:** high risk sites, recurrent BCC, BBC largest diameter > 20 mm
Mosterd 2008[30] Roozeboom 2013[32] 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; **Location**: 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
Rhodes 2004[19] Rhodes 2007[31]; 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; **Location**: 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.
Szeimies 2008[18] 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 ± SD: PDT = 12.5 ± 3.7; Surgery = 12.6 ± 3.7. Number per patient, mean ± SD, 1.4 ± 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.
Arits 2013[20] Roozeboom 2016[21] Jansen 2017[22];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: **Location**: 13% head or neck; 60% trunk; 14% upper extremities; 13% lower extremities. Median size (mm^2) 59 (range 5–5,472); median size (mm^2) was 52 in MAL-PDT group and 63 in both imiquimod and fluorouracil groups.	**Standard,-plus the exclusions:** tumour on scalp
Smucler 2008[26] Within patient RCT Czech Republic	n = 286 (858 recurrent nBCC); 94 F: 192 M; Age, mean ± SD, 65.1 ± 7.3; Skin type I 29%, II 69.9%, III 1.1%	Recurrent nBCC	**Inclusions:** At least 3 recurring nBCCs (histologically verified). At least 30mm between tumours. Refractory to at least one surgical excision, cryosurgery or laser ablation. **Exclusions:** Inability to attend regular checkups (patients from abroad were excluded from the study).
Haak 2015[27] 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.	**Standard, plus the inclusions:** 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. **and, plus the exclusions:** Skin type IV–VI, risk of poor compliance

Study	Population (age in years)	Lesion characteristics	Inclusion and exclusion criteria
Choi 2016[28] Parallel groups RCT South Korea	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 ≤ 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
Osiecka 2012[44] Parallel groups RCT Poland	n = 34 (34 recurrent); Age range 50–68.	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.
De Haas 2006[23] Parallel groups RCT Netherlands	n = 155 patients (505 sBCC): **Single illumination**, Age, mean 57 (range 32–81): **Fractionated illumination**, Age, mean 56 (range 31–83)	sBCC	**Inclusions:** Clinically or histologically diagnosed sBCC (with at least one histologically diagnosed primary sBCC per patient). **Exclusions:** Child or not white-Caucasian.
De Vijlder 2012[24]	n = 195 patients (573 sBCC) (plus further 50 patients with 172 sBCC treated by fractionated illumination): **Single illumination**, Age, mean 56.7 (range 31–88): **Fractionated illumination**, Age, mean 56.9 (range 32–84): **Fractionated illumination with later enrolment**, Age, mean 65.5 (range 39–90);	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[25]	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 (range 38–85)	Primary sBCC: **MAL-PDT**: head/neck 1%, trunk 73%, upper extremities 8.8%, lower extremities 18%: tumour size mm, mean ± SD; 11.2 ± 7.1 **ALA-PDT 2-fold**: head/neck 7%, trunk 45%, upper extremities 16%, lower extremities 17%: tumour size mm, mean ± SD; 10.8 ± 5.3	**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.

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 ≥ 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	BCC	Conventional PDT Treatment [Skin preparation; Prodrug; Incubation (hours); Wavelength (nm); Irradiance ($mWcm^{-2}$); Sessions; Light dose per session (Jcm^{-2}); PDT re-treatment]	Comparator Treatment
Foley 2009[15]	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[17]	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[16]	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[29]	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.[47]
Mosterd 2008[30] Roozeboom 2013[32]	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[19] Rhodes 2007[31]	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 ≥ 5 mm margins under LA.
Szeimies 2008[18]	superficial	Surface scrape, no LA; MAL (Metvix); 3; 630 ± 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[20] Roozeboom 2016[21] Jansen 2017[22]	superficial	Surface scrape, no LA, ; MAL (Metvix); 3; ≈ 630, noncoherent; ≈ 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[26]	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[27]	nodular	Partially debulked under LA , ; MAL (Metvix); 3; 630 ± 5, noncoherent; ≈ 77; 2, (7–10 days apart); 37; No	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[28]	nodular	None; MAL (Metvix); 3; 630 ± 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[44]	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[23] De Vijlder 2012[24]	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^{-2} and 80 Jcm^{-2} after 4 and 6 hours respectively.
Kessels 2017[25]	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^{-2} and 80 Jcm^{-2} 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

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
Foley 2009[15] (Placebo-PDT)	Assessed clinically 3 months after initial treatment or retreatment; confirmed histologically by independent laboratory (blinded). Excised at 3 months (clinical nonresponders), or 6 months (clinical responders), after last treatment.	MAL-PDT 73% vs Placebo 27% RR 2.75 95%CI 1.84–4.10, p < 0.00001	No data meeting extraction criteria (all excised < 1 year).	No data meeting extraction criteria (all excised < 1 year).	No data meeting extraction criteria (all excised < 1 year). Variable of interest was histologically verified complete response 6 months after last treatment.
Basset-Seguin 2008[17] (Cryosurgery)	Clinical evaluation of lesion recurrence at 1,2,3,4 and 5 years after last treatment.	MAL-PDT 90% vs Cryo 90% RR 1.01 95%CI 0.89–1.14, p = 0.90	MAL-PDT 91% vs Cryo 92% RR 0.99 95%CI 0.88–1.11, p = 0.82	MAL-PDT 57% vs Cryo 79% RR 0.72 95%CI 0.55–0.95, p = 0.02	1–2 years MAL-PDT 14% vs Cryo 6% RR 2.20 95%CI 0.66–8.01, p = 0.23 1–3 years MAL-PDT 22% vs Cryo 6% RR 3.45 95%CI 1.02–11.62, p = 0.05 1–4 years MAL-PDT 22% vs Cryo 6% RR 3.45 95%CI 1.02–11.62, p = 0.05 1–5 years MAL-PDT 22% vs Cryo 8% RR 2.59 95%CI 0.88–7.58, p = 0.08
Wang 2001[16] (Cryosurgery)	Histological assessment of punch biopsies 12 months after initial treatment.	No data meeting extraction criteria	No data meeting extraction criteria	No data meeting extraction criteria	sBCC 1-year ALA 36% vs Cryo 6% RR 6.18 95%CI 0.85–44.78, p = 0.07 nBCC 1-year ALA 12% vs Cryo 21% RR 0.58 95%CI 0.15–2.15, p = 0.41
Berroeta 2007[29] (Surgery)	PDT repeated at 3 months if BCC clinically evident. If at 6 months BCC persists referred for alternative treatment.	No data meeting extraction criteria	MAL-PDT 61% vs Surgery 79% RR 0.78 95%CI 0.52–1.18	No data meeting extraction criteria	No data meeting extraction criteria
Mosterd 2008[30] Roozeboom 2013[32] (Surgery)	At 3, 6, 12, 18, 24, 36, 48 and 60 months, recurring tumour (histologically confirmed BCC within 5mm of scar) recorded. Patients lost to follow-up censored at last examination. Median follow-up 67 months (range 0–106)	ALA 93% vs Surgery 98% RR 0.95 95%CI 0.89–1.02	ALA 87% vs Surgery 96% RR 0.90 95%CI 0.82–0.99	ALA 53% vs Surgery 74% RR 0.71 95%CI 0.56–0.91, p = 0.006	1–2 years ALA 7% vs Surgery 0% RR 13.20 95%CI 0.74–234.59 1–5 years ALA 17% vs Surgery 0% RR 30.00 95%CI 1.81–497.72, p = 0.02
Rhodes 2004[19] Rhodes 2007[31] (Surgery)	Complete response assessed at 3 months after last treatment by the same investigator. Lesions assessed annually for 5 years. Any clinical recurrence was histologically confirmed.	MAL-PDT 91% vs Surgery 98% RR 0.92 95%CI 0.84–1.02	MAL-PDT 92% vs Surgery 98% RR 0.94 95%CI 0.85–1.03	MAL-PDT 60% vs Surgery 71% RR 0.83 95%CI 0.63–1.11, p = 0.21	1–2 years MAL-PDT 7% vs Surgery 2% RR 3.14 95%CI 0.37–31.60 1–5 years MAL-PDT 10% vs Surgery 4% RR 2.65 95%CI 0.54–13.05, p = 0.23
Szeimies 2008[18] (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 = 0.76	MAL-PDT 91% vs Surgery 100% RR 0.91 95%CI 0.85–0.96, p = 0.001	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.
Arits 2013[20] Roozeboom 2016[21] Jansen 2017[22] (Imiquimod or fluorouracil)	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%CI 0.87–1.04, p = 0.26 MAL-PDT 82% FU 87% RR 0.94 95%CI 0.87–1.03, p = 0.18	MAL-PDT 82% vs IMQ 90% RR 0.91 95%CI 0.83–0.99, p = 0.03 MAL-PDT 82% vs FU 89% RR 0.92 95%CI 0.85–1.01, p = 0.09	Sustained clearance at 3 years MAL-PDT 70% vs IMQ 84% RR 0.84 95%CI 0.74–0.94, p = 0.03: MAL-PDT 70% vs FU 79% RR 0.89 95%CI 0.78–1.00, p = 0.06 Sustained clearance at 5 years MAL-PDT 59% vs IMQ 73% RR 0.81 95%CI 0.70–0.95, p = 0.01 : MAL-PDT 59% vs FU 67% RR 0.88 95%CI 0.75–1.04, p = 0.14	No data meeting extraction criteria
Smucler 2008[26] (Er:YAG laser, Er:YAG laser/PDT)	Clinical evaluation 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 87% vs MAL-PDT 86% RR 1.01 95%CI 0.94–1.08, p = 0.81	Er:YAG laser/PDT 77% vs MAL-PDT 75% RR 1.04 95%CI 0.94–1.14, p = 0.49	No data meeting extraction criteria	No data meeting extraction criteria

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
Haak 2015[27] (CO_2-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%CI 0.92–1.41, p = 0.24	Per patient AFL-MAL-PDT 81% vs MAL-PDT 64% RR 1.26 95%CI 0.80–1.99, p = 0.31 Per lesion AFL-MAL-PDT 63% vs MAL-PDT 64% RR 0.97 95%CI 0.56–1.68, p = 0.92	Study terminated at 1 year	No data meeting extraction criteria
Choi 2016[28] (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%CI 1.03–3.08, p = 0.04	No data meeting extraction criteria	No data meeting extraction criteria	AFL/ALA-PDT 6% vs MAL-PDT 56% RR 0.11 95%CI 0.02–0.82, p = 0.03
Osiecka 2012[44] (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%CI 0.22–1.75, p = 0.37
De Haas 2006[23] De Vijlder 2012[24] (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%CI 1.05–1.17, p = 0.0002	ALA-PDT (fractionated) 80% vs ALA-PDT (single) 60% RR 1.33 95%CI 1.19–1.47, p < 0.00001	No data meeting extraction criteria
Kessels 2017[25] (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%CI 0.91–1.07, p = 0.79	Frac-ALA-PDT 96% vs MAL-PDT 87% RR 1.11 95%CI 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; CI, confidence interval; RR, risk ratio; FU, 5-fluorouracil; IMQ, imiquimod; AFL, Ablative Fractional Laser; Er:YAG, Erbium-doped Yttrium-Aluminium-Garnet; CO_2-AFL, carbon dioxide Ablative Fractional Laser; Frac, Fractionated.

Table 5 Cosmetic outcome

Study (Comparator)	Assessment method	Investigator assessed cosmetic outcome	Patient assessed cosmetic outcome
Foley 2009[15] (Placebo-PDT)	Investigator: 4-point scale*	6 months, good-excellent, MAL-PDT 56% vs Placebo 19% RR 3.00: 95%CI 1.80–5.01, p < 0.0001	No data meeting extraction criteria
Basset-Seguin 2008[17] (Cryosurgery)	Investigator: Complete response on 4-point scale*, 'excellent' (no scarring, atrophy, 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.	3 months, excellent, MAL-PDT 27% vs Cryo 3% RR 7.95: 95%CI 1.92–32.92, p < 0.004 1 year, excellent, MAL-PDT 32% vs Cryo 12% RR 2.67: 95%CI 1.22–5.85 2 years, excellent, MAL-PDT 40% vs Cryo 7% RR 5.85: 95%CI 2.17–15.78, p = 0.0005 3 years, excellent, MAL-PDT 31% vs Cryo 9% RR 3.55: 95%CI 1.42–8.90, p = 0.007 4 years, excellent, MAL-PDT 31% vs Cryo 9% RR 3.55: 95%CI 1.42–8.90, p = 0.007 5 years, excellent, MAL-PDT 31% vs Cryo 12% RR 2.54: 95%CI 1.15–5.59, p = 0.02	3 months, excellent, MAL-PDT 40% vs Cryo 19% RR 2.13: 95%CI 1.15–3.92, p = 0.02 1 year, excellent, MAL-PDT 35% vs Cryo 24% RR 1.47: 95%CI 0.83–2.59, p = 0.18 2 years, excellent, MAL-PDT 37% vs Cryosurgery 26% RR 1.43: 95%CI 0.83–2.47, p = 0.19
Wang 2001[16] (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%CI 1.96–19.00	No data meeting extraction criteria
Berroeta 2007[29] (Surgery)	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
Mosterd 2008[30] Roozeboom 2013[32] (Surgery)	Cosmetic outcome not assessed	No data meeting extraction criteria	No data meeting extraction criteria
Rhodes 2004[19] Rhodes 2007[31] (Surgery)	Investigator assessment, 4-point scale*, 3 months, 1, 2, and 5 years. Patient 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%CI 1.44–3.54, p = 0.0004 1 year, good-excellent, MAL-PDT 66% vs Surgery 36% RR 1.82: 95%CI 1.19–2.80, p = 0.006 2 years, good-excellent, MAL-PDT 48% vs Surgery 34% RR 1.41: 95%CI 0.86–2.31, p = 0.17 5 years, good-excellent, MAL-PDT 54% vs Surgery 40% RR 1.34: 95%CI 0.87–2.06, p = 0.19	3 months, good-excellent, MAL-PDT 78% vs Surgery 79% RR 0.99: 95%CI 0.80–1.22, p = 0.93 1 year, good-excellent, MAL-PDT 82% vs Surgery 77% RR 1.07: 95%CI 0.87–1.31, p = 0.51 2 years, good-excellent, MAL-PDT 56% vs Surgery 57% RR 0.97: 95%CI 0.69–1.38, p = 0.89
Szeimies 2008[18] (Surgery)	Primary outcome: investigator assessment, 12 months, 4-point scale (poor, fair, good, excellent). Secondary outcomes: investigator assessment, 3, 6 months; patient assessment, 3, 6, 12 months (same scale).	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%CI 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
Arits 2013[20] Roozeboom 2016[21] Jansen 2017[22] (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

Study (Comparator)	Assessment method	Investigator assessed cosmetic outcome	Patient assessed cosmetic outcome
Smucler 2008[26] (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 ± SD: Er:YAG-laser-PDT, 2.00 ± 0.57; Er:YAG-laser, 1.62 ± 0.76; p < 0.00001: Er:YAG-laser-PDT, 2 ± 0.57; MAL-PDT, 3.17 ± 0.57; p < 0.00001. 6 months, aesthetic result, mean ± SD: Er:YAG-laser-PDT, 1.17 ± 0.24; Er:YAG-laser, 1.50 ± 0.70; p < 0.00001: Er:YAG-laser-PDT, 1.17 ± 0.24; MAL-PDT, 1.50 ± 0.43; p < 0.00001. 9 months, aesthetic result, mean ± SD: Er:YAG-laser-PDT, 1.23 ± 0.44; Er:YAG-laser, 1.83 ± 0.95; p < 0.00001: Er:YAG-laser-PDT, 1.23 ± 0.44; MAL-PDT, 1.67 ± 0.76; p < 0.00001.	No data meeting extraction criteria
Haak 2015[27] (CO_2-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.	Per patient, 3 months, excellent: AFL-PDT 69% vs MAL-PDT 56% RR 1.22: 95%CI 0.71–2.11, p = 0.47 Per patient, 6 months, excellent: AFL-PDT 75% vs MAL-PDT 38% RR 2.00: 95%CI 1.00–4.00, p = 0.05 Per patient, 9 months, excellent: AFL-PDT 50% vs MAL-PDT 44% RR 1.14: 95%CI 0.54–2.40, p = 0.72 Per patient, 1 year, excellent: AFL-PDT 50% vs MAL-PDT 25% RR 2.00: 95%CI 0.75–5.33, p = 0.17	Per patient, 3 months, excellent: AFL-PDT 81% vs MAL-PDT 50% RR 1.63: 95%CI 0.94–2.80, p = 0.08 Per patient, 6 months, excellent: AFL-PDT 75% vs MAL-PDT 50% RR 1.50: 95%CI 0.85–2.64, p = 0.16 Per patient, 9 months, excellent: AFL-PDT 63% vs MAL-PDT 50% RR 1.25: 95%CI 0.67–2.32, p = 0.48 Per patient, 1 year, excellent: AFL-PDT 56% vs MAL-PDT 44% RR 1.29: 95%CI 0.64–2.60, p = 0.48
Choi 2016[28] (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%CI 0.59–1.69, p = 1.00	No data meeting extraction criteria
Osiecka 2012[44] (PDT/IMQ)	No formal assessment of cosmesis	No data meeting extraction criteria	No data meeting extraction criteria
De Haas 2006[23] De Vijlder 2012[24] (Fractionated PDT)	No formal assessment of cosmesis	No data meeting extraction criteria	No data meeting extraction criteria
Kessels 2017[25] (Fractionated ALA-PDT)	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

*scale as in Basset-Seguin[17]; Abbreviations: MAL, methyl aminolaevulinate; ALA, 5-aminolaevulinic acid; PDT, photodynamic therapy; CI, confidence interval; RR, risk ratio; FU, 5-fluorouracil; IMQ, imiquimod; AFL, Ablative Fractional Laser; Er:YAG, Erbium-doped Yttrium-Aluminium-Garnet; CO_2-AFL, carbon dioxide Ablative Fractional Laser; Frac, Fractionated. SD, standard deviation

Table 6 Pain

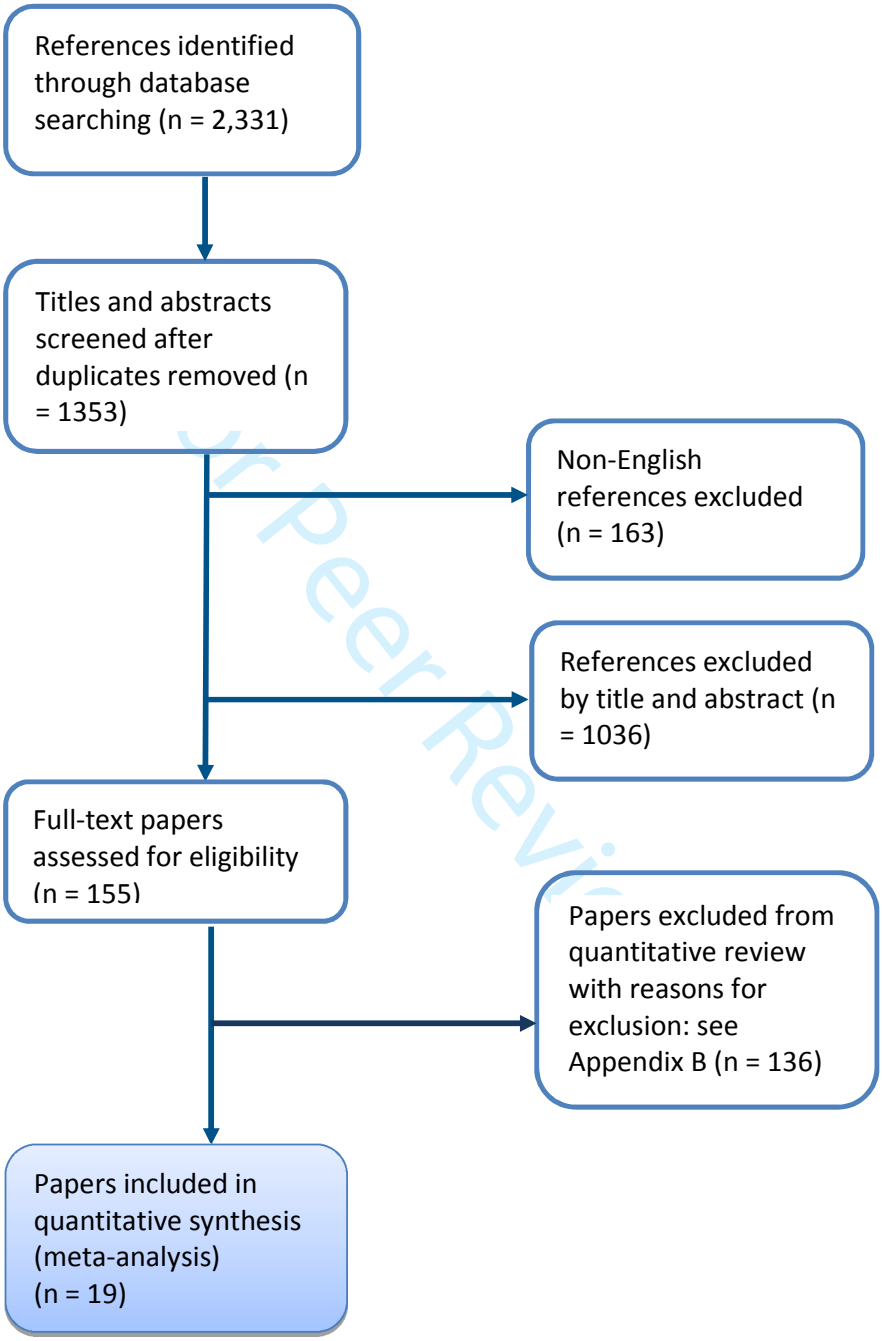
Study (Comparator)	Analgesia	Assessment of pain	Severe pain*	Low or manageable pain
Foley 2009[15] (Placebo-PDT)	None stated	During treatment and follow-up, nurse (blinded) noted severity, duration, analgesia.	MAL-PDT 0% vs Placebo 0%	MAL-PDT 90% vs Placebo 66% RR 1.37: 95%CI 1.14–1.66, p < 0.001
Basset-Seguin 2008[17] (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%CI 0.30–26.22	MAL-PDT 75% vs Cryo 72% RR 1.02: 95%CI 0.83–1.27, p < 0.83
Wang 2001[16] (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%CI 0.11–62.73	No data meeting extraction criteria
Berroeta 2007[29] (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[30] Roozeboom 2013[32] (Surgery)	Surgery under infiltrative LA.	Documented at review	No data meeting extraction criteria	No data meeting extraction criteria
Rhodes 2004[19] Rhodes 2007[31] (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%CI 1.09–3.01, p = 0.02
Szeimies 2008[18] (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[20] Roozeboom 2016[21] Jansen 2017[22] (IMQ or FU)		Patient recorded weekly, and on first and second PDT session, maximum score for pain and burning sensation on a VAS.	MAL-PDT 9% vs IMQ 7% ; RR 0.93: 95% CI 0.61–1.41, p = 0.72: MAL-PDT 9% vs FU 4% ;: RR 1.93: 95% CI 1.13–3.30, p = 0.02. MAL-PDT severe pain mostly during illumination.	MAL-PDT 85% vs IMQ 85% ; RR 1.00: 95%CI 0.92–1.08, p = 0.96 : MAL-PDT 85% vs FU 88% RR 0.97: 95%CI 0.89–1.05, p = 0.40
Smucler 2008[26] (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[27] (CO_2.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[28] (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 2012[44] (PDT/IMQ)	None described	None described	None described	None described
De Haas 2006[23] De Vijlder 2012[24] (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%CI 1.34–17.53, p = 0.02	
Kessels 2017[25] (Fractionated ALA-PDT)			No patient discontinued treatment because of pain.	Pain score, mean NRS ± SD: MAL-PDT vs ALA-PDT 2-fold: 1st session; 2.25 ± 2.54 vs 1.88 ± 2.36, p = 0.369; 2nd session; 2.48 ± 2.57 vs 3.36 ± 2.57, p = 0.039.[25] 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; CI, 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_2-AFL, carbon dioxide Ablative Fractional Laser; NRS, numeric rating scale (score 0-10); SD: standard deviation

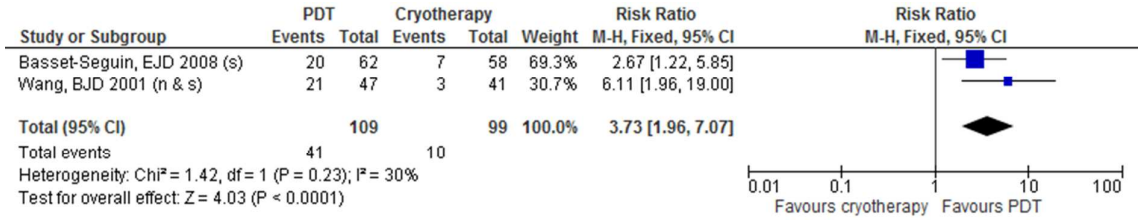
Figures

Figure 1 PRISMA* flow chart of literature search strategy



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; n, number

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

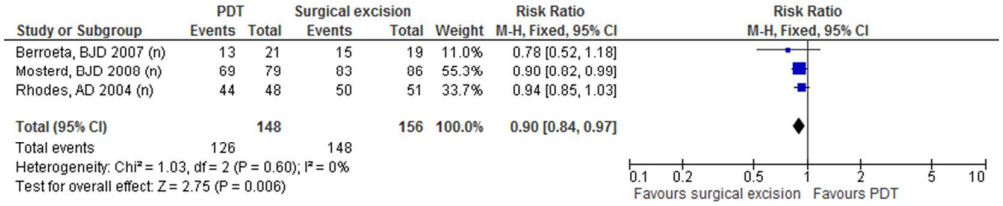


PDT, photodynamic therapy; nBCC, nodular basal cell carcinoma; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom. NB: Wang (2001) treated one lesion per patient (ALA-PDT); Basset-Seguin (2008) treated all lesions for each patient (MAL-PDT)

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

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

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



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

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

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

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 neoplasm*) OR (basal cell cancer*)	1112	37778	38167
2	PubMed photodynamic therapy [MeSH Terms] OR photodynamic therapy OR PDT) MEDLINE and EMBASE (photodynamic ADJ0 therapy) OR PDT Cochrane (photodynamic therapy) OR PDT	1547	41500	21718
3	PubMed skin[MeSH Terms] OR cutaneous OR skin) MEDLINE and EMBASE Cutaneous OR skin Cochrane Cutaneous OR skin	49701	1718477	778174
4	1 AND 2 AND 3	**101(a)**	**1572(b)**	**658(c)**
a (101) + **b (1572)** + **c(658)** references combined in EndNote X7, with automatic and manual de-duplications yielding **(1353)** unique records				

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

Table S2 Papers excluded from quantitative analysis

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

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

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

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

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

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

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

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

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

Table S3 Cochrane risk of bias

Publication	Outcome	BIAS						
		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

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

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

Table S4 GRADE evidence

PDT vs placebo-PDT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT	Placebo-PDT	Relative (95% CI)	Absolute		
Clearance of treated BCC (3 months initial lesion clearance) lesion: MAL-PDT vs placebo												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/75 (73.3%)	26.7%	RR 2.75 (1.84 to 4.1)	467 more per 1000 (from 224 more to 828 more)	⊕⊕⊕O MODERATE	CRITICAL
Severe pain (leading to break in treatment/use of local analgesia) patient: MAL-PDT vs placebo												
1	randomised trials	serious[1]	[2]	no serious indirectness	[2]	none	0/66 (0%)	0%	not pooled	not pooled	[2]	CRITICAL
Cosmetic outcome (excellent or good) lesion: MAL-PDT vs placebo												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/75 (56%)	18.7%	RR 3 (1.8 to 5.01)	374 more per 1000 (from 150 more to 750 more)	⊕⊕OO LOW	IMPORTANT
Treatment tolerability - low or manageable pain, patient: MAL-PDT vs placebo												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	60/66 (90.9%)	66.2%	RR 1.37 (1.14 to 1.66)	245 more per 1000 (from 93 more to 437 more)	⊕⊕OO LOW	IMPORTANT

[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] Unable to assess inconsistency, imprecision or outcome due to lack of events in either arm

[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 cryosurgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT	Cryosurgery	Relative (95% CI)	Absolute		
Clearance of treated BCC (3 months initial lesion clearance) lesion: PDT vs cryosurgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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
Sustained clearance of treated BCC (1 year) patient: MAL-PDT vs Cryosurgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	51/56 (91.1%)	92.3%	RR 0.99 (0.88 to 1.11)	9 fewer per 1000 (from 111 fewer to 102 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustained clearance of treated BCC (5 years) patient: MAL-PDT vs Cryosurgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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
Recurrence rate (1 year) patient (superficial): PDT vs cryosurgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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
Recurrence rate (1 year) patient (nodular): PDT vs cryosurgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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
Recurrence rate (>1 year <2 years) patient: PDT vs cryosurgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/51 (13.7%)	6.3%	RR 2.2 (0.6 to 8.01)	76 more per 1000 (from 25 fewer to 442 more)	⊕OOO VERY LOW	CRITICAL

Recurrence rate (>1 year <3 years) patient: PDT vs cryosurgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	CRITICAL
Recurrence rate (>1 year <4 years) patient: PDT vs cryosurgery												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	CRITICAL
Recurrence rate (>1 year <5 years) patient: PDT vs cryosurgery												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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)	⊕OOO VERY LOW	CRITICAL
Severe pain (leading to break in treatment/use of local analgesia) patient: PDT vs cryosurgery												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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	CRITICAL
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (3 months) assessed by investigator												
1	randomised trials	very serious[1]	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	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (3 months) assessed by patient												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	25/62 (40.3%)	19%	RR 2.13 (1.15 to 3.92)	215 more per 1000 (from 28 more to 555 more)	⊕OOO VERY LOW	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (1 year) assessed by investigator												
2	randomised trials	very serious[1]	no serious inconsistency	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)	⊕⊕OO LOW	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (1 year) assessed by patient												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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)	⊕OOO VERY LOW	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (2 years) assessed by investigator												
1	randomised trials	very serious[1]	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)	⊕⊕OO LOW	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (2 years) assessed by patient												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (3 years) assessed by investigator												
1	randomised trials	very serious[1]	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	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (4 years) assessed by investigator												
1	randomised trials	very serious[1]	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	IMPORTANT
Cosmetic outcome (excellent) patient: PDT vs cryosurgery (5 years) assessed by investigator												
1	randomised trials	very serious[1]	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	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs cryosurgery												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	46/62 (74.2%)	72.4%	RR 1.02 (0.83 to 1.27)	14 more per 1000 (from 123 fewer to 195 more)	⊕⊕⊕O MODERATE	IMPORTANT

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

PDT vs surgical excision

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT	Surgical	Relative (95% CI)	Absolute		
Clearance of treated sBCC (3 months initial lesion clearance) lesion: PDT vs surgical excision												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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
Clearance of treated nBCC (3 months initial lesion clearance) lesion: PDT vs surgical excision												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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
Sustained clearance of treated sBCC (1 year) lesion: PDT vs surgical excision												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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
Sustained clearance of treated nBCC (1 year) lesion: PDT vs surgical excision												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	57/69 (82.6%)	88.5%	RR 0.9 (0.8 to 1.01)	89 fewer per 1000 (from 177 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustained clearance of treated BCC (5 years) patient: PDT vs surgical excision												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	CRITICAL
Recurrence rate (>1 year <2 years) lesion: PDT vs surgical excision												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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	CRITICAL
Recurrence rate (>1 year <5 years) lesion: PDT vs surgical excision												
1	randomised	very	no serious	no serious	very serious[3]	none	5/49	3.9%	RR 2.65 (0.54	64 more per 1000 (from	⊕OOO	CRITICAL

	trials	serious[1]	inconsistency	indirectness			(10.2%)		to 13.05)	18 fewer to 470 more)	VERY LOW	
Cosmetic outcome (excellent or good) patient: PDT vs surgical excision (3 months) assessed by investigator												
1	randomised trials	serious[1]	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	IMPORTANT
Cosmetic outcome (excellent or good) patient: PDT vs surgical excision (3 months) assessed by patient												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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	IMPORTANT
Cosmetic outcome (excellent or good) sBCC patient: PDT vs surgical excision (1 year) assessed by investigator												
1	randomised trials	serious[1]	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)	⊕⊕⊕O MODERATE	IMPORTANT
Cosmetic outcome (excellent or good) nBCC patient: PDT vs surgical excision (1 year) assessed by investigator												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	IMPORTANT
Cosmetic outcome (excellent or good) nBCC patient: PDT vs surgical excision (1 year) assessed by patient												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	IMPORTANT
Cosmetic outcome (excellent or good) nBCC patient: PDT vs surgical excision (2 years) assessed by investigator												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	24/50 (48%)	34%	RR 1.41 (0.86 to 2.31)	139 more per 1000 (from 48 fewer to 445 more)	⊕OOO VERY LOW	IMPORTANT
Cosmetic outcome (excellent or good) nBCC patient: PDT vs surgical excision (2 years) assessed by patient												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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	IMPORTANT
Cosmetic outcome (excellent or good) nBCC patient: PDT vs surgical excision (5 years) assessed by investigator												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	11	-	MD 3.57 higher (1.7 to 5.44 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	11	-	MD 3.57 higher (1.7 to 5.44 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15	11	-	MD 1.06 higher (0.41 lower to 2.53 higher)	⊕OOO VERY LOW	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision (6 hours after treatment) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15	11	-	MD 0.66 lower (2.3 lower to 0.98 higher)	⊕OOO VERY LOW	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision (24 hours after treatment) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15	11	-	MD 0.4 lower (1.7 lower to 0.9 higher)	⊕OOO VERY LOW	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision (48 hours after treatment) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	11	-	MD 0.6 lower (1.72 lower to 0.52 higher)	⊕⊕OO LOW	IMPORTANT
Treatment tolerability - low or manageable pain PDT vs Surgical excision (1 week after treatment) (Better indicated by lower values)												
1	randomised trials	serious[1]	[4]	no serious indirectness	[4]	none	15	11	-	not pooled	[4]	IMPORTANT

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

PDT vs topicals

Quality assessment							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 of treated BCC (3 months initial lesion clearance) patient: PDT vs topicals (imiquimod)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	165/202 (81.7%)	85.9%	RR 0.95 (0.87 to 1.04)	43 fewer per 1000 (from 112 fewer to 34 more)	⊕⊕OO LOW	CRITICAL
Clearance of treated BCC (3 months initial lesion clearance) patient: PDT vs topicals (fluorouracil)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	165/202 (81.7%)	86.6%	RR 0.94 (0.87 to 1.03)	52 fewer per 1000 (from 113 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
Sustained clearance of treated BCC (1 year) patient: PDT vs topicals (imiquimod)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	135/165 (81.8%)	90%	RR 0.91 (0.83 to 0.99)	81 fewer per 1000 (from 9 fewer to 153 fewer)	⊕⊕OO LOW	CRITICAL
Sustained clearance of treated BCC (1 year) patient: PDT vs topicals (fluorouracil)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	135/165 (81.8%)	88.5%	RR 0.92 (0.85 to 1.01)	71 fewer per 1000 (from 133 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
Sustained clearance of treated BCC (3 years) patient: PDT vs topicals (imiquimod)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	116/165 (70.3%)	84.1%	RR 0.84 (0.74 to 0.94)	135 fewer per 1000 (from 50 fewer to 219 fewer)	⊕OOO VERY LOW	CRITICAL
Sustained clearance of treated BCC (3 years) patient: PDT vs topicals (fluorouracil)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	116/165 (70.3%)	79.3%	RR 0.89 (0.78 to 1)	87 fewer per 1000 (from 174 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Severe pain patient: MAL-PDT vs topical (imiquimod)												
1	randomised	serious[1]	no serious	no serious	very serious[3]	none	35/202	18.7%	RR 0.93 (0.61	13 fewer per 1000 (from	⊕OOO	CRITICAL

	trials		inconsistency	indirectness			(17.3%)		to 1.41)	73 fewer to 77 more)	VERY LOW	
Severe pain patient: MAL-PDT vs topical (fluorouracil)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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
Cosmetic outcome (excellent or good) patient: PDT vs topicals (imiquimod)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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	IMPORTANT
Cosmetic outcome (excellent or good) patient: PDT vs topicals (fluorouracil)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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	IMPORTANT
Other adverse effects (serious and unexpected reactions): PDT vs topicals (imiquimod)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3,4]	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	IMPORTANT
Other adverse effects (serious and unexpected reactions): PDT vs topicals (fluorouracil)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3,4]	none	0/202 (0%)	2%	RR 0.11 (0.01 to 2.04)	18 fewer per 1000 (from 20 fewer to 21 more)	⊕OOO VERY LOW	IMPORTANT

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

Combination PDT vs PDT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination PDT	PDT	Relative (95% CI)	Absolute		
Clearance of treated BCC (3 months initial lesion clearance) patient: ALA-PDT + imiquimod vs ALA-PDT												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/24 (75%)	60%	OR 2 (0.42 to 9.58)	150 more per 1000 (from 213 fewer to 335 more)	⊕OOO VERY LOW	CRITICAL
Recurrence rate (>1 year) patient: ALA-PDT + imiquimod vs ALA-PDT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/24 (4.2%)	0%	RR 1.32 (0.06 to 29.92)	-	⊕⊕OO LOW	CRITICAL
Clearance of treated BCC (3 months initial lesion clearance) patient: AFXL-MAL-PDT vs MAL-PDT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	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	CRITICAL
Clearance of treated BCC (3 months initial lesion clearance) lesion: AFL-PDT (Er:YAG) vs MAL-PDT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	16/21 (76.2%)	42.9%	RR 1.78 (1.03 to 3.08)	335 more per 1000 (from 13 more to 892 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustained clearance of treated BCC (1 year) patient: AFXL-MAL-PDT vs MAL-PDT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	13/16 (81.3%)	64.3%	RR 1.26 (0.8 to 1.99)	167 more per 1000 (from 129 fewer to 637 more)	⊕⊕⊕O MODERATE	CRITICAL
Sustained clearance of treated BCC (1 year) lesion: AFL-PDT (Er:YAG) vs MAL-PDT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	15/16 (93.8%)	44.4%	RR 2.11 (1.01 to 4.43)	493 more per 1000 (from 4 more to 1000	⊕⊕⊕O MODERATE	CRITICAL

										more)		
Recurrence rate (1 year) lesion: AFXL-MAL-PDT vs MAL-PDT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	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	CRITICAL
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (3 months) assessed by investigator												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	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	IMPORTANT
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (3 months) assessed by patient												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	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	IMPORTANT
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (6 months) assessed by investigator												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	12/16 (75%)	37.5%	RR 2 (1 to 4)	375 more per 1000 (from 0 more to 1000 more)	⊕⊕⊕O MODERATE	IMPORTANT
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (6 months) assessed by patient												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	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	IMPORTANT
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (9 months) assessed by investigator												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	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	IMPORTANT
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (9 months) assessed by patient												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	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	IMPORTANT
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (1 year) assessed by investigator												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	8/16 (50%)	25%	RR 2 (0.75 to 5.33)	250 more per 1000 (from 62 fewer to 1000 more)	⊕⊕⊕O MODERATE	IMPORTANT
Cosmetic outcome (excellent) patient: AFXL-MAL-PDT vs MAL-PDT (1 year) assessed by patient												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/16 (56.3%)	43.8%	RR 1.29 (0.64 to 2.6)	127 more per 1000 (from 158 fewer to 701 more)	⊕⊕OO LOW	IMPORTANT
Cosmetic outcome (excellent) lesion: AFL-PDT (Er:YAG) vs MAL-PDT assessed by investigator												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/21 (57.1%)	57.1%	RR 1 (0.59 to 1.69)	0 fewer per 1000 (from 234 fewer to 394 more)	⊕⊕OO LOW	IMPORTANT
Other adverse effects (hyperpigmentation) patient: AFL-PDT (Er:YAG) vs MAL-PDT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/18 (66.7%)	56.3%	RR 1.19 (0.69 to 2.04)	107 more per 1000 (from 175 fewer to 586 more)	⊕⊕OO LOW	IMPORTANT
Other adverse effects (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (3 months)												
1	randomised trials	no serious risk of bias	[3]	no serious indirectness	[3]	none	0/16 (0%)	0%	not pooled	not pooled		IMPORTANT
Other adverse effects (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	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	IMPORTANT
Other adverse effects (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (9 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	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	IMPORTANT
Other adverse effects (hyperpigmentation) patient: AFXL-MAL-PDT vs MAL-PDT (1 year)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	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	IMPORTANT
Treatment tolerability - low or manageable pain: AFL-PDT (Er:YAG) vs MAL-PDT												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	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	IMPORTANT

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

3 Unable to assess inconsistency, imprecision or outcome due to lack of events in either arm

Combination PDT vs surgical excision

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination PDT	Surgical	Relative (95% CI)	Absolute		
Clearance of treated BCC (3 months initial lesion clearance) nodular lesion: Combination PDT vs surgical excision												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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 clearance of treated BCC (1 year) nodular lesion: Combination PDT vs surgical excision												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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 clearance of treated BCC (5 years) lesion: Combination PDT vs surgical excision												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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
Recurrence rate (>1 year <2 years) lesion: Combination PDT vs surgical excision												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3,4]	none	5/69 (7.2%)	0%	RR 13.2 (0.74 to 234.59)	-	⊕OOO VERY LOW	CRITICAL
Recurrence rate (>1 year <5 years) lesion: Combination PDT vs surgical excision												
1	randomised	very	no serious	no serious	serious[3,4]	none	12/69	0%	RR 30 (1.81 to	-	⊕OOO	CRITICAL
	trials	serious[1]	inconsistency	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 assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractionated PDT	PDT	Relative (95% CI)	Absolute		
Sustained clearance of treated BCC (1 year) lesion: ALA-PDT (2-fold) vs ALA-PDT (single)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	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 clearance of treated BCC (5 years) lesion: PDT (2-fold) vs PDT (single)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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 pain (leading to break in treatment/use of local analgesia) patient: ALA-PDT (2-fold) vs ALA-PDT (single)												
1	randomised trials	serious[1]	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	CRITICAL

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

Table S5 Non-pain adverse events (AE)

Study (Comparator)	Assessment of adverse effects*	Notes on adverse effects other than pain*
Foley 2009[1] (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[2] (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[3] (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%, severe 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[4] (Surgery)		Not stated
Mosterd 2008[5] Roozeboom 2013[6] (Surgery)	Adverse events of the two treatment modalities were documented at review	Secondary wound infection was observed once after ALA–PDT treatment
Rhodes 2004[7] Rhodes 2007[8] (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[9] (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[10] Roozeboom 2016[11] Jansen 2017[12] (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%), blistering (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[13] (Er:YAG-laser, Er:YAG-laser/PDT)	None described	Not described
Haak 2015[14] (CO_2-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) at1 year AFL-MAL-PDT 0% vs MAL-PDT 13% : RR 0.20: 95%CI 0.01–3.86, p = 0.29
Choi 2016[15] (Er:YAG-AFL/PDT)		Although no patient discontinued the study because of adverse events, all patients in both groups experienced some adverse events, most commonly crusting. No patients discontinued the study because of adverse events but all patients reported ≥ 1 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[16] (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 (Comparator)	Assessment of adverse effects*	Notes on adverse effects other than pain*
De Haas 2006[17] De Vijlder 2012[18] (Fractionated PDT)		
Kessels 2017[19] (Fractionated ALA-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 17.8% vs 20%, p = 0.835; not available 9.6% vs 10%.

*These are adverse events other than pain, therefore excluding reference to pain, burning sensation, stinging, tingling etc.
MAL, methyl aminolaevulinate; ALA, 5-aminolaevulinic acid; PDT, photodynamic therapy; CI, 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; CO2-AFL, carbon dioxide Ablative Fractional Laser.

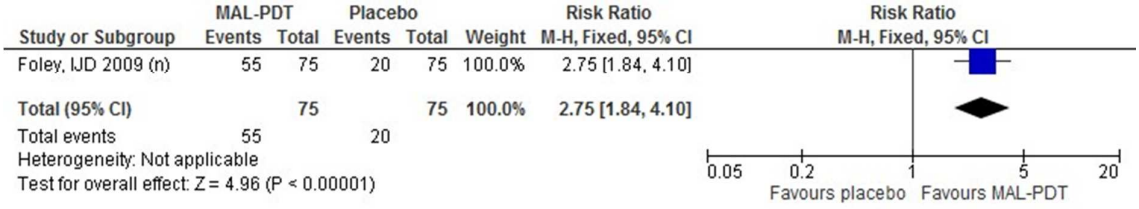
Appendix S1 Forest plots

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

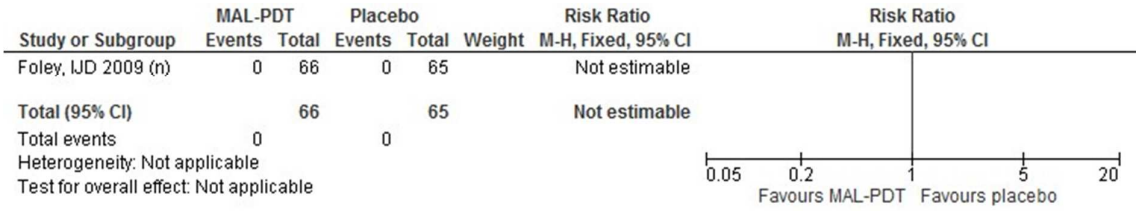
NB: If the outcome being measured is positive i.e. clearance the intervention will appear on the righthand axis of the forest plots. If negative i.e. severe pain, the intervention will appear on the left hand axis of the forest plots.

PDT vs. Placebo-PDT

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

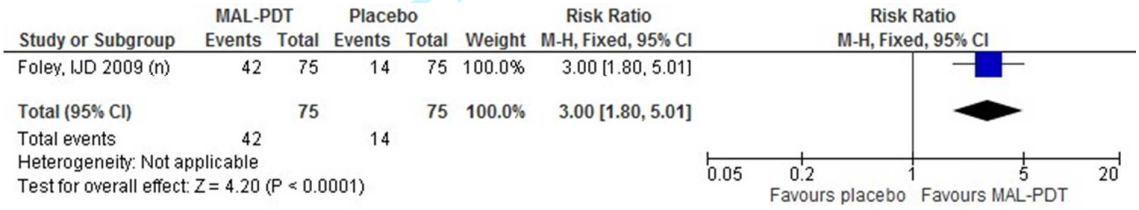


Severe pain (leading to break in treatment/use of local analgesia) nBCC patient: MAL-PDT vs placebo-PDT (vehicle cream)

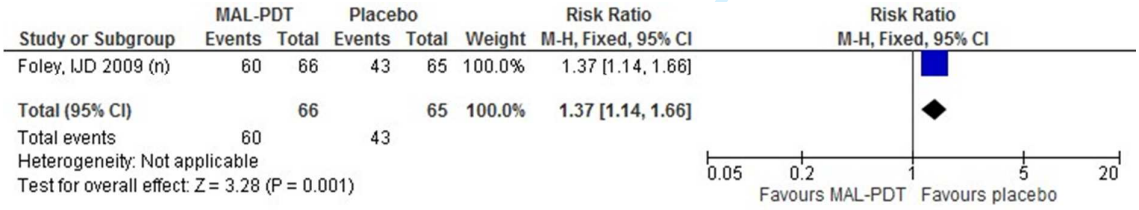


(NB. The risk ratio cannot be estimated when there are no events on either arm)

Cosmetic outcome (excellent or good) nBCC lesion: MAL-PDT vs placebo-PDT (vehicle cream)

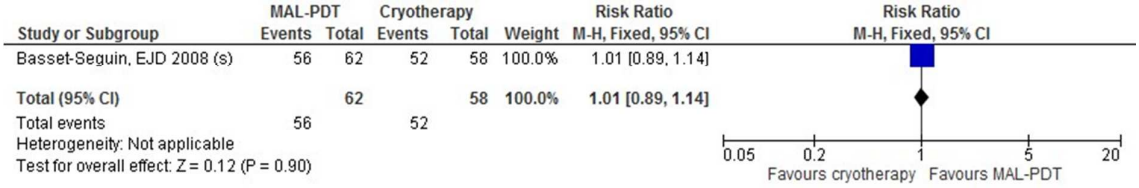


Treatment tolerability - low or manageable pain, nBCC patient: MAL-PDT vs placebo-PDT (vehicle cream)



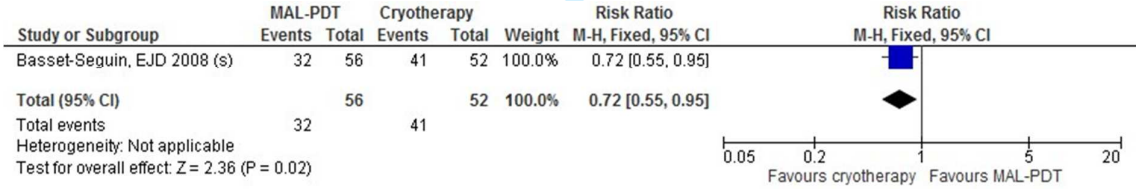
PDT vs. Cryosurgery

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

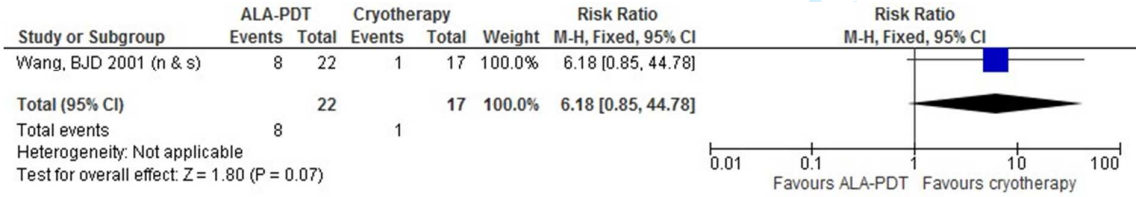


Sustained clearance of treated sBCC (1 year) patient: MAL-PDT vs cryosurgery

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

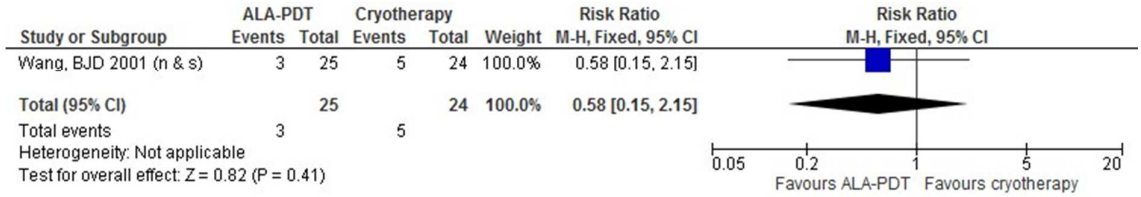


Recurrence rate (1 year) sBCC patient: ALA-PDT vs cryosurgery



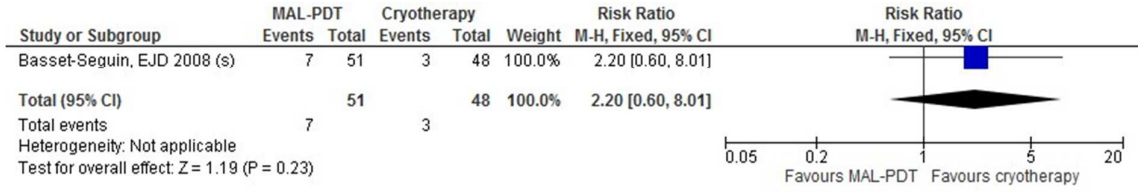
NB: Change in scale

Recurrence rate (1 year) nBCC patient: ALA-PDT vs cryosurgery

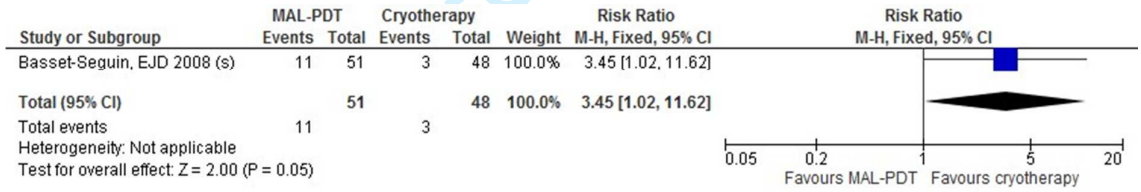


NB: Change in scale

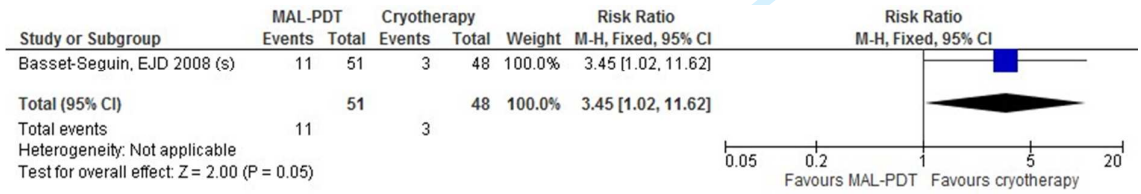
Recurrence rate (>1 year <2 years) sBCC patient: MAL-PDT vs cryosurgery



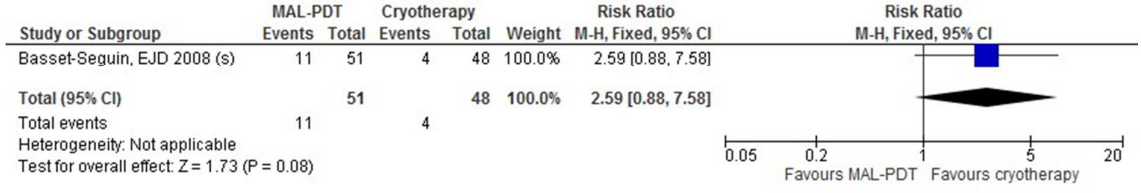
Recurrence rate (>1 year <3 years) sBCC patient: MAL-PDT vs cryosurgery



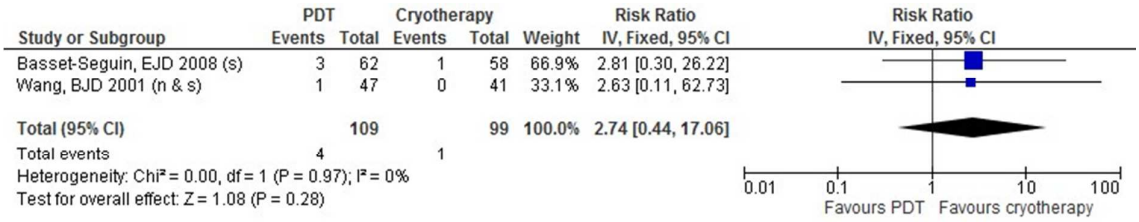
Recurrence rate (>1 year <4 years) sBCC patient: MAL-PDT vs cryosurgery



Recurrence rate (>1 year <5 years) sBCC patient: MAL-PDT vs cryosurgery

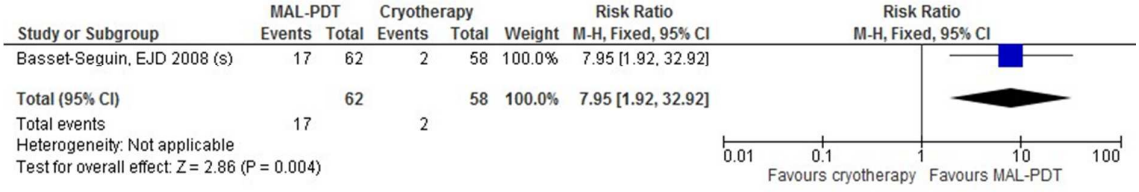


Severe pain (leading to break in treatment/use of local analgesia) BCC patient: PDT vs cryosurgery

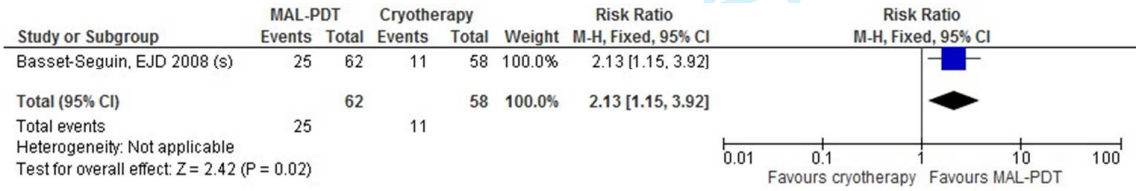


NB: Change in scale

Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (3 months) assessed by investigator



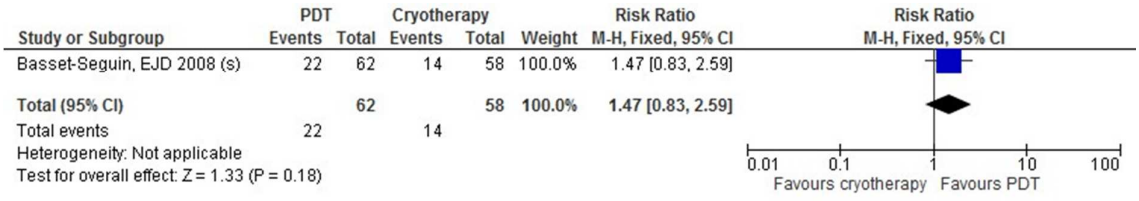
Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (3 months) assessed by patient



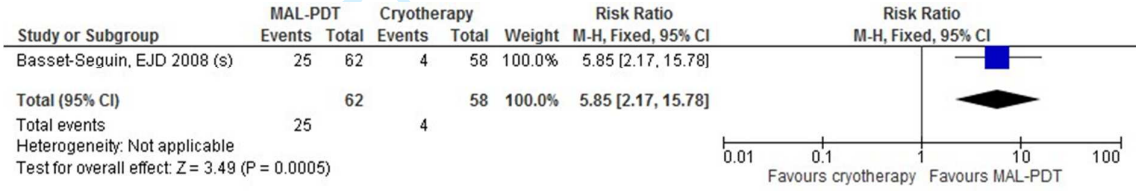
Cosmetic outcome (excellent) BCC patient: PDT vs cryosurgery (1 year) assessed by investigator

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

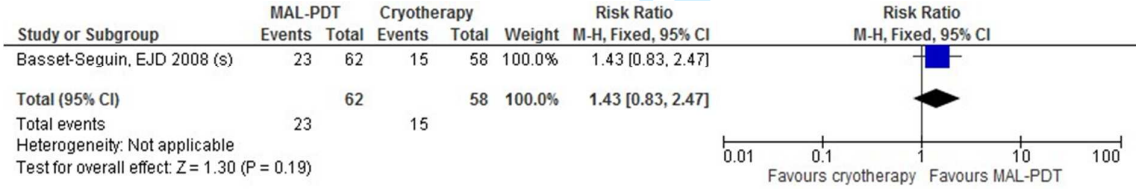
Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (1 year) assessed by patient



Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (2 years) assessed by investigator



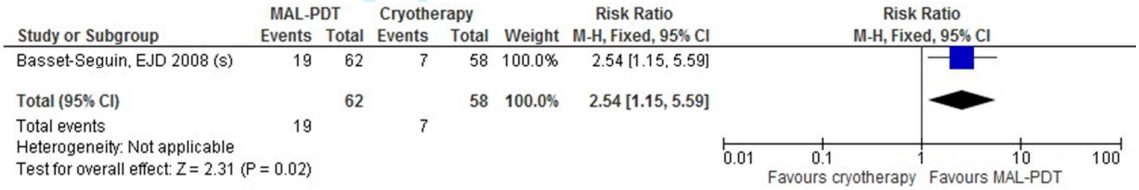
Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (2 years) assessed by patient



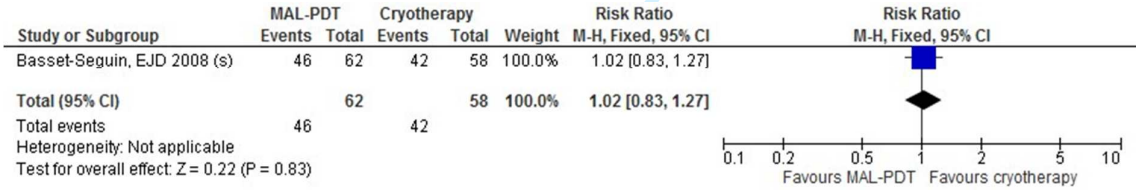
Cosmetic outcome (excellent) sBCC patient: MAL-PDT vs cryosurgery (3 years) assessed by investigator

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

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



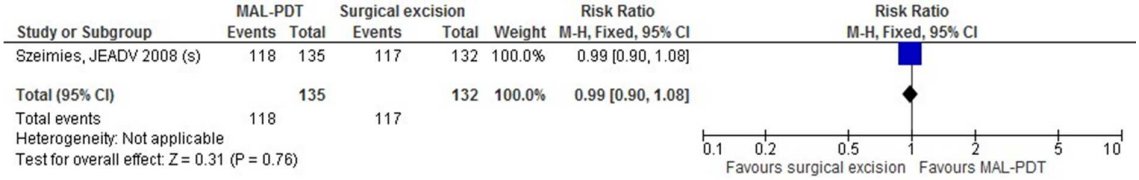
Treatment tolerability - low or manageable pain sBCC: MAL-PDT vs cryosurgery



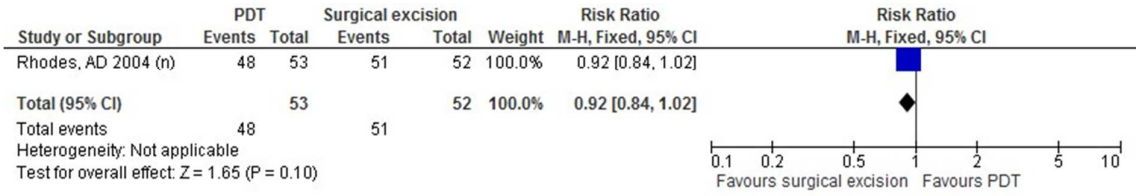
NB: Change in scale

PDT vs. Surgical excision

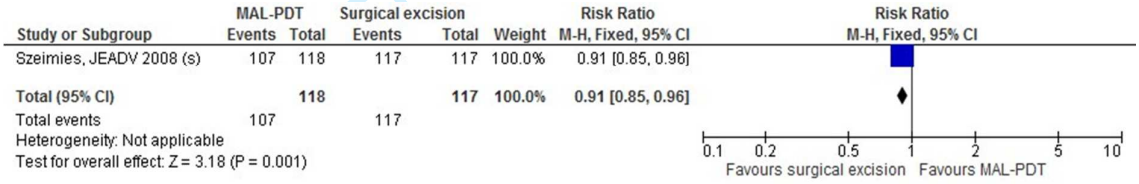
Clearance of treated sBCC (3 months initial lesion clearance) lesion: MAL-PDT vs surgical excision



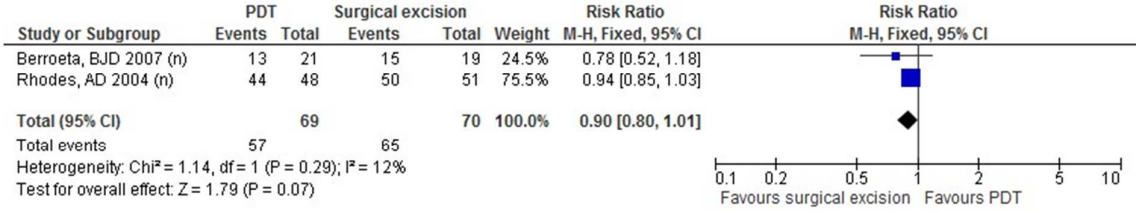
Clearance of treated nBCC (3 months initial lesion clearance) lesion: PDT vs surgical excision



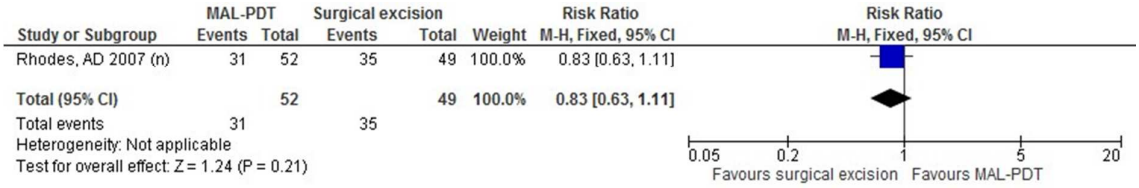
Sustained clearance of treated sBCC (1 year) lesion: MAL-PDT vs surgical excision



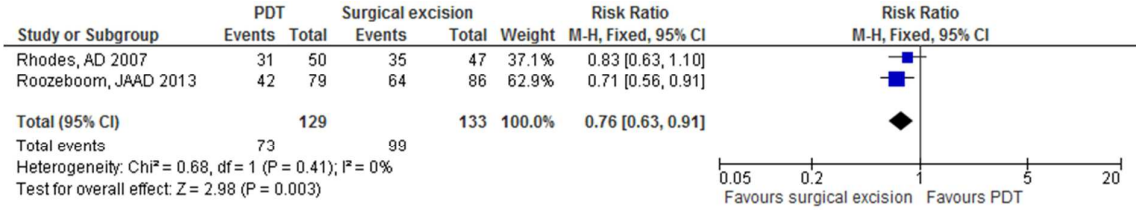
Sustained clearance of treated nBCC (1 year) lesion: PDT vs surgical excision



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

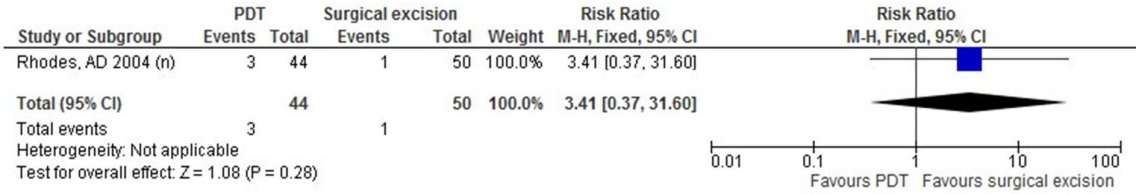


Sustained clearance of treated NMSC (5 years) lesion: PDT vs surgical excision



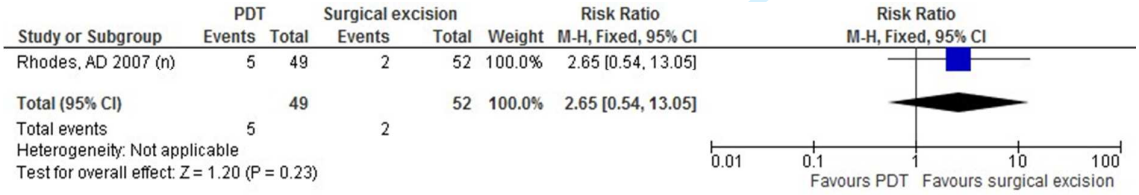
NB: Change in scale

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

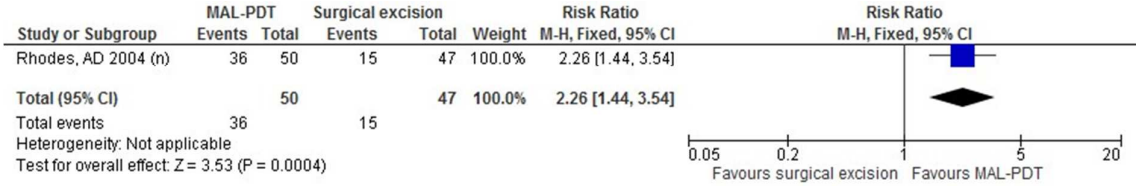


NB: Change in scale

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

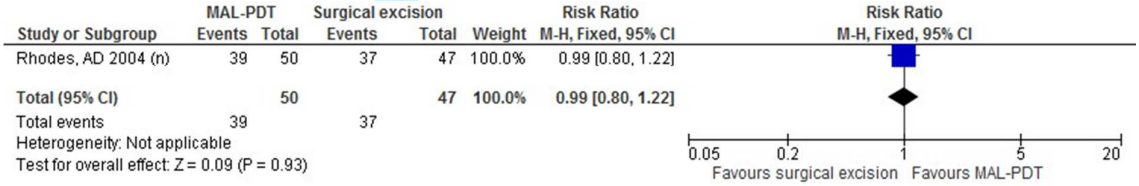


Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (3 months) assessed by investigator

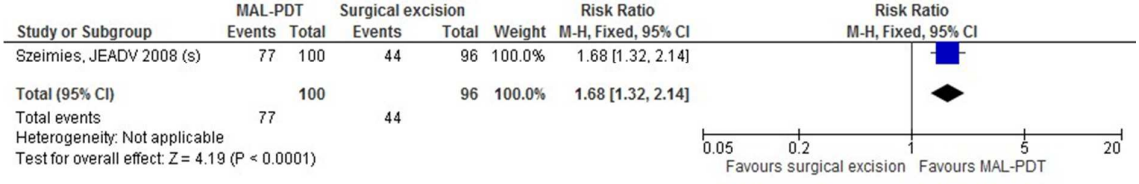


NB: Change in scale

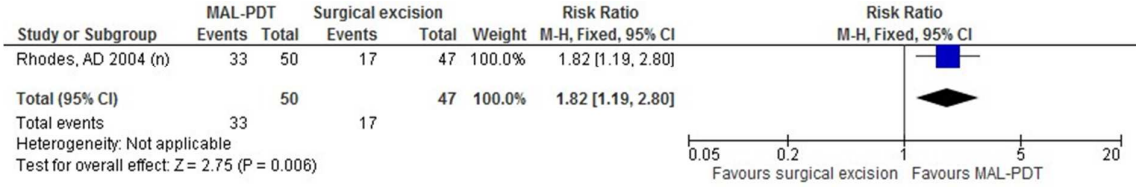
Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (3 months) assessed by patient



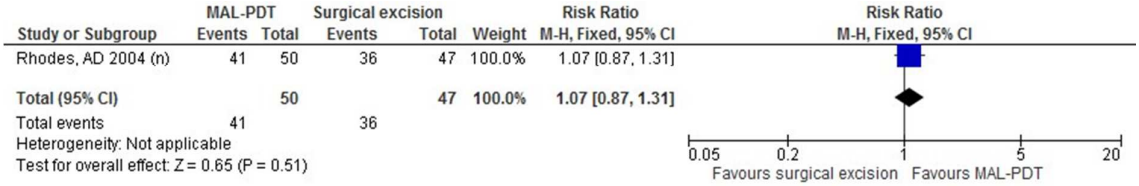
Cosmetic outcome (excellent or good) sBCC patient: MAL-PDT vs surgical excision (1 year) assessed by investigator



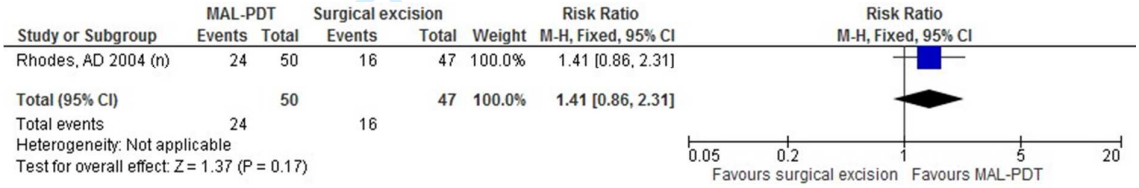
Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (1 year) assessed by investigator



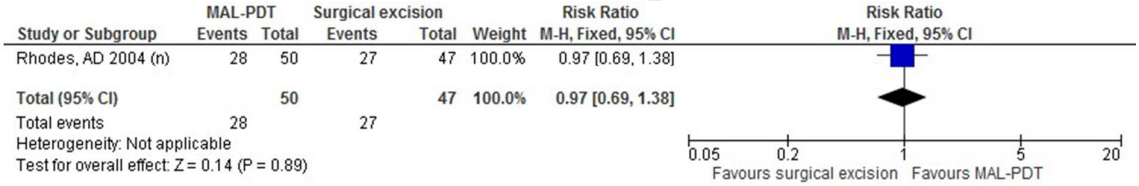
Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (1 year) assessed by patient



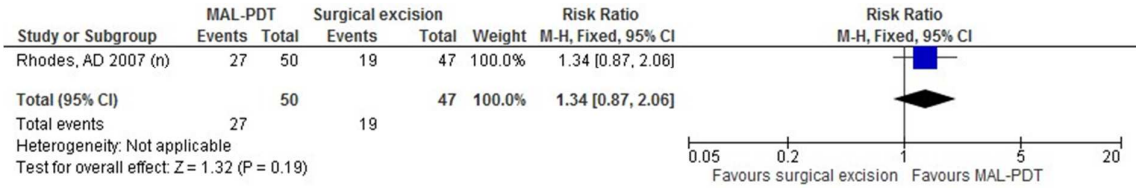
Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (2 years) assessed by investigator



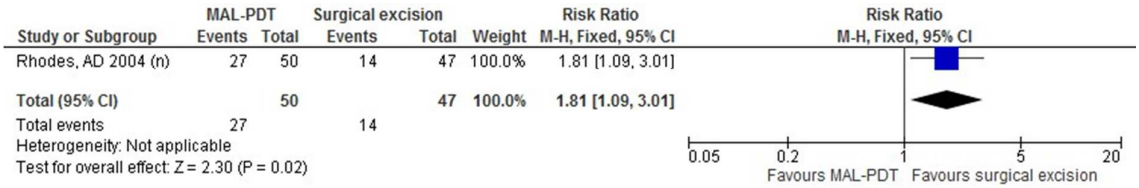
Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (2 years) assessed by patient



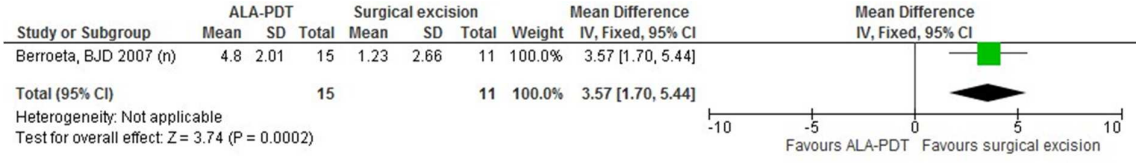
Cosmetic outcome (excellent or good) nBCC patient: MAL-PDT vs surgical excision (5 years) assessed by investigator



Treatment tolerability - low or manageable pain nBCC: MAL-PDT vs surgical excision

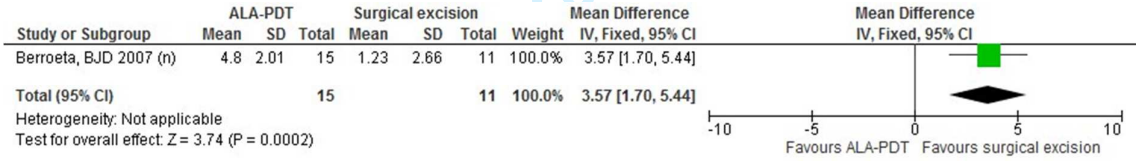


Treatment tolerability - low or manageable pain PDT vs Surgical excision (during treatment)

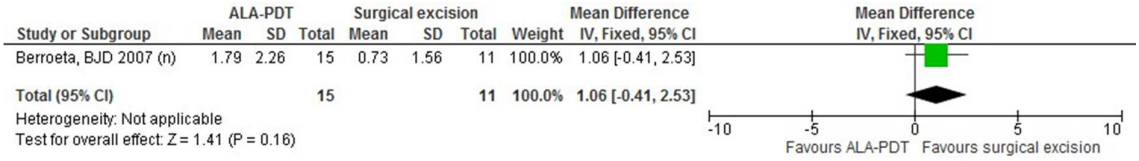


NB: Change in scale

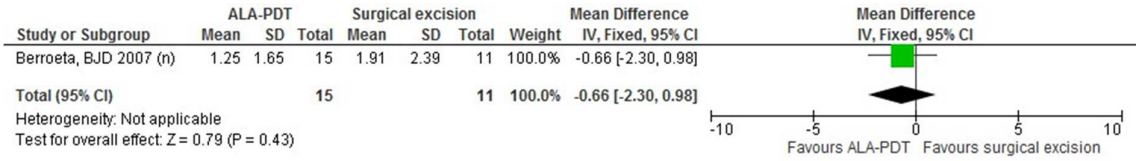
Treatment tolerability - low or manageable pain PDT vs Surgical excision (immediately after treatment)



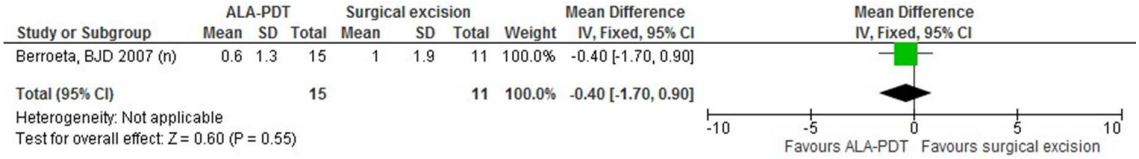
Treatment tolerability - low or manageable pain PDT vs Surgical excision (3 hours after treatment)



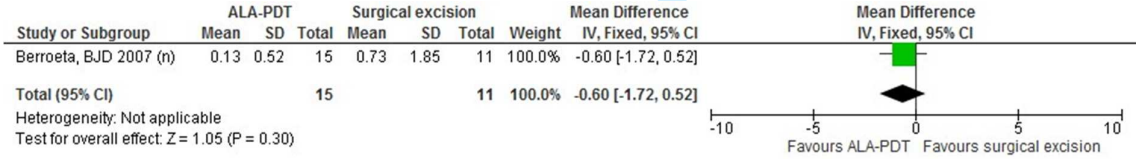
Treatment tolerability - low or manageable pain PDT vs Surgical excision (6 hours after treatment)



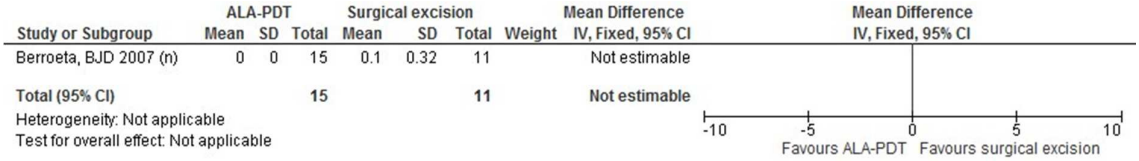
Treatment tolerability - low or manageable pain PDT vs Surgical excision (24 hours after treatment)



Treatment tolerability - low or manageable pain PDT vs Surgical excision (48 hours after treatment)



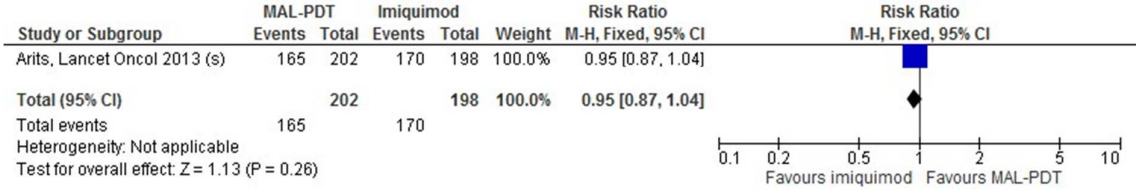
Treatment tolerability - low or manageable pain PDT vs Surgical excision (1 week after treatment)



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

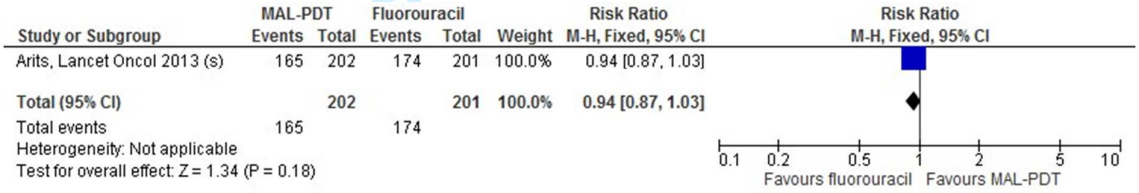
PDT vs. Topicals

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

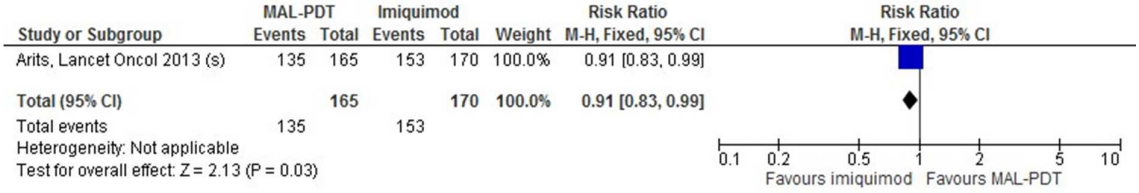


NB: Change in scale

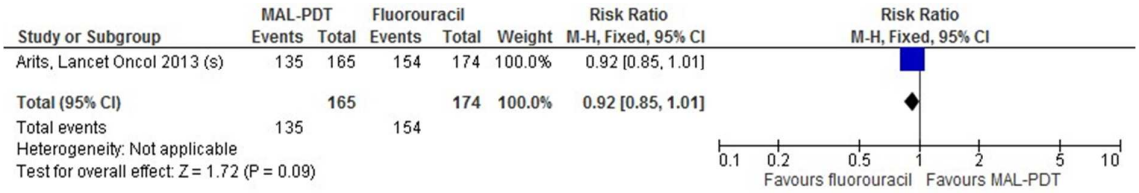
Clearance of treated sBCC (3 months initial lesion clearance) patient: MAL-PDT vs fluorouracil



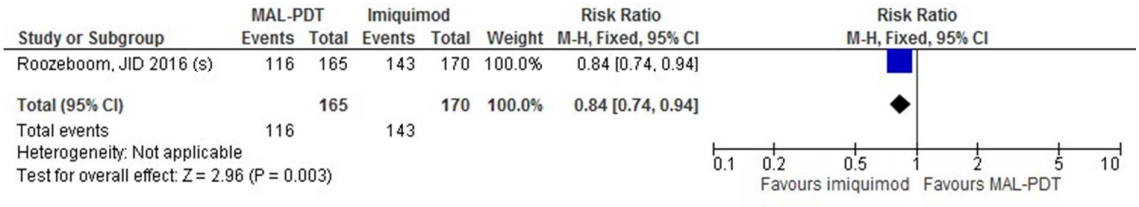
Sustained clearance of treated sBCC (1 year) patient: MAL-PDT vs imiquimod



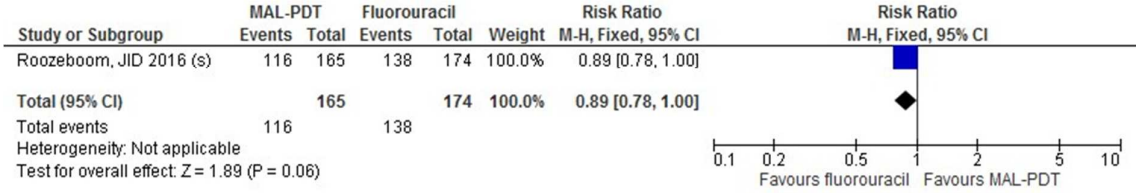
Sustained clearance of treated sBCC (1 year) patient: MAL-PDT vs fluorouracil



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



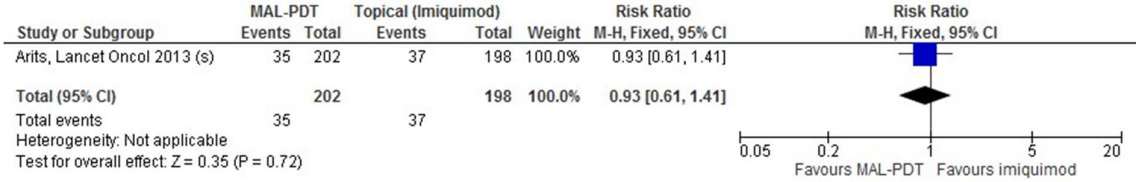
Sustained clearance of treated sBCC (3 years) patient: MAL-PDT vs fluorouracil



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

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

Severe pain sBCC patient: MAL-PDT vs imiquimod



NB: (1) Change in scale

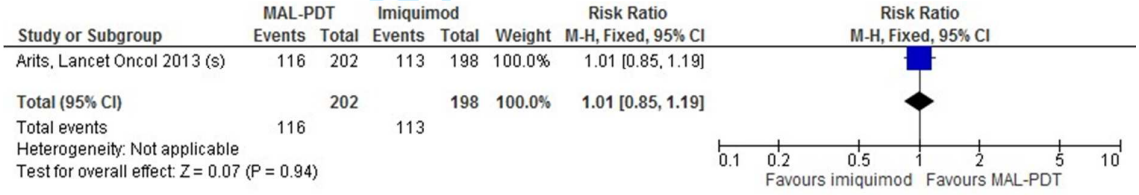
(2) Pain is measured at treatment and then each week for 2 weeks for PDT and each week for 4 weeks for fluorouracil and for 6 weeks for imiquimod. The events record is the cumulative number of patients that reported pain at each timepoint. This will almost certainly count patients who have experienced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

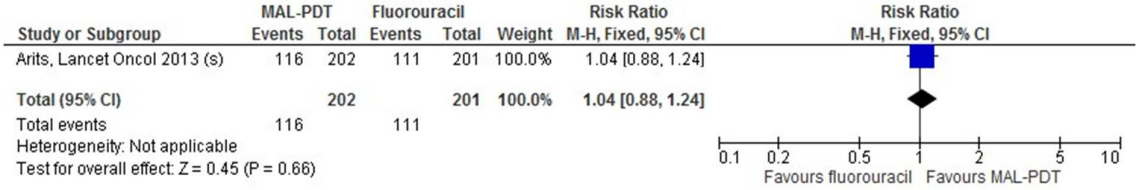
NB: Pain is measured at treatment and then each week for 2 weeks for PDT and each week for 4 weeks for fluorouracil and for 6 weeks for imiquimod. The events record is the cumulative number of patients that reported pain at each timepoint. This will almost certainly count patients who have experienced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

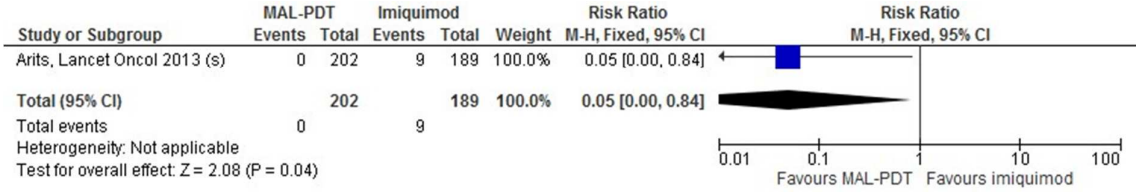


NB: Change in scale

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

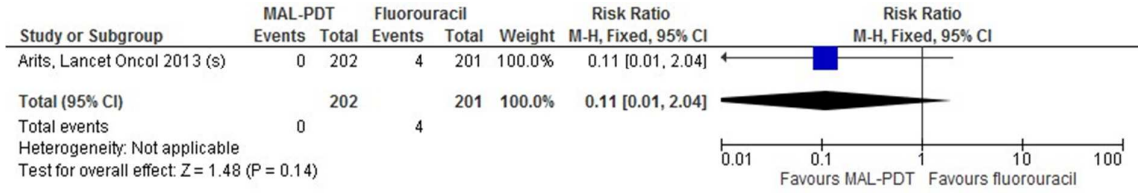


Other adverse effects (serious and unexpected reactions): PDT vs imiquimod



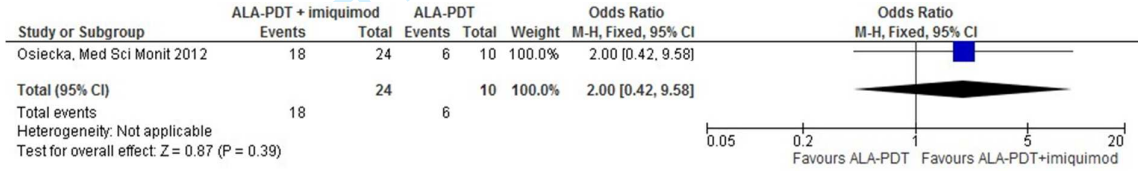
NB: Change in scale

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



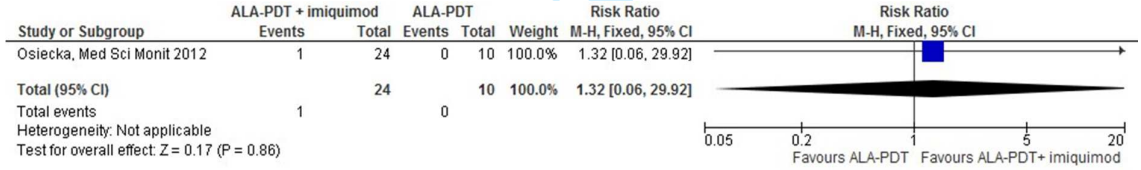
Combination PDT vs. PDT

Clearance of treated BCC (3 months initial lesion clearance) patient: ALA-PDT + imiquimod vs ALA-PDT



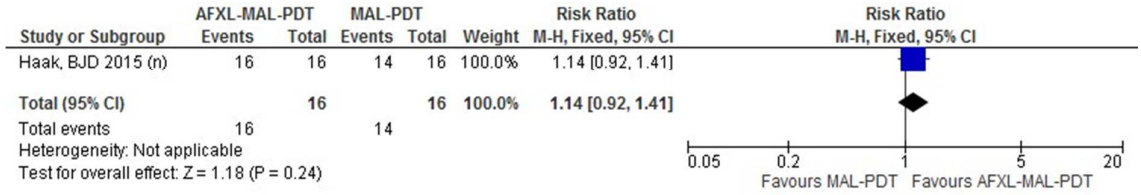
NB: Sub-type of BCC not stated.

Recurrence rate (>1 year) BCC patient: ALA-PDT + imiquimod vs ALA-PDT



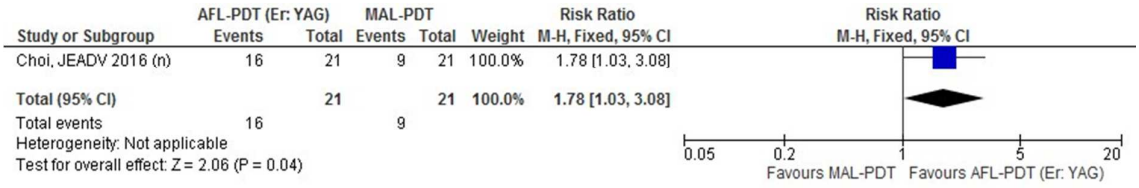
NB: Sub-type of BCC not stated.

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



NB: Change in scale

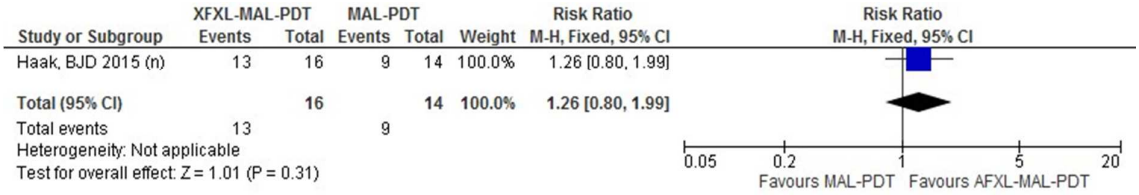
Clearance of treated nBCC (3 months initial lesion clearance) lesion: Er:YAG ablative fractional laser-PDT vs MAL-PDT



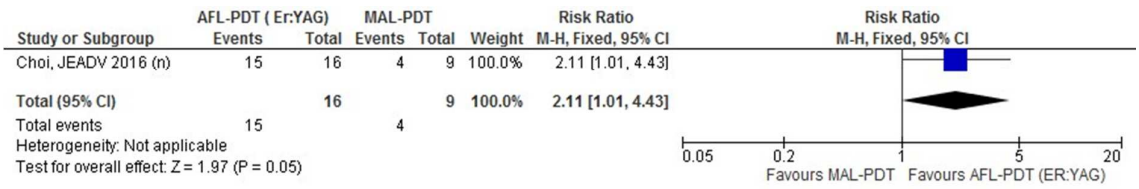
Clearance of treated nBCC (3 months initial lesion clearance) patient: Er:YAG-laser-PDT vs Er:YAG laser

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

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

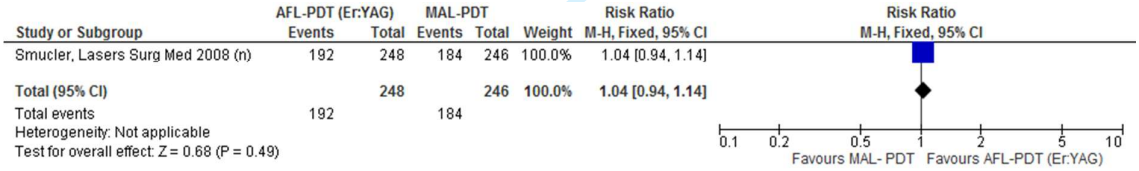


Sustained clearance of treated nBCC (1 year) lesion: Er:YAG ablative fractional laser-PDT vs MAL-PDT

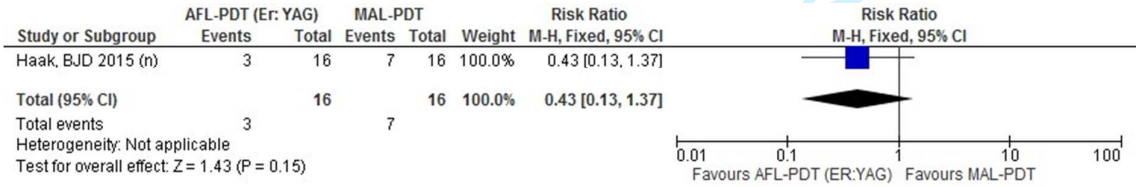


Sustained clearance of treated nBCC (1 year) lesion: Er:YAG-laser-PDT vs Er:YAG laser

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

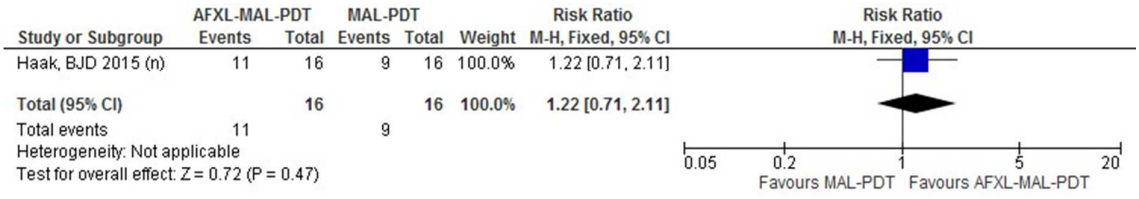


Recurrence rate (1 year) nBCC lesion: Ablative fractional laser -MAL-PDT vs MAL-PDT



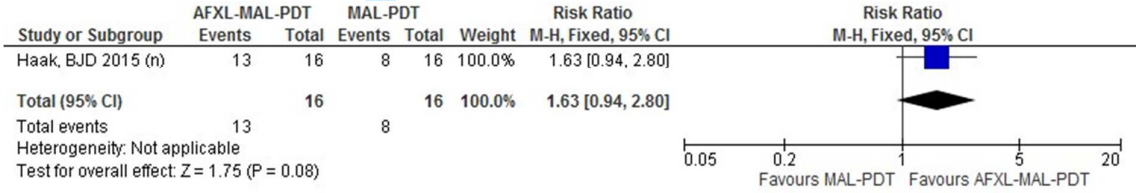
NB: Change of scale

Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (3 months) assessed by investigator

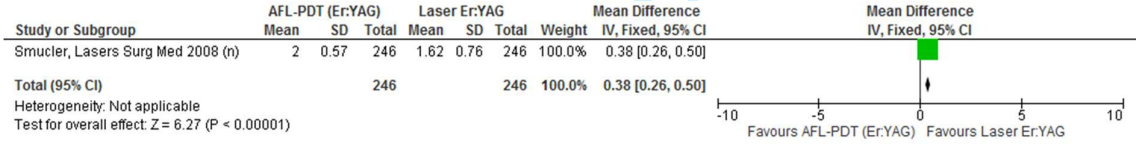


NB: Change in scale

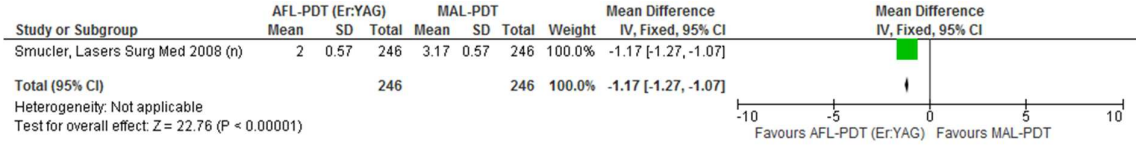
Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (3 months) assessed by patient



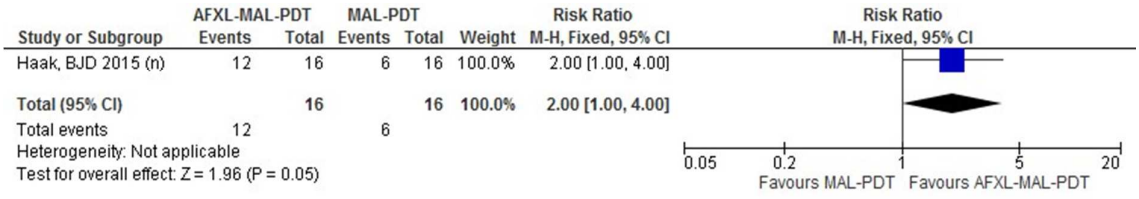
Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs Er:YAG (3 months) assessed by evaluator



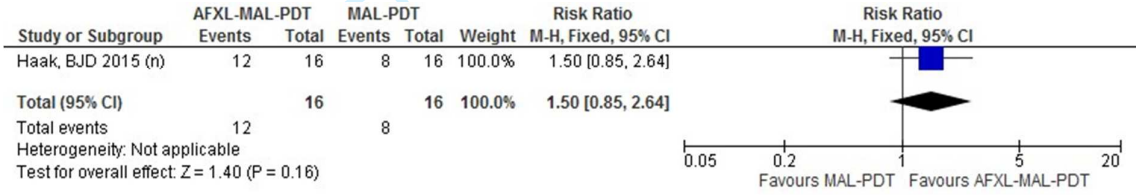
Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs MAL-PDT (3 months) assessed by evaluator



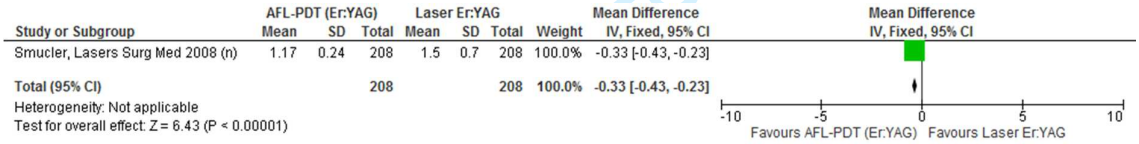
Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (6 months) assessed by investigator



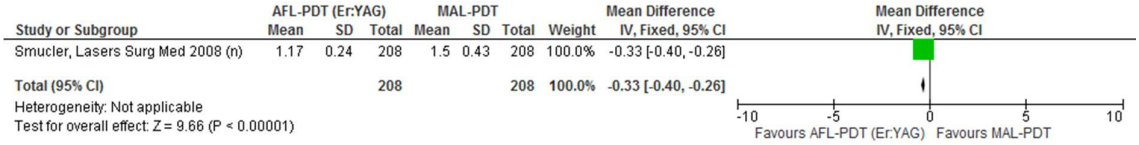
Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (6 months) assessed by patient



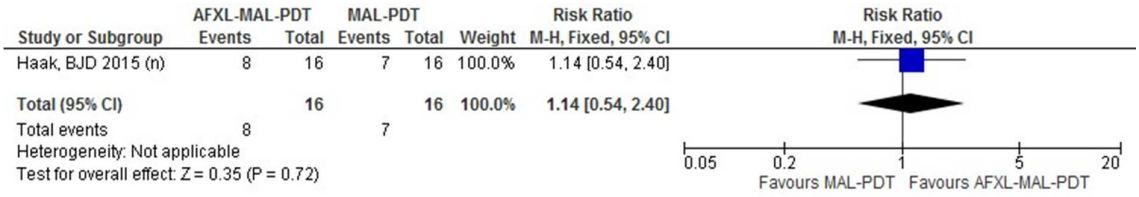
Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs Er:YAG (6 months) assessed by evaluator



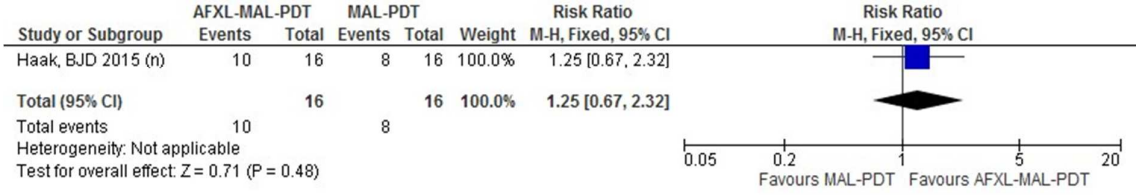
Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs MAL-PDT (6 months) assessed by evaluator



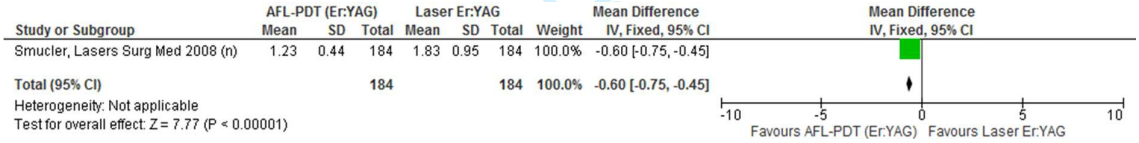
Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (9 months) assessed by investigator



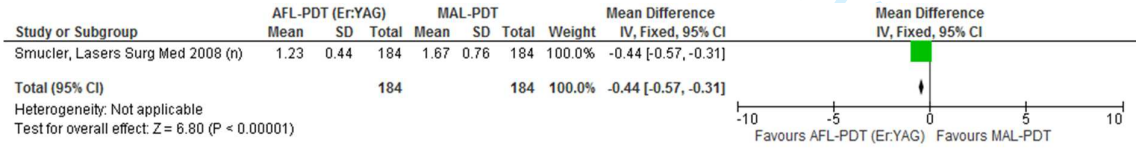
Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (9 months) assessed by patient



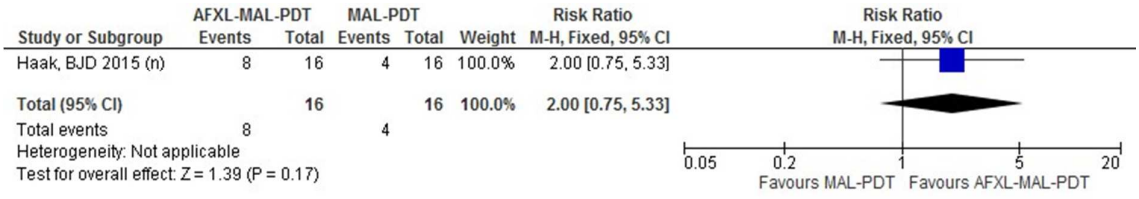
Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs Er:YAG (9 months) assessed by evaluator



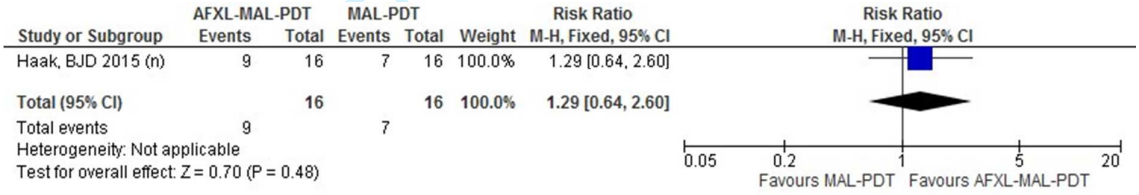
Cosmetic outcome (aesthetic result) nBCC patient: Er:YAG-laser-PDT vs MAL-PDT (9 months) assessed by evaluator



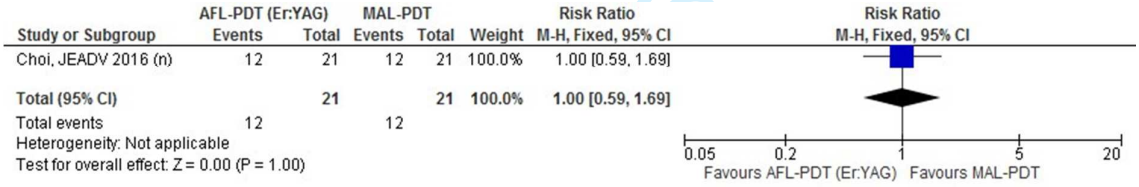
Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (1 year) assessed by investigator



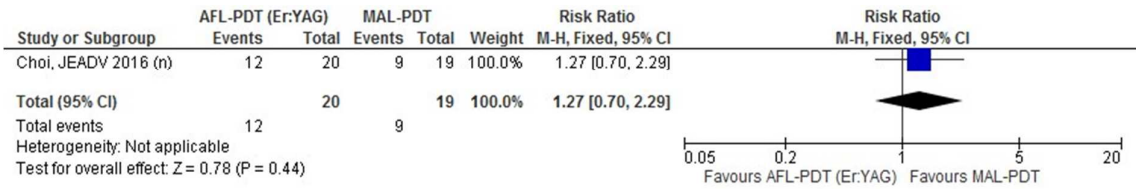
Cosmetic outcome (excellent) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (1 year) assessed by patient



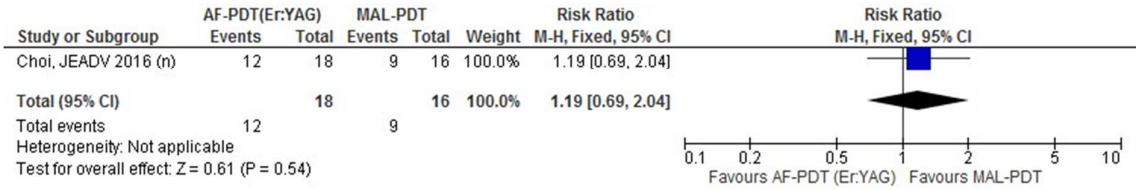
Cosmetic outcome (excellent) nBCC lesion: Er:YAG ablative fractional laser-PDT vs MALPDT assessed by investigator



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

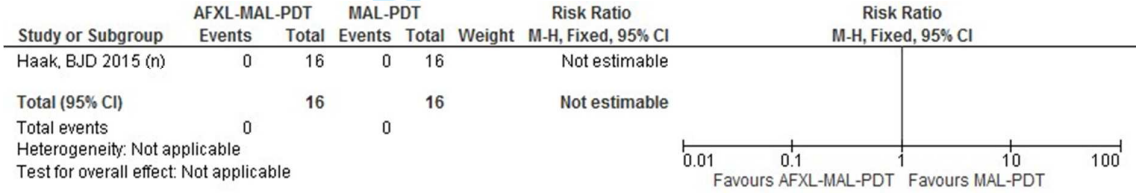


Other adverse effects (hyperpigmentation) patient: Er:YAG ablative fractional laser-PDT vs MAL-PDT



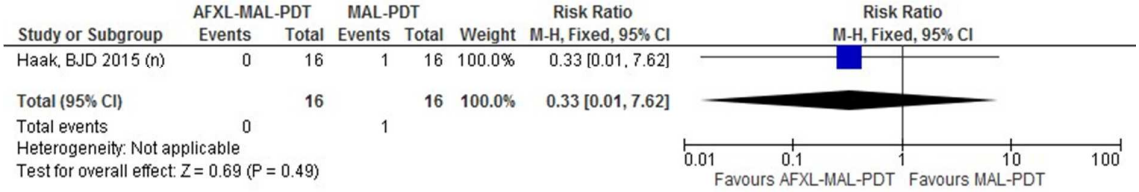
NB: Change in scale

Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (3 months)

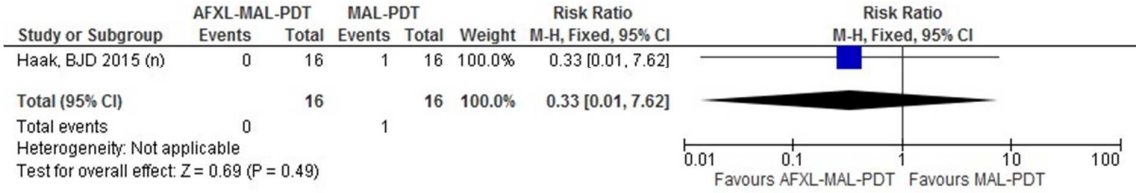


NB: (1) Change in scale, and
(2) the risk ratio cannot be estimated when there are no events on either arm.

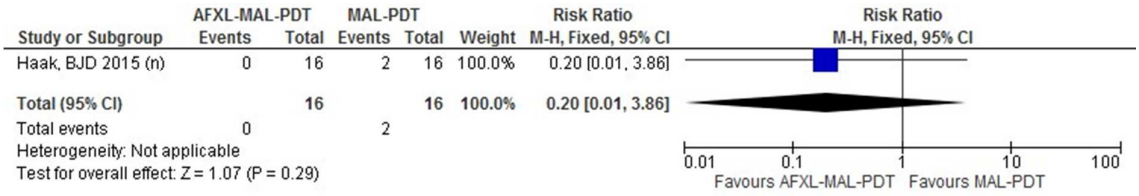
Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (6 months)



Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (9 months)

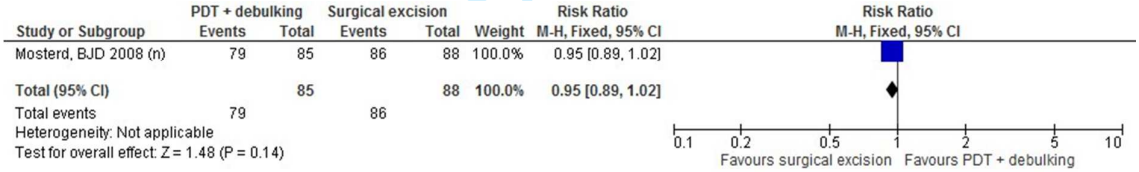


Other adverse effects (hyperpigmentation) nBCC patient: Ablative fractional laser-MAL-PDT vs MAL-PDT (1 year)



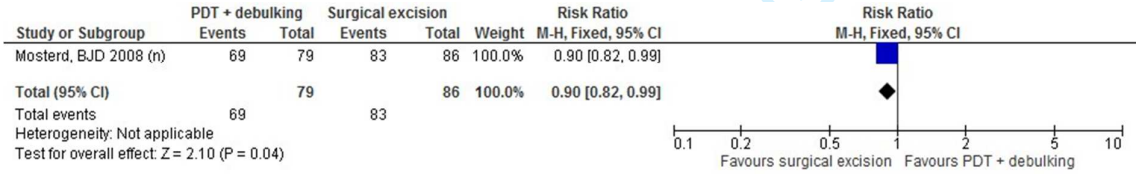
Combination PDT vs. surgical excision

Clearance of treated NMSC (3 months initial lesion clearance) nodular lesion: ALA-PDT + debulking vs surgical excision

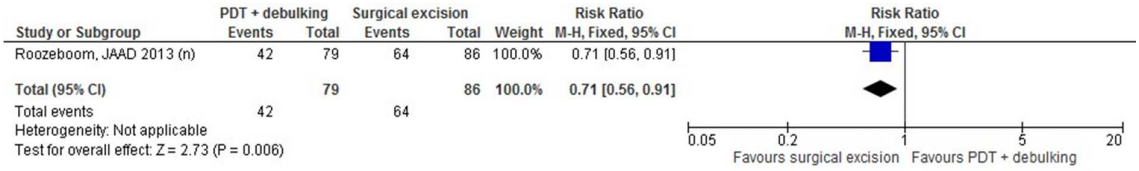


NB: Change in scale

Sustained clearance of treated NMSC (1 year) nodular lesion: ALA-PDT + debulking vs surgical excision

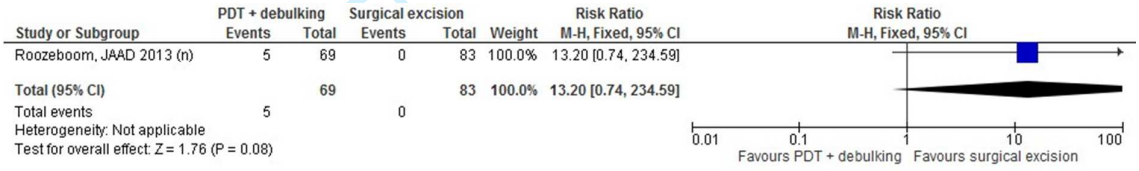


Sustained clearance of treated NMSC (5 years) lesion: ALA-PDT + debulking vs surgical excision



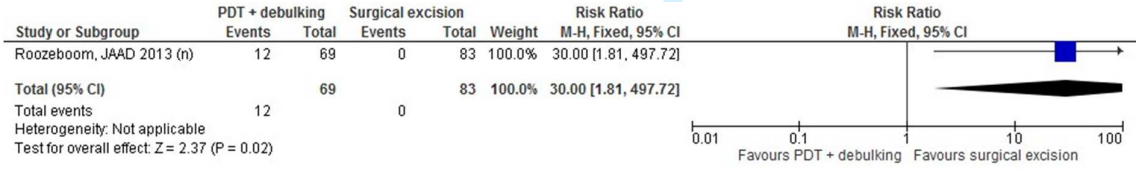
NB: Change in scale

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



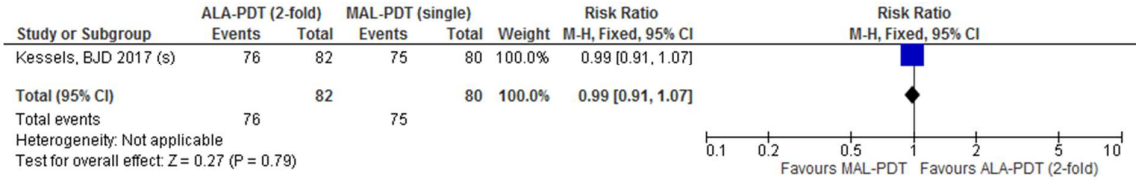
NB: Change in scale

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



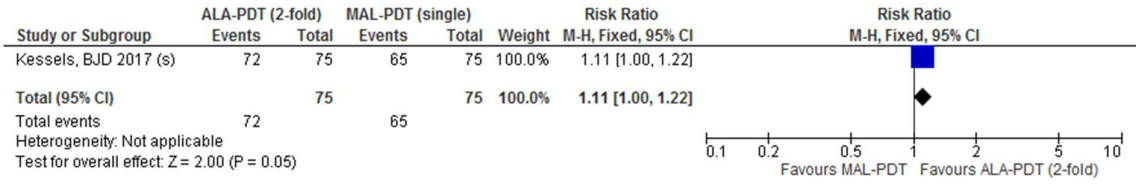
Fractionated PDT vs. PDT

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

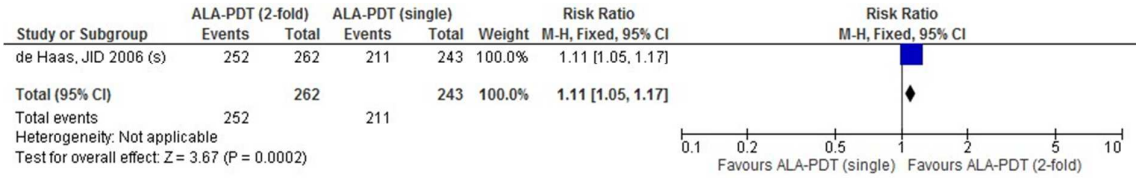


NB: Change in scale

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

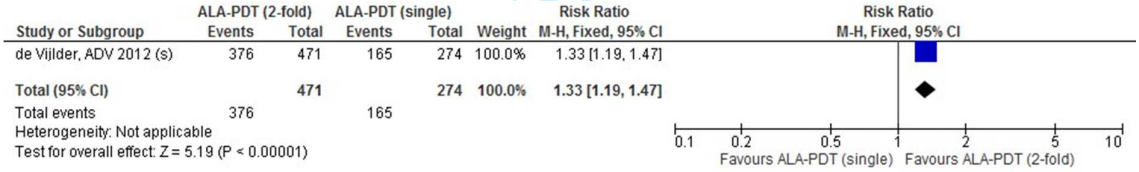


Sustained clearance of treated sBCC (1 year) lesion: Fractionated ALA-PDT vs ALA-PDT

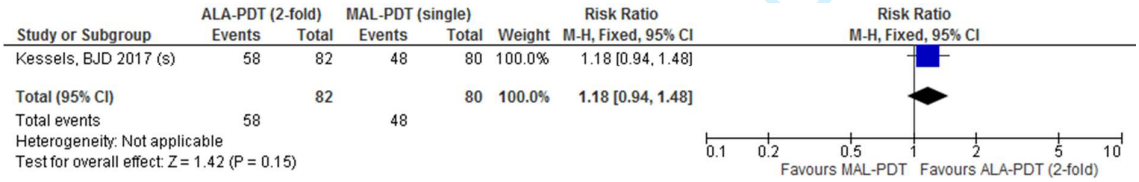


NB: Change in scale

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

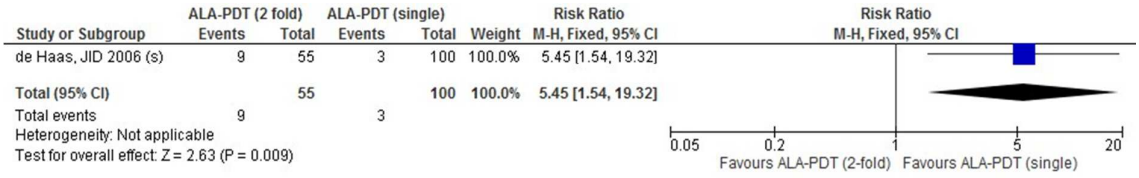


Cosmetic outcome (good or excellent) sBCC patient: Fractionated ALA-PDT vs MAL-PDT



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

Fractionated ALA-PDT vs ALA-PDT



NB: Change in scale

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