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Interventions for basal cell carcinoma of the skin (Review)

Thomson J, Hogan S, Leonardi-Bee J, Williams HC, Bath-Hextall FJ

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Interventions for basal cell carcinoma of the skin

Jason Thomson[1], Sarah Hogan[1], Jo Leonardi-Bee[2], Hywel C Williams[3], Fiona J Bath-Hextall[4]

[1]Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, London, UK. [2]Centre for Evidence Based Healthcare, Division of Epidemiology and Public Health, Clinical Sciences Building Phase 2, University of Nottingham, Nottingham, UK. [3]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK. [4]Emeritus Professor, Evidence Based Health Care, University of Nottingham, Nottingham, UK

Contact address: Jason Thomson, Jason.thomson@nhs.net.

A B S T R A C T

Background

Basal cell carcinoma (BCC) is the commonest cancer affecting white-skinned individuals, and worldwide incidence is increasing. Although rarely fatal, BCC is associated with significant morbidity and costs. First-line treatment is usually surgical excision, but alternatives are available. New published studies and the development of non-surgical treatments meant an update of our Cochrane Review (first published in 2003, and previously updated in 2007) was timely.

Objectives

To assess the effects of interventions for BCC in immunocompetent adults.

Search methods

We updated our searches of the following databases to November 2019: Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, and LILACS.

Selection criteria

Randomised controlled trials (RCTs) of interventions for BCC in immunocompetent adults with histologically-proven, primary BCC. Eligible comparators were placebo, active treatment, other treatments, or no treatment.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Primary outcome measures were recurrence at three years and five years (measured clinically) (we included recurrence data outside of these time points if there was no measurement at three or five years) and participant- and observer-rated good/excellent cosmetic outcome. Secondary outcomes included pain during and after treatment, early treatment failure within six months, and adverse effects (AEs). We used GRADE to assess evidence certainty for each outcome.

Main results

We included 52 RCTs (26 new) involving 6690 participants (median 89) in this update. All studies recruited from secondary care outpatient clinics. More males than females were included. Study duration ranged from six weeks to 10 years (average 13 months). Most studies (48/52) included only low-risk BCC (superficial (sBCC) and nodular (nBCC) histological subtypes). The majority of studies were at low or unclear risk of bias for most domains. Twenty-two studies were industry-funded: commercial sponsors conducted most of the studies assessing imiquimod, and just under half of the photodynamic therapy (PDT) studies.

Overall, surgical interventions have the lowest recurrence rates. For high-risk facial BCC (high-risk histological subtype or located in the facial 'H-zone' or both), there may be slightly fewer recurrences with Mohs micrographic surgery (MMS) compared to surgical excision (SE) at three years (1.9% versus 2.9%, respectively) (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.16 to 2.64; 1 study, 331 participants; low-certainty evidence) and at five years (3.2% versus 5.2%, respectively) (RR 0.61, 95% CI 0.18 to 2.04; 1 study, 259 participants; low-certainty evidence). However, the 95% CI also includes the possibility of increased risk of recurrence and no difference between treatments. There may be little to no difference regarding improvement of cosmetic outcomes between MMS and SE, judged by participants and observers 18 months post-operatively (one study; low-certainty evidence); however, no raw data were available for this outcome.

When comparing imiquimod and SE for nBCC or sBCC at low-risk sites, imiquimod probably results in more recurrences than SE at three years (16.4% versus 1.6%, respectively) (RR 10.30, 95% CI 3.22 to 32.94; 1 study, 401 participants; moderate-certainty evidence) and five years (17.5% versus 2.3%, respectively) (RR 7.73, 95% CI 2.81 to 21.3; 1 study, 383 participants; moderate-certainty evidence). There may be little to no difference in the number of participant-rated good/excellent cosmetic outcomes (RR 1.00, 95% CI 0.94 to 1.06; 1 study, 326 participants; low-certainty evidence). However, imiquimod may result in greater numbers of good/excellent cosmetic outcomes compared to SE when observer-rated (60.6% versus 35.6%, respectively) (RR 1.70, 95% CI 1.35 to 2.15; 1 study, 344 participants; low-certainty evidence). Both cosmetic outcomes were measured at three years.

Based on one study of 347 participants with high- and low-risk primary BCC of the face, radiotherapy may result in more recurrences compared to SE under frozen section margin control at three years (5.2% versus 0%, respectively) (RR 19.11, 95% CI 1.12 to 325.78; low-certainty evidence) and at four years (6.4% versus 0.6%, respectively) (RR 11.06, 95% CI 1.44 to 84.77; low-certainty evidence). Radiotherapy probably results in a smaller number of good participant- (RR 0.76, 95% CI 0.63 to 0.91; 50.3% versus 66.1%, respectively) or observer-rated (RR 0.48, 95% CI 0.37 to 0.62; 28.9% versus 60.3%, respectively) good/excellent cosmetic outcomes compared to SE, when measured at four years, where dyspigmentation and telangiectasia can occur (both moderate-certainty evidence).

Methyl-aminolevulinate (MAL)-PDT may result in more recurrences compared to SE at three years (36.4% versus 0%, respectively) (RR 26.47, 95% CI 1.63 to 429.92; 1 study; 68 participants with low-risk nBCC in the head and neck area; low-certainty evidence). There were no useable data for measurement at five years. MAL-PDT probably results in greater numbers of participant- (RR 1.18, 95% CI 1.09 to 1.27; 97.3% versus 82.5%) or observer-rated (RR 1.87, 95% CI 1.54 to 2.26; 87.1% versus 46.6%) good/excellent cosmetic outcomes at one year compared to SE (2 studies, 309 participants with low-risk nBCC and sBCC; moderate-certainty evidence).

Based on moderate-certainty evidence (single low-risk sBCC), imiquimod probably results in fewer recurrences at three years compared to MAL-PDT (22.8% versus 51.6%, respectively) (RR 0.44, 95% CI 0.32 to 0.62; 277 participants) and five years (28.6% versus 68.6%, respectively) (RR 0.42, 95% CI 0.31 to 0.57; 228 participants). There is probably little to no difference in numbers of observer-rated good/excellent cosmetic outcomes at one year (RR 0.98, 95% CI 0.84 to 1.16; 370 participants). Participant-rated cosmetic outcomes were not measured for this comparison.

AEs with surgical interventions include wound infections, graft necrosis and post-operative bleeding. Local AEs such as itching, weeping, pain and redness occur frequently with non-surgical interventions. Treatment-related AEs resulting in study modification or withdrawal occurred with imiquimod and MAL-PDT.

Authors' conclusions

Surgical interventions have the lowest recurrence rates, and there may be slightly fewer recurrences with MMS over SE for high-risk facial primary BCC (low-certainty evidence). Non-surgical treatments, when used for low-risk BCC, are less effective than surgical treatments, but recurrence rates are acceptable and cosmetic outcomes are probably superior. Of the non-surgical treatments, imiquimod has the best evidence to support its efficacy.

Overall, evidence certainty was low to moderate. Priorities for future research include core outcome measures and studies with longer-term follow-up.

PLAIN LANGUAGE SUMMARY

Interventions for basal cell carcinoma of the skin

Why is this question important?

Basal cell carcinoma (BCC) is the most common form of skin cancer among people with white skin.

BCC is not usually life-threatening but if left untreated, it can cause important disfigurement, especially on the face.

Surgical removal of the affected area and surrounding skin is usually the first option for treating BCC. Several different surgical approaches exist as well as non-surgical treatments, such as radiotherapy (high doses of radiation that kill cancer cells), and anti-cancer creams, gels and ointments.

We reviewed the evidence from research studies, to find out which treatments work best for BCC.

How did we identify and evaluate the evidence?

We searched for randomised controlled studies (studies where people are randomly put into one of two or more treatment groups), because these provide the most robust evidence about the effects of a treatment. We compared and summarised the evidence from all the studies. Finally, we rated our confidence in the evidence, based on factors such as study methods and sizes, and the consistency of findings across studies.

What did we find?

We found 52 studies that involved a total of 6690 adults with BCC. Most studies (48 out of 52) included hospital outpatients with small, superficial or nodular BCC. Studies lasted for between six weeks and 10 years (average duration: 13 months). Twenty-two studies were funded by pharmaceutical companies.

Our confidence in the evidence presented here is low to moderate, mainly because many studies were small.

Comparison between different surgical treatments

- Mohs micrographic surgery (a specialised surgical approach that removes less skin) may slightly decrease recurrence rates at three and five years compared to surgical excision (one of the most common surgical treatments for BCC).

-There may be little to no difference in how well scars heal between these two surgical treatments according to patients and observers (one study).

Surgery versus non-surgical treatments

Compared against surgical excision:

- Imiquimod (an anti-cancer cream) probably increases BCC recurrence rates at three and five years. There may be little to no difference in scar healing according to patients, although imiquimod may increase chances of scars healing well when healing is rated by an observer (one study).
- Radiotherapy may increase BCC recurrence rates at three and four years, and probably decreases chances of scars healing well (one study).
- MAL-PDT, a type of photodynamic therapy (that uses a light source and light-sensitive medicine to kill cancer cells), may increase BCC recurrence rates at three years. MAL-PDT probably increases chances of scars healing well (two studies).

Comparison of different non-surgical treatments

Compared against imiquimod:

- MAL-PDT probably increases BCC recurrence rates at three and five years. There is probably little to no difference in scar healing (one study);

What does this mean?

Overall, the evidence suggests that:

- surgery could reduce chances of BCC recurrence;
- non-surgical treatments such as anti-cancer creams or photodynamic therapy carry an increased chance of BCC recurrence, but could increase chances of scars healing well compared with surgery.

Complications with surgical treatments include wound infections, skin graft failure and bleeding after the procedure. Non-surgical treatments frequently lead to localised itching, weeping, pain and redness. Treatment-related side effects that caused modifications to the study or the withdrawal of participants occurred with imiquimod and MAL-PDT.

How-up-to date is this review?

The evidence in this Cochrane Review is current to November 2019.

SUMMARY OF FINDINGS

Summary of findings 1.   Mohs micrographic surgery compared to surgical excision for basal cell carcinoma of the skin

Mohs micrographic surgery compared to surgical excision for high-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from hospitals in the Netherlands
Intervention: Mohs micrographic surgery
Comparison: surgical excision

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Surgical excision	**Risk with Mohs micrographic surgery**				
Recurrence at 3 years	Study population		RR 0.64 (0.16 to 2.64)	331 (1 RCT)	⊕⊕⊖⊖ LOW [1]	Study measured outcome at 30 months.
	29 per 1000	19 per 1000 (5 to 77)				
Recurrence at 5 years	Study population		RR 0.61 (0.18 to 2.04)	259 (1 RCT)	⊕⊕⊖⊖ LOW [1]	-
	52 per 1000	32 per 1000 (9 to 107)				
Cosmetic outcome	Although a reported outcome, raw data were not available. The authors of Smeets 2004 state that overall, cosmetic outcomes did not significantly differ between groups. The cosmetic outcomes were judged by participants 18 months post-operatively, and photographs of a selected group of tumours (first 139 primary) were judged retrospectively by a panel of six individuals.		not estimable	(1 RCT)	⊕⊕⊖⊖ LOW [2]	-
Pain	No study addressed this outcome.		not estimable	-	-	-
Early treatment failure	No study addressed this outcome.		not estimable	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for very serious imprecision as very wide 95% CI indicating the possibility of important benefit or harm.
[2] Downgraded two levels for very serious indirectness as although the authors did compare the cosmetic outcomes between the two groups, they did not present the data for analysis.

Summary of findings 2.   Imiquimod compared to surgical excision for basal cell carcinoma of the skin

Imiquimod compared to surgical excision for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from hospitals in the UK
Intervention: 5% imiquimod cream
Comparison: surgical excision

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgical excision	Risk with Imiquimod				
Recurrence at 3 years	Study population		RR 10.30 (3.22 to 32.94)	401 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	-
	16 per 1000	164 per 1000 (51 to 526)				
Recurrence at 5 years	Study population		RR 7.73 (2.81 to 21.30)	383 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	-
	23 per 1000	175 per 1000 (64 to 481)				
Cosmetic outcome (good/excellent)	Study population		RR 1.70 (1.35 to 2.15)	344 (1 RCT)	⊕⊕⊖⊖ LOW [2]	Observer-rated at 3 years on a 6-point scale.[4]
	356 per 1000	606 per 1000 (481 to 766)				

Cosmetic outcome (good/excellent)	Study population		RR 1.00 (0.94 to 1.06)	326 (1 RCT)	⊕⊕⊝⊝ LOW [2]	Participant-rated at 3 years on a 6-point scale.[4]
	922 per 1000	922 per 1000 (866 to 977)				
Pain (moderate/severe)	Study population		RR 1.36 (0.98 to 1.88)	443 (1 RCT)	⊕⊕⊝⊝ LOW [3]	Pain measured during treatment.[5]
	219 per 1000	298 per 1000 (215 to 412)				
Pain (moderate/severe)	Study population		RR 0.47 (0.29 to 0.77)	439 (1 RCT)	⊕⊕⊝⊝ LOW [3]	Pain measured during follow-up.[5]
	199 per 1000	94 per 1000 (58 to 153)				
Early treatment failure	No study addressed this outcome		not estimable	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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[1] Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI.

[2] Downgraded one level for serious imprecision as only a single study with a small sample size and one level for serious risk of bias as unable to truly blind due to the nature of interventions (i.e. presence or absence of scar will unblind to treatment allocation).

[3] Downgraded one level for serious imprecision as only a single study with a small sample size and one level for serious risk of attrition bias as fewer pain data were available for the surgical excision group.

[4] 6-point scale: unable to see lesion, very poor, poor, fair, good, excellent.

[5] Measured on a scale from: no pain, mild pain, mild-to-moderate pain, moderate pain, moderate-to-severe pain and severe pain.

Summary of findings 3. Radiotherapy compared to surgical excision (with or without frozen section margin control) for basal cell carcinoma of the skin

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Radiotherapy compared to surgical excision for high- and low-risk BCC

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Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from a single hospital in France
Intervention: radiotherapy
Comparison: surgical excision (with or without frozen section margin control)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgical excision	Risk with radiotherapy				
Recurrence at 3 years	Study population		RR 19.11 (1.12 to 325.78)	347 (1 RCT)	⊕⊕⊝⊝ LOW [1]	-
	0 per 1000	52 per 1000 (6 to 1883)				
Recurrence at 4 years	Study population		RR 11.06 (1.44 to 84.77)	347 (1 RCT)	⊕⊕⊝⊝ LOW [2]	-
	6 per 1000	64 per 1000 (8 to 487)				
Cosmetic outcome (good/excellent)	Study population		RR 0.76 (0.63 to 0.91)	347 (1 RCT)	⊕⊕⊕⊝ MODERATE[3]	Participant-rated at 4 years on a 3-point scale.[4] ITT analysis performed.
	661 per 1000	502 per 1000 (416 to 601)				
Cosmetic outcome (good/excellent)	Study population		RR 0.48 (0.37 to 0.62)	347 (1 RCT)	⊕⊕⊕⊝ MODERATE[3]	Observer-rated at 4 years on a 3-point scale.[4] ITT analysis performed.
	603 per 1000	290 per 1000 (223 to 374)				
Pain	No study addressed this outcome.		not estimable	-	-	-
Early treatment failure	No study addressed this outcome.		not estimable	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **ITT:** intention-to-treat; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for very serious imprecision due to very wide 95% CI (although excludes 1, there is a greater than 100-fold difference).

[2] Downgraded one level for serious indirectness (outcome outside our pre-specified time-points) and downgraded one level for serious imprecision as only a single study with a small sample size.

[3] Downgraded one level for serious risk of bias as unable to truly blind due to the nature of interventions.

[4] 3-point scale: bad, fair, good.

Summary of findings 4.   MAL-PDT compared to surgical excision for basal cell carcinoma of the skin

MAL-PDT compared to surgical excision for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from hospitals in Brazil, the UK, Germany, Switzerland and Australia
Intervention: MAL-PDT
Comparison: surgical excision

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgical excision	Risk with MAL-PDT				
Recurrence at 3 years	Study population		RR 26.47 (1.63 to 429.92)	68 (1 RCT)	⊕⊕⊖⊖ LOW [1]	-
	0 per 1000	364 per 1000 (49 to 13027)				
Cosmetic outcome (excellent/good)	Study population		RR 1.18 (1.09 to 1.27)	309 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	Participant-rated at 1 year on a 4-point scale.[5]
	825 per 1000	973 per 1000 (899 to 1000)				
Cosmetic outcome (excellent/good)	Study population		RR 1.87 (1.54 to 2.26)	256 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	Observer-rated at 1 year on a 4-point scale.[5]
	466 per 1000	871 per 1000 (717 to 1000)				
Pain	Study population		RR 2.20 (0.60 to 8.03)	101 (1 RCT)	⊕⊕⊖⊖ LOW [3]	Study reported frequency of "pain in skin" and "burning sensation of skin" as part of AEs.
	61 per 1000	135 per 1000 (37 to 492)				

Early treatment failure	Study population		RR 6.66 (1.22 to 36.41)	173 (2 RCTs)	⊕⊕⊕⊝ MODERATE [4]	-
	11 per 1000	77 per 1000 (14 to 419)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AEs: adverse effects; **CI:** Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for very serious imprecision due to very wide 95% CI (although excludes 1, there is a greater than 100-fold difference).

[2] Downgraded one level for serious risk of bias as unable to truly blind due to the nature of interventions.

[3] Downgraded two levels for very serious imprecision as very wide 95% CI indicating the possibility of important benefit or harm.

[4] Downgraded one level for serious imprecision due to small sample size and wide 95% CI.

[5] 4-point scale: poor (extensive occurrence of scarring, atrophy, or induration), fair (slight to moderate occurrence of scarring, atrophy or induration), good (no scarring, atrophy or induration and moderate redness or increase in pigmentation compared with adjacent skin), excellent (no scarring, atrophy, or induration and slight or no redness or change in pigmentation compared with adjacent skin).

Summary of findings 5.   Imiquimod cream compared to MAL-PDT for basal cell carcinoma of the skin

Imiquimod cream compared to MAL-PDT for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from seven hospitals in the Netherlands
Intervention: 5% imiquimod cream
Comparison: MAL-PDT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PDT	**Risk with Imiquimod cream**				
Recurrence at 3 years	Study population		RR 0.44 (0.32 to 0.62)	277 (1 RCT)	⊕⊕⊕⊝ MODERATE [1]	-
	516 per 1000	227 per 1000 (165 to 320)				

			RR 0.42 (0.31 to 0.57)	228 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	-
Recurrence at 5 years	Study population					
	686 per 1000	288 per 1000 (213 to 391)				
Cosmetic outcome (excellent/good)	Study population		RR 0.98 (0.84 to 1.16)	370 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	Blinded observer-rated at 1 year on 4-point scale.[3]
	624 per 1000	611 per 1000 (524 to 723)				
Pain (moderate/severe)	Study population		RR 0.60 (0.41 to 0.87)	371 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	During treatment: week of treatment with highest frequency of reported moderate/severe pain (week 6 for imiquimod, treatment cycle 2 for PDT).
	305 per 1000	183 per 1000 (125 to 266)				
Early treatment failure	Study population		RR 0.64 (0.37 to 1.09)	385 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]	-
	158 per 1000	101 per 1000 (59 to 172)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio.

__GRADE Working Group grades of evidence__
__High certainty:__ we are very confident that the true effect lies close to that of the estimate of the effect.
__Moderate certainty:__ we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
__Low certainty:__ our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
__Very low certainty:__ we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for serious imprecision as only a single study with a small sample size.
[2] Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI.
[3] 4-point scale: poor, fair, good, excellent.

BACKGROUND

Description of the condition

Disease definition and burden

Basal cell carcinoma (BCC) is the most common skin cancer and the most common cancer found in white-skinned individuals (Dessinioti 2010; Lomas 2012; Madan 2016; Verkouteren 2017). BCCs are slow-growing, locally invasive, malignant (but not life threatening), epidermal skin tumours (Roewert-Huber 2007; Wong 2003). Patients with BCC place a considerable burden on healthcare systems worldwide due to their high, increasing incidence and associated morbidity. Furthermore, people with BCC are at high risk of developing further BCCs and other ultraviolet radiation (UVR)-related skin cancers. As a result, the disability adjusted life years and healthcare costs of BCCs have risen significantly in recent decades (Verkouteren 2017).

Clinical features

Clinical appearances and morphology of BCC can be diverse (more than 26 subtypes have been described), with no universally accepted classification system. The main clinical subtypes are: nodular, superficial, ulcerated (rodent ulcer), morphoeic (sclerodermiform), fibroepithelial (fibroepithelioma of Pinkus) and advanced BCC (resulting from prolonged neglect) (Madan 2016). Histopathological patterns are also diverse and include: nodular, superficial, morphoeic, micronodular, infiltrative, pigmented and basosquamous or metatypical subtypes (Crowson 2006). Early BCCs may appear as a small red patch or a scab that fails to heal. Symptoms such as pain are rare. Nodular BCC (nBCC) is the most common subtype in the UK, making up to 60% of all BCCs (Scrivener 2002). However, in other countries such as Australia, superficial BCC (sBCC) is the most common subtype (Raasch 2002). BCCs affect the head and neck region in the majority of cases (Scrivener 2002). A recent UK study of first registered BCCs in the population identified BCCs affected the head and neck region around 70% of the time and the trunk and extremities around 30% of the time (Venables 2019).

Clinicopathological features of the tumours can be used to differentiate them into high-risk and low-risk subtypes, which has implications on the management approach. High-risk BCCs include: morphoeic, infiltrative, micronodular histological subtypes; presence of perineural or perivascular invasion; size > 5 cm; recurrent lesion; centrofacial location, including periocular and ears and host immunosuppression (Madan 2016). Low-risk BCCs include: superficial and nodular histological subtypes when they are located on a low-risk site (e.g. not centrofacial location).

Natural history

BCCs are usually slow-growing tumours that only very rarely metastasize (spread) to other distant parts of the body (0.0028% to 0.55% of advanced BCCs metastasize) (Ting 2005). In people with a competent immune system, growth of a BCC is usually localised to the area of origin. BCCs tend to infiltrate surrounding tissues in a three-dimensional fashion through the irregular growth of finger-like projections which may not be apparent clinically (Breuninger 1991; Miller 1991). If left untreated, or inadequately treated, the BCC can cause extensive tissue destruction, particularly on the face. Neglected cases may even infiltrate bone and deeper structures, like the brain. The clinical course of BCC is unpredictable; it may remain small for years with little tendency to grow, it may grow rapidly, or it may proceed by successive spurts of extension of tumour and partial regression (Franchimont 1982).

Epidemiology and causes

Considerable variation exists in the literature for incidence rates of BCC. Latitude, sun exposure and skin type of a country's inhabitants contribute to much of this variation. Additionally, despite being common tumours, numbers of BCCs recorded in cancer registries are frequently underestimated due to their high volume and low perceived risk and often they are treated without a confirmatory biopsy. Depending on the registry, it is estimated that between 30% to 50% of BCCs are unreported (NCIN 2010). However, since 2013 the UK has vastly improved registry data collection and now records all cases of BCC and squamous cell carcinoma (SCC). This has greatly improved the accuracy of epidemiological analysis of keratinocyte cancers and the UK now has the largest population-based keratinocyte cancer registry in the world (Venables 2019). From 2013 to 2015, the European age standardised incidence rate of BCC in the UK was 285 per 100,000 people annually. The highest BCC rate was observed in Southwest England with 362 per 100,000 people annually.

Direct comparison of incidence rates between countries is limited by the fact that studies often use different standardisation methods and because each country will have their own registry with different registration criteria. The highest incidence of BCC is found in Australia where in Queensland from 1997 to 2006, the rate was 1813 per 100,000 males annually and 1269 per 100,000 females annually (Verkouteren 2017). Parts of Africa have the lowest reported incidence rates with less than 1 per 100,000 people annually (Lomas 2012). In mainland Europe, there is large variation dependent on country and sex with the highest rate of 164.7 per 100,000 males annually found in the Netherlands and the lowest rate of 24.5 per 100,000 females annually observed in Croatia (Verkouteren 2017). In the USA, California had the highest incidence rate of 1069 per 100,000 males annually. Data from the USA provides compelling evidence for the role of decreasing geographical latitude on increasing BCC incidence with a rate in New Hampshire (43 degrees) of 309.9 per 100,000 males annually (Karagas 1999) whereas in Arizona (35 degrees) the rate is 935.9 per 100,000 males annually (Harris 2001). The studies reporting these incidence rates both used the same standardisation method.

The incidence of BCC is increasing globally. A systematic review identified that incidence is increasing in Europe by 5.5% annually (Lomas 2012), and the study by Venables 2019 calculated a mean annual percentage increase of 5% between 2013 to 2015 for both BCC and SCC across the UK. In the USA, the incidence is increasing by around 2% annually (Verkouteren 2017). The Australian national surveys have shown that the incidence rate has been increasing since 1985, but that it may now be reaching a plateau (Lomas 2012). There has been a very large increase in BCC incidence in young females in Europe and the USA that has led to a reversal of the male:female ratio, such that the ratio observed now is female > male in the younger population (Verkouteren 2017). Higher frequency of tanning bed use and higher likelihood of seeking medical attention in females are reasons postulated to contribute to this observed trend.

Risk factors for BCC include: advanced age, male sex, fair skin, low ability to tan, intense intermittent UVR exposure during childhood, signs of actinic damage (skin changes due to excessive sun

exposure), personal/family history of skin cancer, excessive sun bed use, phototherapy, radiotherapy, systemic immunosuppression and a genetic predisposition (Verkouteren 2017).

Germ-line mutations can also have a large effect on the risk of developing BCC such as those seen in Gorlin syndrome (naevoid BCC syndrome). This is an autosomal (non-sex determining chromosome) dominantly inherited condition characterised by developmental abnormalities and the occurrence of multiple BCCs. Mutations in people with Gorlin syndrome have been found on the *PTCH1* gene located on chromosome nine, which appears to be crucial for proper embryonic development and for tumour suppression (Johnson 1996).

Description of the intervention

The primary aim of treatment is complete removal or destruction of the BCC lesion to result in cure and minimise the risk of recurrence. This should also be balanced against the patient's requirement for a good/acceptable cosmetic result (Madan 2016). There are numerous interventions currently available for BCC and the choice of intervention is determined by tumour factors such as the histological/clinical subtype of BCC, site, size, whether primary or recurrent tumour, as well as patient factors (e.g. co-morbidities, importance of cosmesis) and other factors such as available resources, costs and local health economics. The different interventions are usually split into surgical and non-surgical interventions. Generally, surgical interventions are used as first-line treatments for both high-risk and low-risk BCC subtypes and non-surgical interventions are usually reserved for low-risk BCC subtypes where histological margins are less important (Madan 2016). Radiotherapy and electrochemotherapy are the exceptions as they tend to be used for high-risk BCCs not amenable to surgical intervention.

Surgical (physical) interventions

- Surgical excision (with predetermined margins)
- Surgical excision (with frozen section margin control)
- Mohs micrographic surgery (MMS - technique that takes serial horizontal frozen sections intraoperatively to examine histologically the entire surgical margin to confirm complete tumour clearance)
- Curettage and cautery (synonymous for electrodesiccation)
- Cryosurgery (synonymous for cryotherapy, delivered by a variety of methods)
- Laser therapy (ablative lasers, pulsed dye laser)

Non-surgical (medical) interventions

- Radiotherapy
- Topical imiquimod
- Topical 5-fluorouracil
- Photodynamic therapy
- Ingenol mebutate
- Intralesional interferon, fluorouracil
- Electrochemotherapy
- Others (solasodine glycosides, sinecatechins, diclofenac, calcitriol)

How the intervention might work

Surgical (physical) interventions

Surgical excision (SE) with predetermined margins is one of the most common treatments for BCC and is often regarded as the gold-standard. SE involves excising the tumour under local anaesthetic with a variable margin of clinically normal surrounding tissue. A key advantage of SE over non-surgical techniques is that it allows the histological examination of the excised specimen and therefore an accurate assessment of the surgical margins. A peripheral margin of 4 mm to 5mm is usually suggested for well-defined, small BCC (Wolf 1987, Kimyai-Asadi 2005) and the use of curettage prior to excision to delineate the margins of the BCC is often performed (Chiller 2000). Excision through subcutaneous fat is generally advisable for the deep surgical margin, however there is a lack of evidence informing this. Factors such as the local anatomy, size and histological subtype of the BCC will influence this decision (Telfer 2008).

Mohs micrographic surgery (MMS) was pioneered in the 1930s by Frederic Mohs and is a specialised surgical procedure in which serial horizontal frozen sections allow the microscopic examination of the entire surgical margin during surgery (in contrast to the 1% to 2% of the margin asseessed by "bread-loafing" of vertical sections examined with standard excision), so that the extent of excision can be defined precisely (Madan 2016). The technique produces very high cure rates and is often used as the gold-standard for high-risk facial BCC. Another important benefit is that it allows for tissue sparing as smaller margins than SE can be taken.

Similar to MMS is the technique of surgical excision with frozen section margin control, which employs a similar serial frozen section technique but often with standard excision margins. Frozen section margin control also differs from MMS in that excision of the tumour and an accompanying annular strip of surrounding tissue is performed with vertical margins (Nizamoglu 2016; Avril 1997).

Curettage and cautery (C&C) and curettage alone are traditional surgical BCC treatment methods that are sometimes used for small, low-risk BCCs. There is wide variation in the protocols and techniques used, including type of curette used (e.g. Volkmann spoon curette, disposable loop curette) and the number of treatment cycles. The procedure normally destroys epidermis and upper dermis and therefore scarring tends to be mild (Madan 2016). Curetted tissue is usually histologically examined but assessment of surgical margins is usually not possible.

Cryosurgery involves the direct application of liquid nitrogen to freeze a BCC lesion to between -50 °C and -60 °C resulting in destruction of both the tumour and a margin of surrounding normal tissue (Telfer 2008). Techniques and liquid nitrogen delivery methods are variable and protocols differ including number of freeze-thaw cycles. Mallon 1996 showed that a double 30-second freeze-thaw cycle achieved higher cure rates than a single freeze-thaw cycle for facial BCC, and that a single freeze-thaw cycle achieves high cure rates for truncal BCC.

Ablative lasers (e.g. carbon dioxide laser) utilise their tissue-heating properties to destroy BCC with high accuracy but this technique does not allow any histological examination and consequently it is not suitable for high-risk lesions. It is therefore not widely used in the treatment of BCC. There are some data suggesting that, following ablative laser treatment, recurrent BCC can develop into a

more aggressive histological subtype (Jung 2011). Pulsed dye laser is generally used to treat vascular skin lesions and is also used as a treatment for thin, low-risk BCCs based on the observation that they are often highly vascular with clinically evident telangiectasias (dilated blood vessels) (Shah 2009).

Non-surgical (medical) interventions

Radiotherapy involves directing ionising radiation to destroy tumour tissue and a margin of surrounding normal tissue. Several different techniques and methods are currently used including conventional X-ray therapy, interstitial brachytherapy and superficial contact therapy with the choice of technique dependent on factors such as size and location of the lesion and performance status of the patient (Telfer 2008). Radiotherapy can be used for high-risk (including recurrent tumours) and low-risk BCCs and is often the first-line for high-risk BCCs in patients who do not want surgical intervention. Radiotherapy is usually only available at specialist hospital centres due to the high costs of the equipment and need for a clinical oncologist to decide on the treatment regimen. Usually the treatment is given in a fractionated regimen which requires multiple hospital visits over several days to weeks. Importantly, radiotherapy should not be used in the treatment of previously radiotherapy-treated recurrent BCCs and is contraindicated in patients with Gorlin syndrome as they have a increased radiosensitivity and can develop multiple BCCs within a field of radiation (Kleinerman 2009).

Imiquimod is an immunomodulator topical treatment that works by stimulating toll-like receptors-7 and -8, present on immune cells, inducing interferon-α which promotes a Th1 innate and adaptive cell-mediated immune response. This results in the recognition and subsequent destruction of tumour cells by the immune system (Dummer 2003). Imiquimod is licensed in the treatment of low-risk BCCs up to 2 cm diameter in immunocompetent patients and the treatment regimen is five times per week for six weeks (sBCC) or 12 weeks (nBCC). It is fairly common for patients to experience influenza-like symptoms (due to the interferon release) and local application-site reactions are common.

5-fluorouracil (5-FU) is a pyrimidine analogue that disrupts DNA and RNA synthesis by inhibiting the enzyme thymidylate synthetase, thereby preventing purine and pyrimidine (DNA/RNA building blocks) from becoming incorporated into DNA during the cell-cycle (Sloan 1990). 5-FU cream is commonly used in the treatment of pre-malignant actinic keratosis (AK) and Bowen disease and is less commonly used in the treatment of small, low-risk BCC. Application site reactions are common. 5-FU can also be administered intralesionally to treat low-risk BCC.

Photodynamic therapy (PDT) is a procedure that involves the application of a photosensitiser to BCC lesions and surrounding normal skin. It relies on the principle that the sensitiser accumulates in higher concentration within rapidly proliferating malignant cells compared to cells in adjacent normal tissues. The photosensitiser is activated by visible light of certain wavelengths which produces cytotoxic oxygen species and free radicals that selectively destroy the tumour cells (Fritsch 1998). Systemic PDT is utilised for some solid organ tumours, however in dermatology the mainstay of PDT is topical using the photosensitisers 5-aminolevulinic acid (ALA; Levulan® Kerastick®, Ameluz® and Alacare®), the methyl ester of ALA, methyl aminolevulinate (MAL; Metvix®/Metvixia®) and more recently hexylaminolevulinate

(HAL, Hexvix®) has been used. These photosensitisers utilise the principles of the haem biosynthesis pathway, acting as pro-drugs that enter and accumulate in cells and are metabolised to form protoporphyrin IX which accumulates in the target tissue (Ibbotson 2016). Protoporphyrin IX is a potent and efficient photosensitiser when it is present in high concentration and can be activated by light of the appropriate wavelengths (Ibbotson 2016).

Ingenol mebutate is a topical treatment derived from the plant *Euphorbia peplus* and is licensed in the treatment of AK. It has a dual mechanism of action whereby it destroys epidermal cells within hours and induces production of antibodies that result in neutrophils targeted to kill any residual dysplastic epidermal cells (Rosen 2012).

Intralesional interferon utilises the principles of the naturally occurring interferon family of proteins. These proteins are secreted by cells in response to viral infections and function by binding to promote Th1 innate and adaptive cell-mediated immune responses than can be harboured to destroy tumour cells (Tucker 2006). The treatment usually needs to be delivered over multiple sessions and is expensive which limits its widespread use. Systemic side-effects are common (Madan 2016).

Electrochemotherapy (ECT) involves permeating cytotoxic agents (classically bleomycin) into the tumour using short electric pulses (a process known as electroporation), resulting in a direct cytotoxic effect (Campana 2017).

Zycure cream is a mixture of 0.005% solasodine glycosides (mainly solasonine and solamargine) found in solanaceous plants of the nightshade family, such as aubergine (Punjabi 2008). The mechanism of action of these compounds is thought to involve direct cell lysis and induction of apoptosis with selectivity towards tumour cells (van der Most 2006).

Sinecatechin ointment contains epigallocatechin-3-gallate (EGCG) which is an active constituent of green tea. It is licensed in the treatment of genital warts and has been shown to have cytotoxic effects on tumours cells through inhibition of cell growth, induction of apoptosis and possible inactivation of β-catenin signalling through the Wingless (Wnt) pathway (Singh 2013).

Sonic hedgehog pathway inhibitors target the approximate 90% of BCC that have mutations in genes causing unregulated activation of the sonic hedgehog pathway. Oral hedgehog pathway inhibitors (vismodegib and sonidegib) are licensed for the treatment of metastatic BCC and locally advanced BCC not appropriate for surgery or radiotherapy (Madan 2016). Trials are under way assessing the safety and efficacy of topical hedgehog inhibitors for BCCs in Gorlin syndrome patients, but none of these studies met our inclusion criteria.

Intervention outcomes

The ideal outcome of any intervention to treat a BCC would be to achieve complete clearance with no recurrence at follow-up, and to fulfil satisfactory cosmetic results with minimal risk of discomfort or adverse effects before or after the intervention. All interventions have the potential to fall short of these expectations to varying degrees. The more complete the removal or destruction of the lesion, the lower the risk of recurrence, but both modes of tumour eradication unfortunately cause localised tissue damage. The resultant inflammation can lead to adverse effects such as pain,

erythema, bleeding, crusting, vesicles, oedema, and paraesthesia. Pain of varying degrees is one of the more common adverse effects, and therefore has the potential to influence the patient's treatment choice and/or adherence. After the initial inflammatory phase lasting a week or so, a healing wound undergoes a three-week proliferation stage during which collagen is deposited and a scar begins to form. This is followed by a remodelling stage lasting a year, during which collagen cross-linking occurs and the scar matures (Mulholland 2012). Other undesired post-inflammatory cosmetic outcomes include hypo- and hyper-pigmentation.

Why it is important to do this review

BCC is common, continuously rising in incidence and is associated with significant morbidity and costs to healthcare systems. Although there are a wide variety of treatment modalities used in the management of BCCs, and the vast majority of the tumours are successfully treated, little research is available which accurately compares these different treatment modalities.

It is essential for both healthcare providers and patients to have the best available evidence so that they can weigh up the risks and benefits of the available treatments; to allow and promote shared decision making.

Since the publication of the previous version of this review (Bath-Hextall 2007), the results of several long-term studies on interventions for BCC have become available and several novel, non-surgical treatments have been developed and entered into clinical trials making this update timely and necessary.

O B J E C T I V E S

To assess the effects of interventions for basal cell carcinoma (BCC) in immunocompetent adults.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised controlled trials (RCTs) of interventions for basal cell carcinoma (BCC). We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Types of participants

All immunocompetent adults who have one or more histologically-proven, primary BCC, who were eligible for randomisation to either active treatment, placebo, other treatment or no treatment were included. Persistent (where a number of treatments have been tried with no success) or recurrent tumours have been excluded. Studies including participants with Gorlin syndrome (basal cell naevus syndrome), organoid naevi or other genetic syndromes have been excluded. Excluding such patients from trials is commonplace as the aetiology of the BCCs are different and treatments are known to work differently (for example radiotherapy can increase risk of developing further BCCs in Gorlin syndrome) and with large numbers of lesions, confounding of results can occur.

Types of interventions

Treatments for BCC including the following.

1. Surgical (physical)

- Surgical excision
- Mohs micrographic surgery
- Curettage and cautery
- Cryosurgery
- Laser therapy (ablative lasers, pulsed dye laser)

2. Non-surgical (medical)

- Radiotherapy
- Topical imiquimod
- Topical 5-fluorouracil
- Photodynamic therapy (using any photosensitiser or light source)
- Ingenol mebutate
- Intralesional interferon
- Electrochemotherapy
- Others (solasodine glycosides, tazarotene, valproic acid, sinecatechins, diclofenac, calcitriol)

Types of outcome measures

Primary outcomes

1. Recurrence at three years and five years, measured clinically (to reflect what actually happens in clinical practice). Rather than exclude potentially clinically useful data, we included recurrence data that fell outside our primary outcome time points if data were not available for three and five years.

2. Cosmetic outcome (participant- and observer-rated). We have included any validated method for assessing cosmetic outcome including the four-point scale, the Vancouver scar scale and the Patient and Observer Scar Assessment Scale (POSAS) (Mosterd 2013). We did not pre-specify a time point for our cosmetic outcome but aimed to include outcomes measured after at least one year (minimum time taken for a scar to mature). If multiple time points were reported, we reported the closest time point to one year (but not less than one year).

Secondary outcomes

1. Pain during treatment and thereafter. We included any pain reported, but prioritised outcomes that included a measure of severity e.g. 'moderate/severe pain' reported by participants as well as pain measured by visual analogue scale (VAS). We did not specify how long after treatment to measure the pain outcome but included any pain measurement if it was recorded in the follow-up period. Due to the varied nature of pain and manner in which it is recorded, we also collated pain data into Table 1.

2. Early treatment failure within six months, measured histologically.

3. Adverse effects (AEs). We did not perform numerical analyses on AEs but provided a narrative synthesis in the results and expanded on this in Table 2.

Due to the large number of studies included in this review update and to improve the overall readability of the review, we have excluded studies that did not measure any of our outcomes of interest.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

For this update, we revised our search strategies in line with current Cochrane Skin practices, and expanded our list of disease terms. Details of the previous search strategies are available in Bath-Hextall 2007.

The Cochrane Skin Information Specialist searched the following databases up to 19 November 2019:

- the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library *(*2019, Issue 11) using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3;
- Embase via Ovid (from 1974) using the strategy in Appendix 4;
- CINAHL via EBSCO (from 1981) using the strategy in Appendix 5; and
- LILACS (Latin American and Caribbean Health Science Information database from 1982) using the strategy in Appendix 6.

Searching other resources

Trials registers

Two review authors (SH and JT) searched the following trials registers up to 3 March 2019 using the term "basal cell carcinoma":

- the ISRCTN registry (www.controlled-trials.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Published and unpublished trials

We checked the reference lists of included studies for further references to eligible trials.
We contacted corresponding authors of study publications to request information on ongoing, unpublished or published trials where we needed additional information.

Adverse effects

We did not perform a separate search for adverse effects of interventions for BCC. However, we did examine data on adverse effects from the included studies we identified, and we extracted these data into a table (see Table 2).

Data collection and analysis

Selection of studies

Three review authors (FB, JT, SH) checked the titles and abstracts identified from the searches and independently assessed the full text of all RCTs of possible relevance. The review authors decided which trials fitted the inclusion criteria and recorded their methodological quality. Any disagreements were resolved by discussion between the review authors. Where there were missing data from the trial reports attempts were made to obtain that data by contacting the trial author.

Data extraction and management

Three review authors (FB, JT, SH) independently performed data extraction, using a pre-derived data extraction form for consistency. Discrepancies were resolved by a fourth review author (HW). Missing data were obtained from the trial authors where possible. Three review authors (FB, JT, SH) checked and entered the data. Data recorded included: demographics, sites, clinical types, histological diagnosis, inclusion criteria, treatment modalities and regimens, rates of recurrence, cosmetic outcomes, pain outcomes, early treatment failure rates, adverse effects data, setting and funding sources.

Assessment of risk of bias in included studies

The Cochrane 'Risk of bias' assessment framework (Higgins 2011) was used to evaluate the internal validity of studies, covering the main sources of bias across the following components:

a) the method of generation of the randomisation sequence (selection bias)

b) the method of allocation concealment - we considered it 'adequate' if the assignment could not have been foreseen (selection bias)

c) who was blinded or not blinded (participants, clinicians, outcome assessors) (performance bias and detection bias)

d) how many participants were lost to follow-up in each arm (attrition bias)

e) if there was selective outcome reporting (reporting bias)

Two authors (JT, SH) independently assessed risk of bias in included studies. Any disagreements were resolved through discussion between the authors including a third author (HW). The overall 'Risk of bias' assessment for each study's bias sources (presented in the Characteristics of included studies table) was performed in relation to our recurrence rate primary outcomes.

Measures of treatment effect

We expressed the results as risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous outcomes, and difference in means (MD) with 95% CIs for continuous outcomes.

Unit of analysis issues

The unit of analysis in the included studies was based on either participants or lesions. Where possible, data at participant level were used in preference. Where there were multiple intervention groups within a trial, we made pair-wise comparisons of similar active interventions versus placebo, or another active intervention. We analysed internally-controlled trials using appropriate techniques for paired designs (for example, for continuous outcomes using Wilcoxon Signed Ranks test or paired t-test; or for dichotomous data using McNemars test), where available, and we did not pool them with studies of other designs.

Where dichotomous data permitted, we estimated paired odds ratios (OR) with 95% CIs. Where paired data could not be extracted from the papers, we presented the data narratively.

Dealing with missing data

If participant dropout led to missing data we conducted an intention-to-treat analysis, as reported in the publications of the trials. We contacted trial authors to provide missing statistics, such as standard deviations (SDs), where appropriate.

Assessment of heterogeneity

We assessed statistical heterogeneity using the I^2 statistic.

Assessment of reporting biases

Study registrations and protocols were identified where available and any differences between registered and reported outcomes were flagged as potential reporting bias. We did not test publication bias as none of the comparisons in our review had the minimum number of 10 studies required in a meta-analysis to apply tests for funnel plot asymmetry (Page 2019).

Data synthesis

We calculated a weighted treatment effect (using random effects) across trials since the treatment effects for interventions are likely to vary by participant and methodological variations between studies, as per the standard methods used within Cochrane Skin. The results were expressed as RR and 95% CI for dichotomous outcomes. All analyses were conducted using RevMan 5.4.

Wherever possible, a meta-analysis was conducted to assess the overall intervention effect of different primary research studies that considered the effectiveness of the same intervention. This approach has the benefits of improving the accuracy of the results and addressing disputes between studies (Higgins 2011).

Where we performed a meta-analysis, we calculated a weighted treatment effect across trials, using a random-effects model. Where it was not possible to perform a meta-analysis, we summarised the data for each trial and have only presented forest plots. If raw data could not be extracted, we extracted the results from appropriate statistical analyses presented in the paper and reported these in the review. We considered a P value < 0.05 as statistically significant.

Subgroup analysis and investigation of heterogeneity

Due to insufficient studies being included across the comparisons, we were unable able to perform any subgroup analyses.

Sensitivity analysis

We planned to conduct sensitivity analyses to examine the effects of excluding studies with a moderate or high risk of bias (Higgins 2011), but insufficient numbers of studies were included in meta-analyses.

Summary of findings and assessment of the certainty of the evidence

'Summary of findings' tables were produced for the outcomes that we determined to be the most clinically relevant. This was based on the experiences of study authors and an electronic survey sent to clinicians in our centre, on what were felt to be the most important outcomes and comparisons to patients and clinicians.

For 'Summary of findings' tables we included the following comparisons.

- MMS (Mohs micrographic surgery) versus SE (surgical excision)
- Imiquimod cream versus SE
- Radiotherapy versus SE (with or without frozen section margin control)
- MAL-PDT versus SE
- Imiquimod cream versus MAL-PDT

MMS versus SE was our main comparison based on our authors' own clinical experiences and the fact that this issue has been debated for years between dermatologists and plastics surgeons. Additionally, the experience of our centre also suggested this was the most important comparison which we established through our electronic survey.

All of our pre-defined outcomes were reported in each 'Summary of findings' table except adverse effects data which were not included. Instead these were presented as a narrative synthesis within the results and discussion sections and collated into Table 2.

'Summary of findings' tables are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) principles (Schünemann 2013), and we used GRADEpro to assess the certainty of evidence for each review outcome. Evidence from the included RCTs was downgraded from 'high certainty' by one level for each serious study limitation found in the domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Where confidence intervals included important benefit and serious harm (i.e. > 1.25 and < 0.75), we rated down two levels for very serious imprecision as described in the GRADE handbook (Schünemann 2013). We also rated down two levels for imprecision if there was a very wide confidence interval (more than 100-fold difference) even if it excluded no effect (RR of 1.0). We rated down three levels when confidence intervals were so wide that we cannot have any certainty in the results and defined this as a confidence interval that includes no effect with a more than 100-fold difference.

Other

A consumer (an experienced patient representative) was consulted throughout, particularly for readability and understanding of the plain language summary.

R E S U L T S

Description of studies

For a full description of the studies please see the Characteristics of included studies tables.

Results of the search

The database searches (see Electronic searches) for this update retrieved a total of 4566 records. We did not identify any records of trials from our scanning of reference lists or correspondence with pharmaceutical companies (see Searching other resources). After removing 179 duplicates, we had 4387 records. We screened these and excluded 4309 records based on titles and abstracts.

We obtained the full text of the remaining 78 records. Twenty-eight studies did not meet our inclusion criteria and were excluded (see

Characteristics of excluded studies). One study included from the previous review (Lui 2004) was also excluded as we identified that not all lesions included were histologically proven and it included a large number of Gorlin syndrome patients.

Six studies were not classified as we did not have enough information to decide if they met our eligibility criteria despite attempts to contact the authors to obtain the full study details for review (Bunker 2000; IRCT 2017 030732933N1; ISRCTN 92678315; Kang 2018; Ma 2018; RPCEC00000147; see Studies awaiting

classification). Three studies are ongoing with no results available yet (EudraCT 2016-002255-25; NCT02242929; NCT03573401).

This left us with 41 records. Nine of these were related to studies included in the previous version of this review. The remaining 32 records reported 26 new studies which we included. We combined them with 26 included studies (reported in 43 references) from the previous version of the review. We then had a total of 52 included studies reported in 75 references (see Characteristics of included studies). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009) (Figure 1).

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Figure 1.   PRISMA study flow diagram.
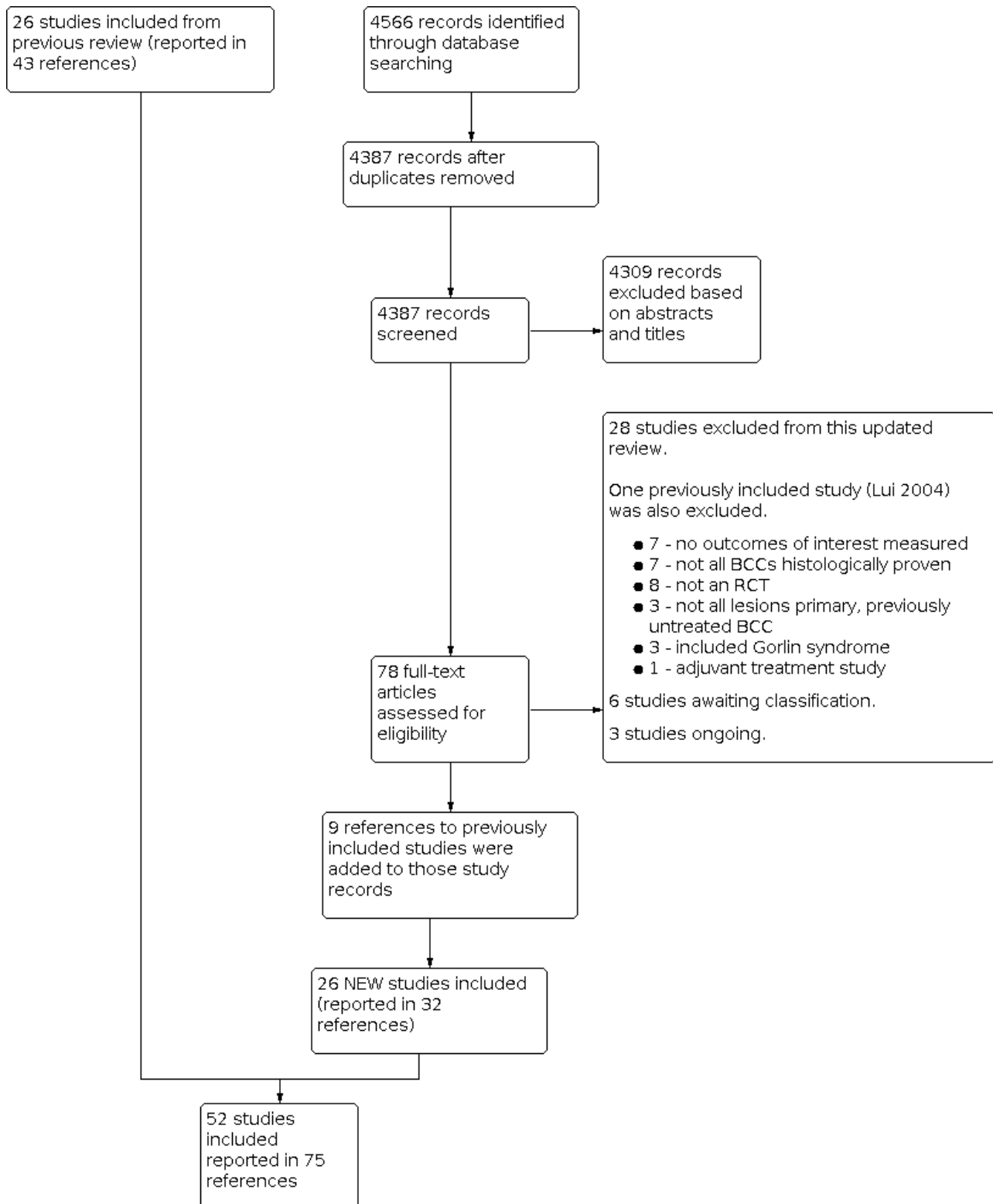
We contacted 21 corresponding authors to obtain further information. The authors of Clover 2016 and Kuijpers 2007 kindly responded and provided further information.

Included studies

Nine papers were identified from our search that had follow-up data from earlier studies: Basset-Seguin 2008; Punjabi 2008;

Rhodes 2004; Smeets 2004 (four references), Kuijpers 2007 (was Thissen 2000); Foley 2009a; Foley 2009b (was Tope 2005).

Design

All studies were prospective, RCTs with a parallel-group design. Eight RCTs were reported as pilot studies (Abd El-Naby 2019; Beutner 1999; Choi 2016; Eimpunth 2014; Haak 2015; Kuijpers 2006; Romagosa 2000; Tran 2012). The most common comparators were non-surgical treatments, with 20 RCTs comparing a non-surgical treatment against another non-surgical treatment. Fourteen RCTs compared a non-surgical treatment against placebo. Eighteen RCTs had a surgical treatment comparator, with 10 RCTs comparing a surgical treatment against a non-surgical treatment, five RCTs comparing a surgical treatment against a surgical treatment, and three RCTs comparing a surgical treatment against placebo.

Twenty-six of our included studies compared an intervention against at least one active treatment (head-to-head studies), 13 compared different regimens of the same active treatment, and 13 compared against placebo/vehicle/sham/no treatment. Seventeen studies had multiple intervention arms (three or four arms).

All intervention groups were deemed to be relevant in these multi-arm studies, but due to the large number of comparisons in the review, we only presented the active treatment-arm comparisons.

The duration of the included studies ranged from six weeks to 10 years, with an average of 13 months. Just under half of the studies were multi-centre (24/52), with 26/52 single-centre studies. We were unable to ascertain the number of study centres for two studies.

Setting

All of the studies included in this review recruited participants from secondary care clinics, with the vast majority being dermatology outpatient clinics. The studies were conducted in many parts of the world. Thirty-two studies were conducted in Europe, 11 in North America, five in Australasia, three in Asia/middle East and one in South America.

Participants

A total of 6690 participants were randomised across the 52 RCTs included in this review. Studies recruited participants ranging in age from 20 to 95 years old with a median age of 64.9 years. Twelve studies did not provide data on the age of participants. Ten studies did not provide data on the gender of participants. Based on the studies that did provide data on gender, there were more male participants than females (ratio 1.48 males:1 female).

The vast majority (48/52) of studies exclusively included basal cell carcinomas (BCC) of low-risk histological subtypes (nodular, superficial). Only four studies included high-risk histological subtypes (Alpsoy 1996; Avril 1997; Clover 2016; Smeets 2004), but none of these exclusively included high-risk histological subtypes and the majority of BCCs in these studies were low-risk histological subtypes.

Most studies (27/52) included BCCs located on the head, neck and body regions. Six studies excluded BCCs located on the head and neck region (Karsai 2015; Kessels 2017; Romagosa 2000; Salmivuori 2019; Spelman 2014; Tran 2012). Nine studies included BCCs only located on the head and neck region (Abbade 2015; Abd El-Naby

2019; Avril 1997; Garcia-Martin 2011; Haak 2015; Kuijpers 2007; Landthaler 1989; Salmanpoor 2012; Smeets 2004). Three studies included BCCs exclusively on high-risk facial sites (H-zone of the face) (Smeets 2004; Haak 2015; Garcia-Martin 2011). Ten studies did not report the location of BCCs (Choi 2016; Clover 2016; Edwards 1990; Eimpunth 2014; Marks 2001; Punjabi 2008; Rogozinski 1997; Siller 2010; Soler 2000; 2005-001474-27).

Sample sizes

The number of participants randomised in each study ranged from 13 (Romagosa 2000) to 724 (Geisse 2004) with a median of 89 participants. We did not re-count the participants in the follow-up studies, and therefore there were a total of 6690 participants randomised in the 52 primary RCTs included in this review. Thirty-eight RCTs used participants as the unit of analysis, and 14 RCTs used lesions as the unit of analysis. A total of 7241 lesions were included in this review.

Funding

Overall, 22 studies were industry funded, with studies of imiquimod and photodynamic therapy being over-represented in this group. Seventy-nine per cent of studies (11/14) assessing imiquimod were funded by the same company (3M), and seven out of 16 PDT studies were industry-funded (five by PhotoCure/Galderma).

Interventions

The trials fell into 15 broad therapeutic categories. For a full description of the studies, please see the Characteristics of included studies table. *Denotes study new to this update.

1. Surgical excision (SE)

Ten RCTs.

- Mohs micrographic surgery versus SE (Smeets 2004)
- Imiquimod versus SE (Bath-Hextall 2014*)
- Radiotherapy versus SE (with option for frozen section margin control) (Avril 1997)
- Curettage versus curettage and cautery versus SE (Salmanpoor 2012*)
- Curettage and cryosurgery versus SE (Kuijpers 2007*)
- MAL-PDT versus SE (Abbade 2015*; Rhodes 2004; Szeimies 2008)
- ALA-PDT versus SE (Mosterd 2008*)
- Electrochemotherapy versus SE (Clover 2016*)

2. Radiotherapy

Four RCTs.

- Radiotherapy versus SE (Avril 1997)
- Imiquimod versus radiotherapy (Garcia-Martin 2011*)
- Low dose versus high-dose radiotherapy (Landthaler 1989*)
- Radiotherapy versus cryosurgery (Hall 1986)

3. Cryosurgery

Four RCTs.

- Radiotherapy versus cryosurgery (Hall 1986)
- Curettage and cryosurgery versus SE (Kuijpers 2007)
- PDT versus cryosurgery (Wang 2001; Basset-Seguin 2008*)

4. Curettage and cautery (C&C)

One RCT.

- Curettage versus curettage and cautery versus SE (Salmanpoor 2012*)

5. Photodynamic therapy (PDT)

Sixteen RCTs.

- MAL-PDT versus SE (Abbade 2015*; Rhodes 2004; Szeimies 2008)
- ALA-PDT versus SE (Mosterd 2008*)
- ALA-PDT versus MAL-PDT (Kuijpers 2006*)
- MAL-PDT versus HAL-PDT versus BF200-ALA-PDT (Salmivuori 2019*)
- BF-200 ALA-PDT versus MAL-PDT (Morton 2018*)
- Two-fold ALA-PDT versus conventional MAL-PDT (Kessels 2018*)
- PDT versus cryosurgery (Wang 2001; Basset-Seguin 2008)
- Imiquimod cream versus MAL-PDT (Arits 2013*)
- 5-FU cream versus MAL-PDT(Arits 2013*)
- Laser ALA-PDT versus broadband halogen light ALA-PDT (Soler 2000)
- Ablative fractional laser-assisted MAL-PDT versus MAL-PDT (Choi 2016*; Haak 2015*)
- MAL-PDT versus placebo (Foley 2009a; Foley 2009b)

6. Imiquimod (5% cream unless otherwise stated)

Fourteen RCTs.

- Imiquimod versus MAL-PDT (Arits 2013*)
- Imiquimod versus 5-FU cream (Arits 2013*)
- Imiquimod versus SE (Bath-Hextall 2014*)
- Imiquimod versus radiotherapy (Garcia-Martin 2011*)
- Dose response trial of imiquimod with and without occlusion for BCC - one trial for sBCC and one trial for nBCC (Sterry 2002a; Sterry 2002b)
- Five different doses of imiquimod for sBCC and nBCC versus vehicle (Beutner 1999)
- Open-label dose response trial of imiquimod for primary superficial BCC (Marks 2001)
- Open-label dose response trial of imiquimod for nBCC (Shumack 2002a)
- Dose response trial of imiquimod versus vehicle for sBCC (Geisse 2002; Geisse 2004; Schulze 2005; Shumack 2002b)
- Two different doses of imiquimod (Ezughah 2008*; Eigentler 2007*)

7. Fluorouracil (5-FU)

Three RCTs.

- 5-FU cream versus MAL-PDT (Arits 2013*)
- Imiquimod cream versus 5-FU cream (Arits 2013*)
- 5-FU cream in phosphatidyl choline versus 5-FU cream in petrolatum (Romagosa 2000)
- Varying treatment regimens of 5-FU/epinephrine injectable gel (Miller 1997)

8. Electrochemotherapy (ECT)

One RCT.

- Electrochemotherapy versus SE (Clover 2016*)

9. Ingenol mebutate

Two RCTs.

- Ingenol mebutate gel 0.0025% versus ingenol mebutate gel 0.01% versus ingenol mebutate gel 0.05% versus vehicle gel (Siller 2010*)
- Ingenol mebutate gel + full occlusive aluminium disk versus ingenol mebutate gel and semi-occlusive dressing with Opsite or Ingenol mebutate gel with no occlusion (Spelman 2014*)

10. Solasodine glycosides

One RCT.

- Solasodine glycoside (Zycure) cream versus matching vehicle (Punjabi 2008)

11. Topical valproic acid gel and tazarotene gel

One RCT.

- Valproic acid (Baceca®) gel followed by Tazarotene gel versus placebo gel followed by Tazarotene gel (placebo cross-over after eight weeks) (2005-001474-27*)

12. Topical diclofenac and vitamin D

One RCT.

- Diclofenac-3% gel versus calcitriol 3ug/g ointment versus diclofenac-3% gel plus calcitriol 3ug/g ointment versus no topical treatment (Brinkhuizen 2016*)

13. Pulsed dye laser (PDL)

Four RCTs.

- PDL versus sham (Karsai 2015*)
- PDL single session versus PDL two sessions (Abd El-Naby 2019*)
- PDL 7mm spot-size, single pulses versus PDL 10mm spot-size, stacked pulses (Tran 2012*)
- PDL 10mm spot-size, one stacked pulse session versus no treatment (Eimpunth 2014*)

14. Intralesional interferon (IFN) therapy

Four RCTs.

- IFN alpha-2a, 2b or alpha-2a and 2b (Alpsoy 1996)
- IFN alpha 2b versus vehicle (Cornell 1990)
- Number of dosages of IFN alpha 2b (Edwards 1990)
- IFN beta versus placebo (Rogozinski 1997)

15. Topical sinecatechins

One RCT.

- Sinecatechin 10% ointment versus vehicle (Kessels 2017*)

Outcomes

Out of the 52 comparisons, only 21% (11/52) reported our 3-year recurrence primary outcome and only 17% (9/52) reported our 5-year recurrence primary outcome. Cosmetic outcome data were reported for 37% (19/52) of the comparisons (14/52 had data available for analysis). Early treatment failure was reported in 75% (39/52) of comparisons. Pain data were reported in 46% (24/52) of the comparisons (10/52 had data available for analysis). Adverse effects data were reported for most comparisons (81%, 42/52), but due to their heterogeneity we did not perform any analyses and instead summarised these data in Table 2.

Excluded studies

We excluded 29 studies due to the following reasons: no outcomes of interest measured (8); not all lesions histologically proven (7); not an RCT (8); not all lesions primary, untreated BCC (3); inclusion of Gorlin syndrome participants (3) and a study on adjuvant treatment (1). Please see the Characteristics of excluded studies tables for further details.

Studies awaiting classification

We were unable to make a final decision on whether to include or exclude six studies despite attempts to contact the study investigators. See the Studies awaiting classification tables for further details.

Ongoing studies

Three studies were identified that are currently ongoing and had no data available for us to include in this review. See the Ongoing studies tables for further details.

Risk of bias in included studies

In order to objectively assess risk of bias, we used Cochrane 'Risk of bias' methods (Higgins 2011). Occasionally, our ability to assess risk was hampered by limited reporting of data. Where there was inadequate information to make a judgement, for example abstract-only studies, attempts to contact the authors were made in order to get access to the data needed. Please see the Characteristics of included studies tables for full details. Figure 2 and Figure 3 summarise the overall data.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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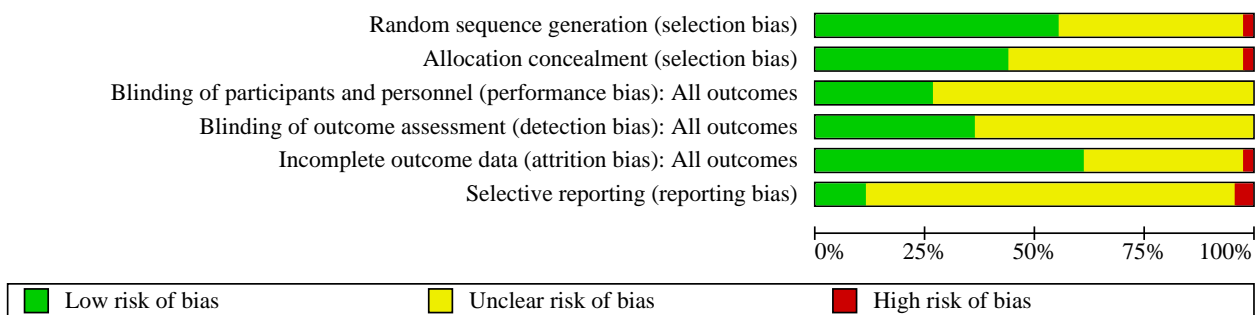
Figure 3. **'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**

Figure 3. (Continued)

Study						
Geisse 2004	+	+	+	?	?	?
Haak 2015	+	+	?	+	?	+
Hall 1986	?	?	?	?	?	?
Karsai 2015	+	+	?	?	+	?
Kessels 2017	+	+	+	+	+	+
Kessels 2018	+	+	?	+	+	+
Kuijpers 2006	?	?	+	+	+	?
Kuijpers 2007	+	+	?	?	?	?
Landthaler 1989	?	?	?	?	+	?
Marks 2001	?	?	?	?	+	?
Miller 1997	?	?	?	?	?	?
Morton 2018	+	+	?	+	+	+
Mosterd 2008	+	+	?	?	?	?
Punjabi 2008	?	?	+	+	−	?
Rhodes 2004	+	+	?	?	?	?
Rogozinski 1997	?	?	?	?	?	?
Romagosa 2000	?	?	+	+	+	?
Salmanpoor 2012	?	?	?	?	?	?
Salmivuori 2019	?	?	?	?	?	?
Schulze 2005	+	+	+	+	+	?
Shumack 2002a	?	?	?	?	?	?
Shumack 2002b	?	?	?	+	?	?
Siller 2010	+	+	?	+	+	?
Smeets 2004	+	+	?	?	+	?
Soler 2000	?	+	?	?	+	?
Spelman 2014	?	?	?	?	?	?
Sterry 2002a	+	?	?	?	+	?
Sterry 2002b	+	?	?	?	+	?
Szeimies 2008	+	+	?	?	+	?
Tran 2012	?	?	+	+	+	?
Wang 2001	+	+	?	?	+	?

Allocation

Random sequence generation and concealment of allocation

The randomisation process in general and concealment of allocation are the most important and sensitive indicators that bias has been minimised in a clinical trial (Schulz 1995).

Twenty-nine studies had a low risk of bias for random sequence generation and 22 studies had an unclear risk of bias. Twenty-three studies had a low risk of bias for allocation of concealment whereas 28 studies had an unclear risk of bias. Only one study (Garcia-Martin 2011) had a high risk of bias for random sequence generation and allocation of concealment.

Blinding

Only 14 studies were rated as having a low risk of bias for blinding of participants/personnel with the remaining 38 studies being assessed as having an unclear risk of performance bias. Unclear risk of bias was chosen in three situations: 1) if the blinding method was

not clearly stated by the study authors 2) the study was unblinded 3) the study was blinded but due to the nature of the interventions it is likely that participants/personnel would be aware of the treatment allocation. The reason we decided to rate all these situations as "unclear" is that it is unclear how lack of blinding would impact our outcomes of interest.

Only 19 studies were assessed as low risk of bias for blinding of the outcome assessor. Thirty-three studies were assessed as having unclear risk of detection bias. We rated the bias as unclear for the same situations as detailed above for performance bias. Even if studies reported that outcome assessors were blinded, for all the studies comparing a surgical intervention against a non-surgical intervention, we felt that it was not possible to truly blind due to the nature of the interventions and again we were unclear whether being unblinded would bias the assessing of clinical response with regards to recurrence rates. However we decided that being unblinded would bias the rating of cosmetic outcomes and in this situation we consider the risk of bias to be high. As recurrence

rate is our primary outcome the risk of bias rating displayed in the Characteristics of included studies table relates to this.

Incomplete outcome data

Analysis should be performed according to intention-to-treat principle to minimise risk of attrition bias (Fergusson 2002). However, in many of the trials analysis of outcome was carried out only in those participants who completed the trial. Thirty-two studies had a low risk of bias for incomplete outcome data. Nineteen studies had an unclear risk and one study (Punjabi 2008) had a high risk of attrition bias as there was a large difference in the number of participants that withdrew from the study between groups and the authors used the "last observation carried forward" method to deal with missing data which is an imputation method that fails to acknowledge uncertainty in the imputed values (Higgins 2011).

Selective reporting

To minimise the risk of selective outcome reporting bias, outcomes for studies should all be specified prior to recruitment in a time-stamped, publicly available trial registry. This has been a prerequisite for publication since 2005 for publication in International Committee of Medical Journal Editors (ICMJE) member journals. Only 11 studies prospectively registered their primary outcomes and of these only six were rated as low risk of selective reporting bias which is a concerningly low number. Forty-four studies were rated as unclear risk of bias and two studies were reported as having a high risk of reporting bias: 2005-001474-27 and Basset-Seguin 2008.

Effects of interventions

See: **Summary of findings 1** Mohs micrographic surgery compared to surgical excision for basal cell carcinoma of the skin; **Summary of findings 2** Imiquimod compared to surgical excision for basal cell carcinoma of the skin; **Summary of findings 3** Radiotherapy compared to surgical excision (with or without frozen section margin control) for basal cell carcinoma of the skin; **Summary of findings 4** MAL-PDT compared to surgical excision for basal cell carcinoma of the skin; **Summary of findings 5** Imiquimod cream compared to MAL-PDT for basal cell carcinoma of the skin

Not all of the comparisons measured or reported all primary and secondary outcomes. If an outcome has not been reported under a comparison, this means it was not measured by any study.

1. Surgical excision

Mohs micrographic surgery (MMS) versus surgical excision (SE)

One study (Smeets 2004) compared SE against MMS in 374 participants (408 lesions) with high-risk facial primary basal cell carcinomas (BCCs) (high-risk histological subtype or located in the 'H-zone' of the face or both). The study also randomised 204 recurrent facial BCCs but we have not included these data as we are only interested in primary BCC. The study used 3 mm margins for both treatments to standardise the two modalities (smaller margins are usually used for MMS). If the defect margins were found to be positive after SE, a re-excision with a 3 mm margin was done. If the margins remained positive after a second excision then MMS was undertaken. The primary outcome was recurrence at 30 months (which we have considered to be approximately three

years). Recurrence at five years and 10 years were published in two further papers. See Summary of findings 1.

Primary outcomes

Recurrence

There may be slightly fewer recurrences with MMS and SE at three years (1.9%, 3/160 versus 2.9%, 5/171, respectively) (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.16 to 2.64; Analysis 1.1), and at five years (3.2%, 4/125 versus 5.2%, 7/134, respectively) (RR 0.61, 95% CI 0.18 to 2.04; Analysis 1.2). We rated the certainty of evidence as low for both these outcomes, rating down two levels for very serious imprecision due to the very wide 95% CIs. This CI indicates that the true MMS recurrence rate may represent an important improvement or worsening of recurrence rates when compared to SE.

Cosmetic outcome (participant- and observer-rated).

The authors state that overall, participant- and observer-rated cosmetic outcomes did not significantly differ between MMS and SE when measured at 18 months. We rated the certainty of evidence as low, rating down two levels for very serious indirectness as although the authors did compare the cosmetic outcomes between the two groups, they did not present the data for analysis.

Secondary outcomes

Adverse effects

The study reported in their text that there was quote: "no difference in post-operative complications between SE and MMS"; however raw data were not presented for this outcome to verify this. See Table 2 for further adverse effect (AE) data from this study.

Imiquimod cream versus surgical excision (SE)

One study (Bath-Hextall 2014) compared imiquimod to SE in 501 participants with nodular BCC (nBCC) or superficial BCC (sBCC) at low-risk sites in a non-inferiority trial design with five-year follow-up. Participants randomised to imiquimod treatment applied the cream daily for six weeks (sBCC) or 12 weeks (nBCC). The licensed imiquimod regimen for sBCC is five days a week for six weeks and for nBCC is five days a week for 12 weeks. SE margins were 4 mm. See Summary of findings 2.

Primary outcomes

Recurrence

Imiquimod probably results in more recurrences (16.4%, 35/213) than SE (1.6%, 3/188) at three years corresponding to a 10-fold increased risk of recurrence with imiquimod (RR 10.30, 95% CI 3.22 to 32.94; Analysis 2.1). We rated the certainty of evidence as moderate, rating down for serious imprecision due to the wide 95% CI and because this was only a single study.

By five years, imiquimod may result in more recurrences (17.5%, 36/206) compared with SE (2.3%, 4/177) with a nearly 8 fold increased risk of recurrence (RR 7.73, 95% CI 2.81 to 21.30; Analysis 2.2). We rated the certainty of evidence as moderate, rating down for imprecision (wide 95% CI, single study).

Cosmetic outcome (participant- and observer-rated)

Cosmetic outcome was assessed at six months and three years by participants and two independent dermatologists using a six-point

scale (unable to see lesion, very poor, poor, fair, good, excellent). Our analyses focused on using data from three-year follow-up due to the reasons outlined in the methods section.

When participant-rated, there may be little to no difference between imiquimod (91.9%, 147/160) and SE (92.2%, 153/166) on the rate of good/excellent cosmetic outcomes (RR 1.00, 95% CI 0.94 to 1.06; Analysis 2.3). When dermatologist-rated, imiquimod may improve rate of good/excellent cosmetic outcomes (60.6%, 103/170) compared to SE (35.6%, 62/174), corresponding to a 70% increase rate for imiquimod (RR 1.70, 95% CI 1.35 to 2.15; Analysis 2.3). We rated the certainty of evidence as low for both these comparisons, rating down for serious risk of bias (unable to truly blind due to nature of interventions) and serious risk of imprecision (only one study).

Secondary outcomes

Pain during and after treatment

Patient diaries were used to record information about the level of pain felt before and after the lesion was treated. During treatment, imiquimod probably worsens the risk of moderate/severe pain compared to SE (30%, 72/242 versus 22%, 44/201, respectively) corresponding to a 36% increased risk with imiquimod (RR 1.36, 95% CI 0.98 to 1.88; Analysis 2.4). We rated the certainty of evidence as low, rating down for serious imprecision (wide 95% CI, including the null effect which indicates there may be no difference between the two treatments) and serious risk of attrition bias.

However, during the 16-week follow-up period imiquimod probably reduces the risk of moderate/severe pain compared to SE (9%, 22/233 versus 20%, 41/206) corresponding to a 53% decreased risk with imiquimod (RR 0.47, 95% CI 0.29 to 0.77; Analysis 2.4). We rated the certainty of evidence as low, rating down for serious risk of imprecision (only one study) and serious risk of attrition bias. See Table 1 for further pain data from this study.

Adverse effects

There were slightly more mild/moderate AEs reported during the first six months of treatment in the imiquimod group compared to the SE group (94% of participants versus 88%, respectively). Itching at the tumour site was frequently reported (85%, 211/249 imiquimod versus 56%, 129/229 SE), but weeping at the tumour site was also common (64%, 160/249 for imiquimod versus 35%, 81/229 for SE). Five participants treated with imiquimod withdrew from the study because of AEs related to the treatment whereas no participants withdrew because of AEs related to SE. Thirty-eight (15%) of participants needed a dose reduction in the imiquimod group due to AEs. See Table 2 for further AE data.

Radiotherapy versus surgical excision (SE) with or without frozen section margin control

One study (Avril 1997) involving 347 participants (347 lesions) compared SE (at least 2 mm margin with the option of frozen section margin control) against radiotherapy in primary BCCs of the face, involving tumours less than 4 cm in diameter. BCCs included nodular, ulcerated, superficial and pagetoid and morphoeaform. The main outcome measure was histologically-confirmed persistent tumour or recurrent disease at four years. Three radiation techniques were used: interstitial brachytherapy (n = 95), superficial contact therapy (n = 50) and conventional radiotherapy (n = 20). See Summary of findings 3.

Primary outcomes

Recurrence

At three years the recurrence rates were 5.2% (9/173) and 0% (0/174) for radiotherapy and SE, respectively. (RR 19.11, 95% CI 1.12 to 325.78; Analysis 3.1). We rated the certainty of evidence as low, rating down two levels for very serious imprecision due to the very wide 95% CI, which although does not include the null effect, indicates that radiotherapy may lead to a slight or markedly increased risk of recurrence when compared to SE.

As the study set their primary outcome of recurrence at four years, we have included these data. By four years, radiotherapy may result in a higher risk of recurrence compared to SE with a recurrence rate of 6.4% (11/173) versus 0.6% (1/174), respectively (RR 11.06, 95% CI 1.44 to 84.77; Analysis 3.2). We rated the certainty of evidence as low, rating down for serious indirectness as the outcome was measured outside our three-year and five-year time points and for serious imprecision due to the wide 95% CI.

Cosmetic outcome (participant- and observer-rated)

Comparing the rate of participant-reported good cosmetic outcomes (three-point scale: bad, fair or good) at four years between the groups, radiotherapy probably worsens the rate of good cosmetic outcome compared to SE frozen (RR 0.76, 95% CI 0.63 to 0.91; Analysis 3.3). At four years, radiotherapy probably worsens the rate of dermatologist-assessed cosmesis based on the scar (bad, clearly marked or slightly visible) compared to SE (RR 0.48, 95% CI 0.37 to 0.62; Analysis 3.3). We rated the certainty of evidence for both these outcomes as moderate, rating down for serious risk of bias (high risk of blinding bias). We performed an intention-to-treat analyses on both these outcomes (as detailed in the methods section) due to fairly large dropout numbers at four years.

Secondary outcomes

Adverse effects

After radiotherapy, dyspigmentation and telangiectasia (which may affect the cosmetic appearance) developed in more than 65% of the participants by four years. Radiodystrophy affected 41% of the participants at four years and 5% of the patients in the radiotherapy group had necrosis. These AEs were exclusive to the radiotherapy group. The main characteristics of surgical scars were deformations and constrictions and although these decreased with time they still affected 25% and 5% of participants, respectively at four years. See Table 2 for further AE data for this study.

2. Radiotherapy

Low-dose versus high-dose radiotherapy

Landthaler 1989 compared low-dose (48 Gy) against high-dose radiotherapy (60 Gy) in 319 participants with 290 BCCs (unclear subtype) and 44 SCCs located on the face.

Secondary outcomes

Early treatment failure

There may be little to no difference in the risk of early treatment failure between low dose radiotherapy (8.1%, 12/148) and high dose radiotherapy (9.6%, 14/142) (RR 0.82, 95% CI 0.39 to 1.72; Analysis 7.1). The certainty of evidence was low due to very serious imprecision where the 95% CI indicates that low dose might lead to

an important reduction or an important increase in early treatment failures.

3. Cryosurgery

Radiotherapy versus cryosurgery

One study (Hall 1986) of 93 participants (93 lesions) compared radiotherapy against cryosurgery (unclear subtype, but lesions on nose/ears were excluded). Radiotherapy was applied with 130 kV X-rays and fractionation depended on lesion size. Cryosurgery was performed with two freeze-thaw cycles each lasting one minute.

Primary outcomes

Recurrence

Radiotherapy may reduce the risk of recurrence (4.1%, 2/49) compared to cryosurgery (38.6%, 17/44) at 2 years follow-up (RR 0.11, 95% CI 0.03 to 0.43; Analysis 8.1). However, we rated the certainty of evidence as low, rating down for serious indirectness (as the outcome was measured at two years) and serious imprecision (single study with a fairly wide 95% CI).

Cosmetic outcome (participant- and observer-rated)

The study reported that there was no statistically significant difference in cosmetic outcomes between the interventions; however, the raw data were not presented to verify this.

Secondary outcomes

Pain during and after treatment

The study reported that the degree of pain reported by patients (on questionnaires given during follow-up) was not statistically significant between the two interventions; however, the data were not presented for further analyses.

Adverse effects

Hypopigmentation was more common than hyperpigmentation with both modes of treatment (81% of those in the radiotherapy group and 88% of those in the cryosurgery group). Seven participants treated with radiotherapy developed some radiation telangiectasia. Hypopigmentation and telangiectasia tend to be lifelong. Five participants treated with cryosurgery developed milia - these all resolved by one year. See Table 2 for further AE data from this study.

Curettage and cryosurgery versus surgical excision

One study (Kuijpers 2007) compared curettage and cryosurgery against SE in 88 participants with 100 low-risk BCCs on the head and neck region (96 nBCC, four sBCC) with five years follow-up. Cryosurgery was performed with two 20-second freeze-thaw cycles using a neoprene cone to give a free margin of 5 mm around the tumour. Surgery was performed with 3 mm margins. See Table 3.

Primary outcomes

Recurrence

At three years, curettage and cryosurgery may slightly increase the risk of recurrence compared to SE (13.7%, 7/51 versus 4.1%, 2/49, respectively) (RR 3.36, 95% CI 0.73 to 15.40; Analysis 9.1). We rated the certainty of evidence as low, downgrading two levels for very serious imprecision (very wide 95% CI that indicates both important benefit and harm).

At five years cryosurgery probably increases the risk of recurrence compared to SE (23.7% versus 8.5%) (RR 2.78, 95% CI 0.93 to 8.34; Analysis 9.2). We rated the certainty of evidence as moderate, downgrading one level for serious imprecision (wide 95% CI that includes important benefit and little to no difference).

Cosmetic outcome (participant- and observer-rated)

Cosmetic outcomes were assessed by observers and patients at one year post treatment on a three-point scale (bad, fair, good). When participant-rated, curettage and cryosurgery may slightly decrease the rate of good cosmetic outcomes compared with SE (RR 0.88, 95% CI 0.78 to 0.98; Analysis 9.3).

When dermatologist-rated, curettage and cryosurgery may decrease the rate of good cosmetic outcome compared to SE (RR 0.28, 95% CI 0.16 to 0.47; Analysis 9.3). We rated the certainty of evidence as low for both of these outcomes rating down for serious risk of blinding bias (unable to truly blind due to nature of interventions) and serious risk of imprecision (single study).

Secondary outcomes

Adverse effects

Secondary wound infection, treated with systemic antibiotics, was seen in 5.9% (3/51) participants in the curettage and cryosurgery group. In the SE, group systemic antibiotics were needed for secondary wound infection in 8.2% (4/49) of participants in the first and second weeks after treatment. No further AE data from this study were available.

4. Currettage and cautery

Curettage and cautery versus curettage versus surgical excision

One small study of 55 participants with 69 BCCs on the face and scalp (majority nBCC) compared: curettage and cautery (C&C) versus SE, curettage versus SE and curettage versus curettage and cautery with just two years follow-up (Salmanpoor 2012).

Primary outcomes

Recurrence

It is uncertain whether the risk of recurrence is improved for curettage versus SE (RR 2.40, 95% CI 0.49 to 11.77; Analysis 4.1), C&C versus SE (RR 0.96, 95% CI 0.15 to 6.28; Analysis 5.1), and curettage versus C&C (RR 0.40, 95% CI 0.08 to 1.97; Analysis 6.1). We rated the certainty of evidence as very low for all these comparisons, rating down for very serious imprecision (very wide 95% CIs) and also for serious indirectness as the study only measured recurrence up to two years.

5. Photodynamic therapy (PDT)

PDT versus surgical excision (SE)

Four studies compared PDT with SE, three of which used the photosensitiser methyl aminolevulinate (MAL-PDT) (Rhodes 2004; Szeimies 2008; Abbade 2015), and one which used the photosensitiser 5-aminolevulinate (ALA-PDT) (Mosterd 2008).

Rhodes 2004 compared MAL-PDT against SE for nBCC of the face in 103 participants (118 lesions) with five years follow-up. Abbade 2015 compared MAL-PDT against SE in 57 participants (68 lesions)

with nBCC in the head and neck area with follow-up over three years.

Szeimies 2008 was a non-inferiority study that compared MAL-PDT with SE in 196 participants with 246 sBCCs (between 8 mm and 20 mm located anywhere except mid-face) with one year follow-up. The inferiority margin was set at a difference of 15% in terms of per cent reduction in lesion count three months after the last treatment.

Mosterd 2008, compared fractionated ALA-PDT with SE in 171 primary nBCCs (149 participants) with five years follow-up.

All the MAL-PDT studies followed the standard European PDT protocol which defines one cycle as two PDT sessions separated by a one-week interval. The ALA-PDT (Mosterd 2008) study did two illuminations on the same day separated by 60 minutes and any incomplete responses were re-treated surgically. Rhodes 2004 and Szeimies 2008 performed a gentle curettage of lesions to remove scale/crust and allowed a second PDT cycle if there was not a complete response when assessed clinically at three months follow-up. Mosterd 2008 and Abbade 2015 debulked/shaved tumours under anaesthetic prior to PDT treatments. See Summary of findings 4 and Table 4.

Primary outcomes

Recurrence

Although Rhodes 2004 followed-up patients for five years, they presented the per protocol population data and the denominators to be included for our analyses could not be determined for three-year and five-year recurrence rates. Abbade 2015 showed that at three years, MAL-PDT may increase the risk of recurrence compared to SE (36.36%, 12/33 versus 0%, 0/35) (RR 26.47, 95% CI 1.63 to 429.92; Analysis 10.1). We rated the certainty of evidence as low, rating down two levels for very serious imprecision (very wide 95% CI which indicated a slight increase or very large increase in recurrence risk).

Mosterd 2008 showed that ALA-PDT probably increases the risk of recurrence compared to SE at three years (24.7%, 21/85 versus 2.3%, 2/88, respectively) (RR 10.87, 95% CI 2.63 to 44.95; Analysis 11.1). By five years, ALA-PDT probably increases the risk of recurrence compared to SE (27.1%, 23/85 versus 2.3%, 2/88, respectively) (RR 11.91, 95% CI 2.90 to 48.95; Analysis 11.2). We rated the certainty of evidence for both these outcomes as moderate, rating down for serious imprecision (wide 95% CIs and only one study).

Cosmetic outcome (participant- and observer-rated)

Pooling cosmetic results from Szeimies 2008 and Rhodes 2004, we found that when measured at one year, MAL-PDT probably slightly reduces the rate of participant-rated good/excellent cosmetic outcomes compared to SE (RR 1.18, 95% CI 1.09 to 1.27, I^2=0%; Analysis 10.2). When investigator-rated at one year, MAL-PDT probably increases the rate of investigator rated good/excellent cosmetic outcomes compared to SE (RR 1.87. 95% CI 1.54 to 2.26, I^2 = 0%; Analysis 10.2). We rated the certainty of evidence as moderate for both these outcomes, rating down for serious risk of bias (unable to truly blind due to nature of interventions).

Secondary outcomes

Pain during and after treatment

Rhodes 2004 recorded the frequency of patient reported "pain in skin" and "burning sensation of skin" during treatment and follow-up as part of their AE data. MAL-PDT may result in a higher frequency of pain in the skin than SE (13.4%, 7/52 versus 6.1%, 3/49, respectively) (RR 2.20, 95% CI 0.60 to 8.03; Analysis 10.3). We rated the certainty of evidence as low due to the very wide 95% CI. Szeimies 2008 reported pain during and after treatment as part of a "photosensitivity reaction" which included all expected reactions to PDT such a "skin discomfort, burning sensation, stinging and erythema". See Table 1 for further pain data from these studies.

Early treatment failure

At six months follow-up, it is uncertain whether MAL-PDT increases early treatment failures compared to SE as the certainty of evidence is very low due to the very wide 95% CI that meant we rated down three levels for very serious imprecision (RR 11.65, 95% CI 0.67 to 202.74; Analysis 10.4). Rhodes 2004 and Szeimies 2008 did not histologically confirm their early treatment failures and these data were therefore not extracted.

Mosterd 2008 showed that SE may improve the risk of early treatment failures for nBCCs compared to ALA-PDT (7.2%, 6/83 versus 2.3%, 2/88) (RR 3.18, 95% CI 0.66 to 15.32; Analysis 11.3). We rated the certainty of evidence as low, rating down for very serious imprecision (very wide 95% CI that indicates important improvement or worsening in early treatment failures).

Adverse effects

Based on Rhodes 2004, more participants treated with MAL-PDT than SE reported AEs 52% versus 29%, (P = 0.03, Fisher exact test). Most of the AEs were transient local reactions commonly associated with PDT, such as burning sensation of the skin, pain in the skin or erythema. Szeimies 2008 had similar findings (37% versus 14% reported AEs, respectively). Wound infections were reported in three SE participants in Rhodes 2004, one ALA-PDT participant from Mosterd 2008 and one severe wound infection was reported after SE in Szeimies 2008.

See Table 2 for further AE data from the respective studies.

MAL-PDT versus ALA-PDT

One small pilot study (Kuijpers 2006) compared the topical photosensitisers MAL and ALA in 43 participants with a nBCC (< 20 mm diameter) with eight weeks follow-up. Half of the tumours were debulked prior to PDT and conventional treatment protocols were followed (two PDT sessions one week apart). All treated tumours were excised eight weeks following treatment. A second, non-inferiority study (Morton 2018) compared a newer, stable nanoemulsion ALA formulation (BF-200 ALA gel) against MAL-PDT in 231 participants with 275 sBCC and nBCC with one year follow-up. Conventional treatment protocols were followed for both arms. A third study (Salmivuori 2019) compared BF-200 ALA-PDT, hexylaminolevulinate (HAL)-PDT and MAL-PDT in 95 lesions (sBCC and thin nBCCs) with a non-inferiority trial design.

A fourth study (Kessels 2018) compared two-fold ALA-PDT with conventional MAL-PDT in 162 participants with sBCC over a one-year follow-up. The two-fold group were treated with ALA 20% ointment with both PDT treatments done on the same day,

separated by two hours. The MAL-PDT group had the two PDT treatments separated by one week.

Primary outcomes

Recurrence

Morton 2018 and Kessels 2018 had only one-year follow-up and Salmivuori 2019 is still ongoing therefore no three- or five-year recurrence rates reported. As one year is closer to our early treatment failure time point we have just reported this.

Cosmetic outcome (participant- and observer-rated)

In Morton 2018, a blinded investigator assessed cosmetic outcome at one year using a five-point scale (impaired, unsatisfactory, satisfactory, good, very good). Only complete responders were included in the analysis. There is probably little to no difference between BF-200 ALA-PDT (73.2%, 41/56) and MAL-PDT (68.4%, 39/57) on the rate of good/very good cosmetic outcomes (RR 1.07, 95% CI 0.84 to 1.36; Analysis 12.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (wide 95% CI that indicates important improvement and worsening of cosmetic outcome).

Kessels 2018 used two blinded investigators to assess cosmetic outcome on the standard four-point scale. Two-fold ALA-PDT probably slightly increases the rate of good/excellent cosmetic outcomes compared to MAL-PDT (RR 1.19, 95% CI 0.98 to 1.46; Analysis 12.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (wide 95% CI). The outcomes from these two studies were not pooled as they used different cosmetic outcome scales.

Secondary outcomes

Pain during and after treatment

We pooled the pain data from Morton 2018 and Kuijpers 2006 as they had similar PDT protocols and used the same visual analogue scale (VAS). For both studies, VAS scores were slightly higher during cycle two and mean VAS scores ranged over both cycles from 2.4 to 4.8. During cycle one, there is probably little to no difference between ALA-PDT and MAL-PDT on the risk of pain, measured using VAS (mean difference (MD) 0.56, 95% CI -0.76 to 1.88, I^2 = 57%; Analysis 12.2). We rated the certainty of evidence as low, rating down for serious imprecision due to the fairly wide 95% CI and serious inconsistency as I^2 suggests substantial heterogeneity. During cycle two, there is probably little to no difference between ALA-PDT and MAL-PDT on the risk of pain (MD 0.43, 95% CI -0.18 to 1.05; I^2 = 0%; Analysis 12.2). We rated the certainty of evidence as moderate, rating down for serious imprecision.

Based on Kessels 2018, there is probably little to no difference in numerical pain scores (0-10) between two-fold ALA-PDT and MAL-PDT during cycle one (MD -0.37, 95% CI -1.13 to 0.39; Analysis 12.3). For cycle 2, there is probably a slightly higher numerical pain score with twofold ALA-PDT over MAL-PDT (3.36 +/- 2.57 versus 2.48 +/- 2.57, respectively) (MD 0.88, 95% CI 0.09 to 1.67; Analysis 12.3). We rated the certainty of evidence as moderate for both these outcomes, rating down for serious imprecision.

See Table 1 for further pain data.

Early treatment failure

In Kuijpers 2006, at eight weeks there may be little to no difference between MAL-PDT and ALA-PDT on the risk of early treatment failure rates (28.6%, 6/21 versus 27.3%, 6/22, respectively) (RR 0.95, 95% CI 0.37 to 2.49; Analysis 12.4). We rated the certainty of evidence as low due to very serious imprecision (very wide 95% CI that indicates important benefit and harm). Based on Salmivuori 2019, there may be fewer early treatment failures at 3 months with MAL-PDT compared to BF-200 ALA-PDT (3.2%, 1/31 versus 9.1%, 3/33, respectively) (RR 2.82, 95% CI 0.31 to 25.68; Analysis 13.1). We rated the certainty of evidence as low due to very serious imprecision (very wide 95% CI that indicates important improvement or worsening in early treatment failures). Morton 2018 did not histologically confirm early treatment failures and we have not extracted these data.

Based on Kessels 2018, there may be slightly more early treatment failures with MAL-PDT compared with two-fold ALA-PDT (5.1%, 4/79 versus 3.8%, 3/79, respectively) (RR 0.75, 95% CI 0.17 to 3.24; Analysis 12.4). We rated the certainty of evidence as low due to very serious imprecision (very wide 95% CI that indicates important improvement or worsening in early treatment failures).

Adverse effects

In Morton 2018, the most frequently reported AEs were mild-to-moderate pain, erythema, pruritus and oedema and frequencies were comparable between the two groups. Two-fold ALA-PDT resulted in more post-treatment AEs compared with MAL-PDT. See Table 2 for further AE data.

HAL-PDT versus MAL-PDT

Early treatment failure

Based on Salmivuori 2019 (detailed above), we are uncertain whether there is any difference in the three-month early treatment failure rate between HAL-PDT and MAL-PDT (6.5%, 2/31 versus 3.2%, 1/31, respectively) because the certainty of evidence was rated as very low due to a very wide 95% CI that meant we rated down three levels for imprecision (RR 2.00, 95% CI 0.19 to 20.93; Analysis 14.1).

HAL-PDT versus BF-200 ALA-PDT

Early treatment failure

Based on Salmivuori 2019 (detailed above), there may be fewer early treatment failures at three months with HAL-PDT compared to BF-200 ALA-PDT(6.5%, 2/3 versus 9.1%, 3/33) (RR 0.71, 95% CI 0.13 to 3.97; Analysis 15.1). We rated the certainty of evidence as low (very wide 95% CI that indicates important improvement or worsening in early treatment failures).

Adverse effects

Severity of post-treatment reactions were visually assessed (on a scale: none/minimal/mild/moderate/severe). HAL-PDT had 12 lesions with a moderate reaction and 13 lesions with a severe reaction. BF-200 ALA-PDT had 13 moderate and 11 severe reactions. MAL-PDT had 13 moderate and nine severe reactions. Overall, there was no significant difference between the three groups P = 0.49).

There was one treatment-related withdrawal from the trial, as one patient from the MAL group experienced remarkable swelling, oedema, erythema and haematoma in the treatment area.

PDT versus cryosurgery

Two studies compared PDT against cryosurgery. One study (Basset-Seguin 2008) compared a single session of MAL-PDT against cryosurgery in 118 participants with 219 sBCCs over 5 years follow-up. A second study (Wang 2001) compared a single session of ALA-PDT (against cryosurgery) in 88 participants with nBCC and sBCC over 1 year follow-up. The standard European protocol for PDT is two PDT sessions separated by 1 week and therefore the single PDT sessions performed in these studies would no longer be considered the standard of care. See Table 5.

Primary outcomes

Recurrence

There may be little to no difference between MAL-PDT and cryosurgery on the risk of recurrence at three years (22%, 22/100 versus 19.4%, 18/93) (RR 1.14, 95% CI 0.65 to 1.98; Analysis 16.1). We rated the certainty of evidence as low, rating down for very serious imprecision (very wide 95% CI that indicates important benefit and harm).

At five years there may be little to no difference between MAL-PDT and cryosurgery on the risk of recurrence (22%, 22/100 versus 20%, 19/93, respectively) (RR 1.08, 95% CI 0.62 to 1.86; Analysis 16.2). We rated the certainty of evidence as low for very serious imprecision (very wide 95% CI that indicates important benefit and harm).

Cosmetic outcome (participant- and observer-rated)

When participant-rated at one year on a four-point scale, MAL-PDT probably increases the rate of good/excellent cosmetic outcomes compared to cryosurgery (100%, 51/51 versus 81.3%, 39/48, respectively) (RR 1.23, 95% CI 1.07 to 1.41; Analysis 16.3). When investigator-rated on a four-point scale, MAL-PDT probably increases the rate of good/excellent cosmetic outcomes compared to the cryosurgery (89%, 45/51 versus 61%, 29/48, respectively) (RR 1.46, 95% CI 1.14 to 1.88; Analysis 16.3). Wang 2001 assessed cosmetic outcome based on hypo- and hyperpigmentation, scar and tissue defect and then gave an overall investigator rated assessment based on a four-point scale. The study showed that ALA-PDT probably increases the rate of good/excellent cosmetic outcomes at one year compared to cryosurgery (92.8%, 39/42 versus 54.1%, 20/37) (RR 1.72, 95% CI 1.26 to 2.34; Analysis 17.1). We rated the certainty of evidence as moderate for all these outcomes, rating down for serious risk of blinding bias due to the nature of the interventions.

Secondary outcomes

Pain during and after treatment

Basset-Seguin 2008 presented pain data within the adverse effects data. There may be little to no difference between MAL-PDT and cryosurgery on the risk of pain reported as an AE (33%, 19/58 versus 37%, 22/60, respectively) (RR 1.12, 95% CI 0.68 to 1.84; Analysis 16.4). We rated the certainty of evidence as low (very wide 95% CI that indicates important benefit and harm). Wang 2001 measured pain during and the first week after treatment by providing participants with a self-registration VAS form which ranged from 0 mm (no pain) to 115 mm (unbearable pain). Raw data with standard deviations were available for the mean during treatment VAS scores which showed that ALA-PDT probably results in slightly more pain than cryosurgery (MD 11.00, 95% CI -1.12 to 23.12; Analysis 17.2). We rated the certainty of evidence as

moderate rating down for serious imprecision (only one study and wide 95% CI). In the first week after treatment,

See Table 1 for further pain data.

Early treatment failure

At three months, there may be slightly fewer early treatment failures with MAL-PDT compared to cryosurgery (2.9%, 3/103 versus 5.1%, 5/98, respectively) (RR 0.57, 95% CI 0.57 to 2.33; Analysis 16.5). We rated the certainty of evidence as low, rating down for very serious imprecision (very wide 95% CI that indicates important benefit and harm).

Adverse effects

See Table 2 for further AE data.

Imiquimod cream versus MAL-PDT

One study (Arits 2013) assessed whether imiquimod cream and 5-FU cream were non-inferior to MAL-PDT in 601 participants with a single sBCC (anywhere except high-risk face/scalp) in a three-arm RCT with five years follow-up. A pre-specified non-inferiority margin of 10% was used. See Summary of findings 5.

Primary outcomes

Recurrence

Imiquimod cream probably reduces the risk of recurrence at three years compared to MAL-PDT (22.8%, 34/149 versus 51.6%, 66/128, respectively) (RR 0.44, 95% CI 0.32 to 0.62; Analysis 18.1). We rated the certainty of evidence as moderate, rating down for serious imprecision as this was a single study.

At five years, imiquimod cream probably reduces the risk of recurrence compared to MAL-PDT (28.6%, 36/126 versus 68.6%, 70/102) (RR 0.42, 95% CI 0.31 to 0.57; Analysis 18.2). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Cosmetic outcome (participant- and observer-rated)

A blinded observer-rated cosmetic outcome at one year on a four-point scale. There is probably little to no difference between imiquimod and MAL-PDT on the rate of good/excellent cosmetic outcomes (RR 0.98, 95% CI 0.84 to 1.16; Analysis 18.3). We rated the certainty of evidence as moderate (only one study).

Secondary outcomes

Pain during and after treatment

Maximum pain was recorded on VAS for all interventions at the end of each week of treatment. The scores were then interpreted as absent/mild (0-3), moderate (4-6) and severe (7-10). We selected the week or treatment cycle (presented for PDT only) with the highest reported moderate/severe pain to overcome differences in timing of reported pain with the different interventions. Week six had the highest reported pain for imiquimod (18% of patients reported moderate/severe pain) and treatment cycle two for MAL-PDT (31% of patients reporting moderate/severe pain). Our analysis showed that imiquimod probably reduces the risk of moderate/severe pain compared to MAL-PDT (RR 0.60, 95% CI 0.41 to 0.87; Analysis 18.4). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study). See Table 1 for further pain data from this study.

Early treatment failure

At three months, there may be little to no difference between imiquimod and MAL-PDT on the risk of early treatment failures (10.1%, 19/189 versus 15.8%, 31/196) (RR 0.64, 95% CI 0.37 to 1.09; Analysis 18.5). We rated the certainty of evidence as moderate, rating down for serious imprecision (wide 95% CI, including the null effect which indicates there may be an important difference or no difference between the two treatments).

Adverse effects

Participants treated with imiquimod more often reported moderate to severe local swelling, erosion, crust formation and itching of skin compared to the MAL-PDT group. There were no unexpected serious adverse reactions in the MAL-PDT group, but 4.8% (nine participants) were reported to have a suspected unexpected serious adverse reaction (SUSAR) in the imiquimod group for influenza-like symptoms (n = 8) and a local wound infection; however, none of the participants were admitted to hospital. See Table 2 for further AE data from this study.

5-fluorouracil cream versus MAL-PDT

One study (Arits 2013) assessed the effects of 5-FU cream versus MAL-PDT; this study is described above in section 5. See Table 6.

Primary outcomes

Recurrence

5-FU cream probably reduces the risk of recurrence compared to MAL-PDT at three years (34.2%, 50/146 versus 52.4%, 66/126, respectively) (RR 0.65, 95% CI 0.49 to 0.86; Analysis 19.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Similar findings were also seen at five years, where 5-FU cream probably reduces the risk of recurrence compared to MAL-PDT (46%, 57/124 versus 68.7%, 70/102, respectively) (RR 0.67, 95% CI 0.53 to 0.84; Analysis 19.2). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Cosmetic outcome (participant- and observer-rated)

There is probably little to no difference between 5-FU cream and MAL-PDT on the rate of good/excellent cosmetic outcomes (RR 0.92, 95% CI 0.78 to 1.09; Analysis 19.3). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Secondary outcomes

Pain during and after treatment

The maximum recorded pain for 5-FU cream was recorded during week four (final week) of treatment with 12% of patients reporting moderate/severe pain. 5-FU cream probably reduces the risk of moderate/severe pain compared to MAL-PDT (RR 0.41, 95% CI 0.26 to 0.63; Analysis 19.4). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study). See Table 1 for further pain data.

Early treatment failure

There may be little to no difference between 5-FU cream and MAL-PDT on the risk of early treatment failure (12.1%, 24/198 versus 15.8%, 31/196) (RR 0.77, 95% CI 0.47 to 1.26; Analysis 19.5). We

rated the certainty of evidence as low, rating down two levels for very serious imprecision (very wide 95% CI that indicates important benefit and harm).

Adverse effects

Unexpected serious adverse reactions were reported in 2.1% (four participants) in the 5-FU cream group: two local wound infections, one case of erysipelas of the leg and one leg ulcer. See Table 2 for further AE data.

Laser ALA-PDT versus broadband halogen light ALA-PDT

One study (Soler 2000) of 83 participants (245 lesions) with sBCC compared two different light sources: laser or broadband lamp light with ALA-PDT. The study only had six months follow-up. The laser light was 630 nm from a copper vapour dye laser with doses ranging between 100 J/cm^2 to 150 J/cm^2. The broadband light used a halogen bulb and a filter to produce red light (570 nm to 740 nm) with a dose ranging between 150 J/cm^2 to 200 J/cm^2 as well as infrared radiation (1180 nm to 2700 nm).

Primary outcomes

Cosmetic outcome (participant- and observer-rated)

At six months, cosmetic outcome was rated by two observers (only one blinded) on a four-point scale (poor, fair, good, excellent). Only tumours that had completely responded were scored leading to an unequal attrition rate between the groups. There may be little to no difference on the rate of good/excellent cosmetic outcomes between the two light sources (RR 0.91, 95% CI 0.82 to 1.01; Analysis 20.1). We rated the certainty of evidence as low, rating down for serious imprecision (only one study) and serious risk of attrition bias.

Secondary outcomes

Pain during and after treatment

There is probably little to no difference between laser ALA-PDT and broadband light ALA-PDT on the frequency of pain (reported as any type of discomfort) during and immediately after treatment (83%, 34/41 versus 76%, 32/42) (RR 1.09, 95% CI 0.87 to 1.35; Analysis 20.2). In the first week after treatment, there is probably little to no difference in the frequency of pain reported between the two light sources (RR 0.93, 95% CI 0.70 to 1.22; Analysis 20.2). We rated the certainty of evidence for both these outcomes as moderate, rating down for serious imprecision (only one study). See Table 1 for further pain data from this study.

Early treatment failure

The study did not histologically confirm clinical treatment failures; therefore, we have not extracted the data for this outcome.

Adverse effects

Some discomfort during and after illumination was reported by 83% of participants receiving laser ALA-PDT and 76% of those receiving broadband PDT. No serious AEs were reported during the 6-month follow-up. See Table 2 for further AE data from this study.

Ablative fractional laser (AFXL) MAL-PDT versus MAL-PDT

Two small pilot studies compared ablative fractional laser (AFXL) pre-treatment prior to MAL-PDT against conventional MAL-PDT with one year follow-up. This is based on the rationale that AFXL pre-

treatment increases uptake of MAL deeper into the tumour. One study (Haak 2015) randomised 32 participants with facial nBCC and the other (Choi 2016) randomised 39 participants (42 lesions) with facial nBCC. The first study used a fractional CO_2 laser and the second an erbium:YAG laser.

Primary outcome

Cosmetic outcome (participant- and observer-rated)

Cosmetic outcomes were assessed by a blinded investigator in both studies at one year using a four-point scale. The pooled results from both studies showed there may be little to no difference between AFXL-PDT and MAL-PDT on the rate of good/excellent cosmetic outcomes (RR 1.12, 95% CI 0.54 to 2.31, I^2 = 66%; Analysis 21.1). We rated the certainty of evidence as low, rating down two levels for very serious imprecision (very wide 95% CI that indicates important benefit and harm). Haak 2015 presented participant reported cosmetic outcomes, showing that there is probably little to no difference between AFXL-PDT and MAL-PDT on the rate of good/excellent cosmetic results (RR 0.94, 95% CI 0.75 to 1.17; Analysis 21.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Secondary outcomes

Pain during and after treatment

Pain was recorded using VAS for both studies but individual data were not presented. Both studies reported in their text that there was "no statistically significant difference" in pain scores between the treatment groups. See Table 1 for further pain data from these studies.

Early treatment failure

A pooled analysis of both studies showed that AFXL-PDT probably reduces the risk of early treatment failures compared to MAL-PDT at three months (RR 0.38, 95% CI 0.17 to 0.84, I^2 = 0%; Analysis 21.2). We rated the certainty of evidence as moderate, rating down for serious imprecision (fairly wide 95% CI).

Adverse effects

See Table 2 for further AE data from these studies.

MAL-PDT versus placebo

Two RCTs with the "same design and procedures" (Foley 2009a and Foley 2009b) randomised 131 participants (160 nBCC) to MAL-PDT versus placebo. We have presented the data analyses as one study under Foley 2009a as the data from the separate studies were not available. All tumours were debulked prior to treatment and all treatment sites were excised at three months (clinical non-responders) or six months (clinical responders) after the last treatment.

Primary outcomes

Cosmetic outcome (participant- and observer-rated)

Only the complete clinically/histologically clear lesions were assessed for cosmetic outcome. The authors only presented the investigator-rated data (four-point scale). There is probably little to no difference between MAL-PDT and placebo on the rate of good/excellent cosmetic outcomes (RR 1.05, 95% CI 0.91 to 1.21; Analysis 22.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (fairly wide 95% CI).

Secondary outcomes

Pain during and after treatment

Frequency of "burning sensation of skin", "pain in skin" and "stinging of skin" were reported as part of treatment-related local adverse effects. MAL-PDT probably increases the risk of "pain in skin" compared to placebo (RR 3.94, 95% CI 1.17 to 13.32; Analysis 22.2). We rated the certainty of evidence as moderate, rating down for serious imprecision (fairly wide 95% CI). See Table 1 for further pain data from this study.

Early treatment failure

MAL-PDT may reduce the risk of early treatment failures compared to placebo (RR 0.36, 95% CI 0.24 to 0.54; Analysis 22.3). We rated the certainty of evidence as low, rating down for serious imprecision (only one study).

Adverse effects

See Table 2 for further AE data from this study.

6. Imiquimod cream

Imiquimod cream versus 5-fluorouracil cream

One study (Arits 2013) assessed the effects of imiquimod cream versus 5-FU cream; this study is described above in section 5. See Table 7.

Primary outcomes

Recurrence

Imiquimod probably reduces the risk of recurrence compared to 5-FU cream at three years (23.4%, 34/145 versus 34.2%, 50/146, respectively) (RR 0.68, 95% CI 0.47 to 0.99; Analysis 23.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Imiquimod probably reduces the risk of recurrence compared to 5-FU cream at five years (28.6%, 36/126 versus 46%, 57/124, respectively) (RR 0.62, 95% CI 0.44 to 0.87; Analysis 23.2). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Cosmetic outcome (participant- and observer-rated)

When blinded observer-rated at 1 year, there is probably little to no difference between imiquimod and 5-FU cream on the rate of good/excellent cosmetic outcomes (61.4%, 113/184 versus 57.5%, 111/193, respectively) (RR 1.07, 95% CI 0.90 to 1.26; Analysis 23.3). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Secondary outcomes

Pain during and after treatment

We compared the week with the highest frequency of reported of moderate/severe pain during treatment for each intervention (week six for imiquimod and week 4 for 5-FU cream). There is probably a slightly increased risk of moderate/severe pain with imiquimod compared with 5-FU cream (18.2%, 33/181 versus 12.5%, 23/184) (RR 1.46, 95% CI 0.89 to 2.34; Analysis 23.4). We rated the certainty of evidence as moderate, rating down for serious imprecision (wide 95% CI that indicates increased pain or slightly less pain). See Table 1 for further pain data from this study.

Early treatment failure

There may be little to no difference between imiquimod and 5-FU cream on the risk of early treatment failures (10%, 19/189 versus 12.1%, 24/198) (RR 0.83, 95% CI 0.47 to 1.46; Analysis 23.5). The certainty of evidence is low due to very serious imprecision with a wide 95% CI that indicates there may be an important reduction or an important increase in early treatment failures.

Adverse effects

See Table 2 for further AE data from this study.

Imiquimod cream versus radiotherapy

One small study (Garcia-Martin 2011) randomised 27 participants with nBCC of the eyelid to either imiquimod (five days a week for six weeks) or conventional radiotherapy with two years follow-up. The study was at high risk of selection bias due to the method of randomisation (based on birthday of participant).

Primary outcomes

Recurrence

There were no recurrences in either group during the follow-up period and therefore we were unable to assess effect size.

Cosmetic outcome (participant- and observer-rated)

Cosmesis was patient-rated on a three-point scale (bad, good, excellent), but this was only measured at 6 weeks following treatment. Observer-rated cosmetic outcomes were also recorded on a three-point scale, but the data were not presented in the paper. All participants in the imiquimod group rated the cosmetic result as excellent and all those in the radiotherapy group rated the cosmetic result as good. There may be more participant-rated excellent cosmetic outcomes at 6 weeks with imiquimod compared to radiotherapy (RR 25.19, 95% CI 1.66 to 382.13; Analysis 24.1). We rated the certainty of evidence as low due to the very wide 95% CI.

Secondary outcomes

Pain during and after treatment

Blink discomfort was reported in 60% (9/15) of participants in the imiquimod group and blink discomfort and dry eye were reported in 50% (6/12) participants in the radiotherapy group. Intense conjunctival irritation occurred in 13.3% (2/15) of participants in the imiquimod group.

Early treatment failure

There were no early treatment failures at six weeks following treatment and therefore no effect size was estimable.

Adverse effects

All participants in the radiotherapy group presented with loss of eyelashes in one or both eyelids, 16.6% (2/12) of participants had inferior eyelid retraction with secondary ectropion, and three of the participants reported dry eye symptoms after radiotherapy. Tolerability during treatment was better in the radiotherapy group. Seven of the 15 participants in the imiquimod group reported 'bad' tolerability, but these symptoms disappeared when the period of cream application ended. Only one patient in the radiotherapy group rated 'bad' tolerability. See Table 2 for further AE data and Table 1 for pain data from this study.

Imiquimod with occlusion versus imiquimod without occlusion

Two similar dose-response studies (Sterry 2002a; Sterry 2002b) examined imiquimod cream with or without occlusion in sBCC (93 participants; Sterry 2002a) and nBCC (90 participants; Sterry 2002b). Patients were randomised to one of four groups to apply imiquimod 5% cream two or three days per week either with or without occlusion for six weeks. At the end of the six-week treatment period, the entire target tumour area was excised and histologically examined for evidence of residual tumour. Size and location of lesions were not given.

Secondary outcomes

Early treatment failure

Pooling the data from both studies (we also combined the different dosing regimen group as the number of participants was small) found there may be little to no difference between the occlusion and no occlusion groups (38.2%, 34/89 versus 41.5%, 39/94) on the risk of early treatment failures (RR 0.91, 95% CI 0.64 to 1.33; Analysis 25.1, I² = 0%). We rated the certainty of evidence as low due to very serious imprecision (wide 95% CI that indicates that includes the possibility of important benefit or harm).

Adverse effects

See Table 2 for further AE data from these studies.

Imiquimod versus placebo

One trial (Beutner 1999) randomised 35 participants with sBCC and nBCC to imiquimod cream or vehicle cream in one of five dosing regimens for up to 16 weeks. Another trial of 128 participants (Geisse 2002) compared imiquimod twice daily, once daily, five days per week or three days per week versus vehicle for sBCCs. Marks 2001 compared different dosages of imiquimod cream applied for six weeks in 99 Australian participants with primary sBCCs. Geisse 2004 randomised 724 participants with sBCC to imiquimod cream daily either five times per week or seven times per week for six weeks versus vehicle. One further study (Schulze 2005), randomised 166 participants with sBCC to imiquimod cream or vehicle, once a day for six weeks. Another two similar studies (Shumack 2002a; Shumack 2002b) randomised 99 and 92 participants with nBCC, respectively to four different dosing regimens (three or seven days per week or twice daily for three or seven days per week) of imiquimod cream or vehicle over 12 and six weeks, respectively. All these studies were industry sponsored.

Early treatment failure

Pooled analysis of the five studies showed that imiquimod reduces the risk of early treatment failures compared to vehicle by 75% (RR 0.25, 95% CI 0.19 to 0.32, I² = 57%; Analysis 26.1). We rated the certainty of evidence as high.

Dose-ranging studies

One study (Ezughah 2008) compared the tolerability of two regimens of imiquimod for the treatment of sBCC with one year follow-up: five weeks of once-daily dosing with a one-week interval in the middle of the course (R1) versus eight weeks of treatment with once-daily dosing for alternate weeks (R2). One study (Eigentler 2007) compared imiquimod three times a week over eight weeks versus three times a week over 12 weeks in 102

participants with nBCC up to 1.5 cm, located anywhere on the body (except close to the eyes).

Primary outcomes

Recurrence

Ezughah 2008 only followed up patients for one year and as we have not included the early treatment failure data (as not histologically confirmed) we have included these data. R2 imiquimod dosing may result in fewer recurrences than R1 imiquimod dosing (12.5%, 2/16 versus 57.1%, 8/14, respectively) (RR 4.57, 95% CI 1.16 to 18.05; Analysis 27.1). We rated the certainty of evidence as moderate, rating down for serious imprecision due to the wide 95% CI and the small numbers of participants.

Secondary outcomes

Early treatment failure

Based on Eigentler 2007, at eight weeks post-treatment there may be little to no difference in early treatment failure rates between imiquimod three times a week over eight weeks and three times a week over 12 weeks (35.6%, 16/45 versus 37.8%, 17/45) (RR 0.94, 95% CI 0.55 to 1.62; Analysis 28.1). We rated the certainty of evidence as low, rating down two levels for very serious imprecision (very wide 95% CI that indicates important benefit and harm).

Pain during and after treatment

In Ezughah 2008, a weekly VAS for tolerability was measured using a 10 cm line scale ranging from 0 cm (not unpleasant) to 10 cm (absolutely intolerable). There may be little to no difference between the eight-week and five-week treatment groups on the mean composite VAS scores at eight weeks (median score 0.85 cm versus median score 0.30 cm; 95% CI for difference in medians: 20.40 to 0.9 cm, P = 0.39), as reported in the paper. Eigentler 2007 did not present pain data separately for the two treatment arms. See Table 1 for further pain data from these studies.

Adverse effects

See Table 2 for AE data from these studies.

7. 5-Fluorouracil

Phosphatidyl choline versus petrolatum vehicle

One small pilot study (Romagosa 2000) compared 5-FU cream in petrolatum with 5-FU cream in phosphatidyl choline (a transepidermal carrier to aid penetration) in 13 participants (17 lesions, non sBCC, at least 0.7cm diameter, facial lesions excluded). Participants underwent excision of the treated BCC site at week-16.

Secondary outcomes

Early treatment failure

There may be fewer early treatment failures with 5-FU cream in phosphatidyl choline compared to 5-FU cream in petrolatum (10%, 1/0 versus 42.9%, 3/7, respectively) (RR 0.23, 95% CI 0.03 to 1.81; Analysis 29.1). We rated the certainty of evidence as low, rating down two levels for very serious imprecision (very wide 95% CI that indicates important benefit and harm).

Adverse effects

In the Romagosa 2000 study, local irritation, erythema, ulceration and tenderness were common reactions but were reported to be

well-tolerated by the participants. Minimal itching and discomfort were experienced by some of the participants in both treatment arms. See Table 2 for further AE data from this study.

Intralesional 5-fluorouracil/epinephrine gel

One study (Miller 1997) compared six treatment regimens of intralesional 5-FU/epinephrine gel in 122 participants with sBCC and nBCC located on the head, upper and lower extremities: 1 mL versus 0.5 mL both once a week for six weeks; 1 mL versus 0. 5mL both twice a week for three weeks; 0.5 mL twice a week for four weeks versus 0.5 mL three times a week for two weeks.

Early treatment failure

There may be fewer early treatment failures with 1 mL intralesional 5-FU compared with 0. 5mL intralesional 5-FU when given twice a week for three weeks (5.6%, 1/18 versus 21.1%, 4/19, respectively) (RR 0.26, 95% CI 0.03 to 2.14; Analysis 31.1). We rated the certainty of evidence as low, rating down two levels for very serious imprecision (very wide 95% CI that indicates important benefit and harm). It is uncertain whether there is any difference between the other two intralesional regimens as we rated the certainty of evidence for these comparisons as very low due, rating down three levels for very serious imprecision (Analysis 30.1; Analysis 32.1).

Adverse effects

All participants had transient, moderate to severe stinging, burning or pain at the time of injection. Local tissue reactions were confined to the treatment site and included erythema, swelling, desquamation, erosions and eschar in most participants. See Table 2 for further AE data from this study.

8. Electrochemotherapy

Electrochemotherapy versus surgical excision

One study (Clover 2016) compared bleomycin electrochemotherapy (ECT) to SE in 100 participants with 117 low-risk and high-risk BCC (superficial, nodular, infiltrative and morphoeic subtypes). Noduar and nodular/infiltrative BCC were the most common subtype. Location of lesions was not described. Follow-up was for five years. The author of the abstract was contacted and unpublished data were obtained.

Primary outcomes

Recurrence

ECT may result in more recurrences (10.5%, 4/38 versus 2.8%, 1/36, respectively) than SE at three years (RR 3.79, 95% CI 0.44 to 32.32; Analysis 33.1) and 5 years (13.5%, 5/37 versus 2.8%, 1/36) (RR 4.86, 95% CI 0.60 to 39.63; Analysis 33.2). We rated the certainty of evidence for both these outcomes as low rating down two levels for the very wide 95% CI that includes the possibility of important benefit or harm.

Cosmetic outcome (participant- and observer-rated)

When assessed with the Vancouver scar scale by four blinded plastic surgeons 18 months after treatment, the authors reported there was no significant difference between ECT and SE; however the raw data were not available for further analysis.

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9. Ingenol mebutate

Day 1 and 2 versus day 1 and 8 regimens

One study (Siller 2010) randomised 60 participants with sBCC to one of two different treatment regimens (days 1 and 2 dosing or days 1 and 8 dosing) and then randomised again within each group to treatment with one of three different concentrations of ingenol mebutate gel (0.0025%, 0.01% and 0.05%), or vehicle. The main outcome measures were the incidence and severity of adverse effects and local skin responses.

Secondary outcomes

Pain during and after treatment

Intensity of pain data were not presented. Within the adverse effects data, only two patients reported application site pain and these were in the highest dose ingenol group (0.05%) in the days 1 and 8 regimen. See Table 1 for further pain data from this study.

Early treatment failure

At week-12, in the day 1 and 2 dosing group, ingenol 0.05% gel probably results in fewer early treatment failures than vehicle gel (37.5%, 3/8 versus 100%, 6/6, respectively) (RR 0.42, 95% CI 0.18 to 0.97; Analysis 34.1). We rated the certainty of evidence as moderate, rating down for serious imprecision. For the lower ingenol concentration in the day 1 and 2 dosing group, as well as all concentrations in the day 1 and 8 dosing group, there may be little to no difference between ingenol and vehicle (see analysis Analysis 35.1 and Analysis 36.1 for RRs). We rated the certainty of evidence as low for both these outcomes, rating down for serious imprecision due to the wide 95% CIs and low numbers of participants involved.

Adverse effects

See Table 2 for further AE data from this study.

Occlusion versus no occlusion

One study (Spelman 2014) compared ingenol mebutate 0.05% gel given on three consecutive days with full occlusion (aluminium disk dressing) versus semi-occlusion (Opsite™ Disk) and no occlusion in 75 participants with sBCC (4 mm-15 mm to diameter) on the trunk/extremities in a phase two RCT with four months follow-up.

Secondary outcomes

Early treatment failure

At four months, ingenol with full occlusion may reduce the risk of early treatment failures compared to no occlusion (29.6%, 8/27 versus 45.5%, 11/24, respectively) (RR 0.65, 95% CI 0.31 to 1.34; Analysis 36.1), and semi-occlusion may increase the risk of early treatment failures compared to no occlusion (62.5%, 15/24 versus 45.8%, 11/24, respectively) (RR 1.36, 95% CI 0.80 to 2.33; Analysis 36.1). We rated the certainty of evidence as low for both these outcomes, rating down for serious imprecision due to the wide 95% CI and low numbers of participants involved.

Adverse effects

The percentage of participants with AEs were similar across all three treatment groups. The most common AE was application site pain. See Table 2 for further AE data from this study.

10. Solasodine glycosides

One study (Punjabi 2008) of 94 participants compared solasodine glycoside (Zycure) cream to matching vehicle in BCCs at least 0.5cm diameter (excluding morphoeic BCC). Lesions were treated twice daily under occlusion with solasodine glycoside cream or vehicle for 8 weeks.

Primary outcomes

Cosmetic outcome (participant- and observer-rated)

Cosmetic outcome was evaluated by an assessment of scarring during the follow-up (categorized as none, mild, moderate, severe). The authors reported there was no statistically significant difference between the treatment groups; however, raw data were not presented for further analysis.

Secondary outcomes

Early treatment failure

At the end of 8 weeks of treatment, a 2 mm punch biopsy was performed on all lesions. Solasodine glycoside cream probably reduces the risk of early treatment failures compared to vehicle (33.9%, 21/62 versus 75%, 24/32, respectively) (RR 0.45, 95% CI 0.30 to 0.67; Analysis 37.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Adverse effects

No major treatment-related adverse effects were reported. See Table 2 for further AE data from this study.

11. Topical valproic acid and tazarotene

One study (2005-001474-27) randomised 50 participants (subtype not stated, located anywhere except eyelids, nose, lips, anogenital) to topical valproic acid (Baceca® 3% gel) and tazarotene (Zorac® 0.1% gel) against placebo gel and tazarotene. Treatment lasted eight weeks and involved applying valproic acid or placebo gel before bedtime and 15 to 30 minutes later tazarotene was applied. Participants in both groups that did not show a complete clearance after eight weeks, completed a further eight weeks of treatment with valproic acid and tazarotene (cross-over design).

Early treatment failure

At three months follow-up, there may be slightly fewer early treatment failures in the valproic acid gel and tazarotene group compared with the placebo gel and tazarotene group (31%, 8/25 versus 52%, 13/25, respectively) (RR 0.62, 95% CI 0.31 to 1.22; Analysis 38.1). We rated the certainty of evidence as low, rating down one level for serious imprecision (wide 95% CI that indicates important benefit and slight harm).

Adverse effects

Erythema, itching, ulceration and localised pain were the most frequently reported AEs across both groups. There were no drug-related severe AEs. See Table 2 for further AE data from this study.

12. Topical diclofenac gel and calcitriol ointment (vitamin D)

One study (Brinkhuizen 2016) of 128 participants (64 sBCC and 64 nBCC) compared diclofenac 3% gel (Solaraze™), calcitriol 3 µg/g ointment (Silkis®), a combination of both or no topical treatment. The active treatments were applied twice daily under occlusion for

eight weeks. We have not included the control arm comparisons in our analyses.

Secondary outcomes

Early treatment failure

Early treatment failure was measured at eight weeks of treatment. Diclofenac gel monotherapy may reduce the risk of early treatment failures compared to calcitriol ointment (53.3%, 16/30 versus 97%, 31/32, respectively) (RR of 0.55, 95% CI 0.39 to 0.77; Analysis 39.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

There may be little to no difference between diclofenac gel monotherapy and combination treatment of diclofenac and calcitriol on the risk of early treatment failures (53.3%, 16/30 versus 61.3%, 19/31, respectively) (RR 0.87, 95% CI 0.56 to 1.35; Analysis 40.1). We rated the certainty of evidence as low, rating down for very serious imprecision due to the 95% CI that indicates important benefit and harm.

Calcitriol ointment may increase the risk of early treatment failures compared to combination treatment of diclofenac and calcitriol (97%, 31/32 versus 61.3%, 19/31, respectively) (RR 1.58, 95% CI 1.19 to 2.11; Analysis 41.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Adverse effects

In all intervention groups mild to moderate application-site reactions were reported. See Table 2 for further AE data from this study.

13. Pulsed dye laser (PDL)

One session versus two sessions

One small pilot study (Abd El-Naby 2019) randomised 22 participants with 22 BCCs (17 nBCCs, three sBCC, one pigmented BCC and one cystic BCC located on the face/scalp) to treatment with one or two sessions (two weeks apart) of PDL (595 nm, fluency 7 J/cm^2, pulse width 20 ms, rate 1 Hz with 4 mm margins) with six months follow-up.

Secondary outcomes

Early treatment failure

Four weeks after the last treatment all lesions were excised and early treatment failure rates were very high. Two sessions of PDL may slightly reduce the rate of early treatment failures compared to one session of PDL (81.9%, 9/11 versus 100%, 11/11, respectively) (RR 0.83, 95% CI 0.60 to 1.13; Analysis 42.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (small numbers involved in study and wide 95% CI).

Adverse effects

The paper reported the technique was tolerable and safe with minimal side effects but no further data were given.

7mm spot size single pulses versus 10 mm spot size stacked pulses

One small pilot study (Tran 2012) randomised 17 participants with 20 BCCs (13 nBCCs, 6 multifocal BCCs, one superficial BCC located on trunk/limbs) into three treatment groups: a control (no

treatment) group; PDL (595 nm, fluency 15 J/cm^2, pulse width 3 ms) using 7 mm spot size and single pulses and PDL (595 nm, fluency 7.5 J/cm^2, pulse width 3 ms) using 10 mm spot size and double-stacked pulses. All lesions were treated with a 4 mm margin of clinically normal skin. The rationale for increasing spot size and stacking pulses is to increase the depth of penetration of the laser. Three SCC-in-situ lesions were also treated and we have excluded these from our analyses. We have not analysed the control group data as no placebo/sham treatment was given.

Secondary outcomes

Early treatment failure

Six weeks after treatment, all treated lesions were excised. PDL with a 10 mm spot-size and stacked pulses may reduce early treatment failure rates compared to PDL with a 7 mm spot-size and single pulses (28.6%, 2/7 versus 85.7%, 6/7, respectively) (RR 0.33, 95% CI 0.10 to 1.12; Analysis 43.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (small numbers involved in study and wide 95% CI).

Adverse effects

Mild scarring occurred in both treatment arms and by five months post-treatment hypopigmentation was noted. See Table 2 for further AE data from this study.

PDL versus control (sham laser or no treatment)

One study (Karsai 2015) randomised 39 participants (100 sBCC on trunk/extremities) to PDL (wavelength 595 nm; fluence 8 J cm^2; pulse duration 0.5 ms; spot size 10 mm) or sham treatment with six months follow-up. A total of four treatment sessions at three-week intervals were conducted by a dermatologist experienced in laser therapy. Another small pilot study (Eimpunth 2014) randomised 24 participants (24 sBCC or nBCC) to PDL or no treatment. The PDL treatment was one session of double-stacked pulses of PDL using 10 mm spot size, 3 ms pulse width and a fluence of 7.5 J/cm^2 with a 6 mm margin of normal skin around the clinically apparent tumour also treated. Lesions were all subsequently excised and histologically assessed.

Secondary outcomes

Pain during and after treatment

Pain was recorded on VAS (0-10) during treatment. Data presented did not allow for analysis; however, the authors reported that the maximum median score for PDL was 4/10 and for sham was 0/10. See Table 1 for further pain data from this study.

Early treatment failure

At six months, PDL probably reduces the risk of early treatment failures compared to sham laser (21.4%, 12/56 versus 95%, 42/44, respectively) (RR 0.22, 95% CI 0.14 to 0.37; Analysis 44.1). We rated the certainty of evidence as moderate, rating down for imprecision (only one study). PDL may improve the risk of early treatment failure compared to no treatment RR 0.36, 95% CI 0.15 to 0.86; Analysis 45.1). We rated the certainty of evidence as moderate, rating down for serious imprecision due to wide CI and small sample size.

Adverse effects

The main AEs in the PDL group were crusts, hyper- and hypo-pigmentation. See Table 2 for further AE data from this study.

14. Intralesional interferon therapy

Four trials met our inclusion criteria comparing different dosages of interferon and placebo. There were no active comparator studies.

Interferon versus placebo injections

One study (Cornell 1990) of 165 participants (sBCC and nBCC) compared interferon alpha-2b (1.5 million units three times weekly for three weeks) against vehicle with one-year follow-up. Patients were randomised in a 3:1 ratio, interferon:placebo. Another study (Rogozinski 1997) compared recombinant interferon beta (1 million units three times weekly for three weeks) compared to placebo in 35 participants (subtype, size and location of BCC not reported).

Secondary outcomes

Early treatment failure

Based on the Cornell 1990 study, when measured at week 20, interferon alpha-2b probably reduces the risk of early treatment failures compared to intralesional placebo (14.2%, 17/120 versus 71.4%, 30/42, respectively) (RR 0.20, 95% CI 0.12 to 0.32; Analysis 46.1). We rated the certainty of evidence as moderate, rating down for imprecision (only one study). Based on the Rogozinski 1997 study, interferon beta probably reduces the risk of early treatment failures compared to intralesional placebo (53%, 8/15 versus 100%, 18/18) (RR 0.55, 95% CI 0.34 to 0.87; Analysis 47.1). We rated the certainty of evidence as moderate, rating down for imprecision (only one study).

Adverse effects

In the Cornell 1990 study, influenza-like symptoms occurred more commonly in the interferon-treated group than the vehicle group. In the Rogozinski 1997 study, inflammation at the injection site was found in 11 out of 16 participants in the treatment group and four out of 18 receiving placebo. See Table 2 for further AE data from these studies.

Interferon alpha-2a and interferon alpha-2b versus single interferon

One study (Alpsoy 1996) compared interferon alpha-2a, interferon alpha-2b or both interferon alpha-2a and interferon alpha-2b in 45 participants (sBCC, nBCC and morphoeic BCCs located on the head and trunk) with two years follow-up.

Secondary outcomes

Early treatment failure

Interferon alpha-2a and -2b may slightly reduce the risk of early treatment failure compared to interferon alpha-2a (RR 0.80, 95% CI 0.27 to 2.41; Analysis 48.1). Interferon alpha-2a and -2b may slightly reduce the risk of early treatment failure compared to interferon alpha-2B (RR 0.80, 95% CI 0.27 to 2.41; Analysis 49.1). There may be no difference in risk of early treatment failures when comparing interferon alpha-2b with interferon alpha-2a (RR 1.0, 95% CI 0.36 to 2.75; Analysis 50.1). We rated the certainty of evidence as low for all these comparisons due to very serious imprecision (very wide 95% CI that indicated important benefit or harm).

Adverse effects

Pain was experienced at the injection site and all participants had influenza-like symptoms (fever, chills, headaches, fatigue, myalgia) especially within the first two weeks after the initiation of therapy. See Table 1 and Table 2 and for further pain data and AE data from this study.

Sustained release interferon alpha-2b

One study (Edwards 1990) compared different dosing schedules of sustained release interferon (protamine zinc chelate interferon alpha-2b) in 65 participants with nBCC and sBCC (location not reported). Participants were randomised to a single dose of 10 million international units (IU) versus the same dose weekly for three weeks.

Secondary outcomes

Early treatment failure

The three times weekly injection treatment group probably reduces the risk of early treatment failures compared with the single dose arm (20%, 6/30 versus 48.5%, 16/33, respectively) (RR 0.41, 95% CI 0.19 to 0.92; Analysis 51.1). We rated the certainty of evidence as moderate rating down for serious imprecision (wide 95% CI and only one study).

Adverse effects

All participants experienced at least one adverse reaction. Side effects were similar for both single and repeated dosage groups, and were those common to interferon. See Table 2 for further AE data from this study.

15. Topical Sinecatechins

One study (Kessels 2017) compared treatment with 10% sinecatechin ointment (Veregen®) with vehicle in 42 participants with sBCC over eight weeks follow-up.

Secondary outcomes

Early treatment failure

There is probably little to no difference in the risk of early treatment failures between topical sinecatechin ointment (95.2%, 20/21) and placebo (90.5%, 19/21) (RR 1.05, 95% CI 0.89 to 1.25; Analysis 52.1). We rated the certainty of evidence as moderate, rating down for serious imprecision (only one study).

Adverse effects

See Table 2 for further AE data from this study.

Summary of pain data

Pain was reported on a variety of different scales, for example visual analogue and three point scales. Occasionally, qualitative data was captured; pain could be reported as burning, stinging, throbbing, irritation, lingering, tingling, tenderness or blinking discomfort. Pain was rarely reported distal to the treatment site for example pharyngolaryngeal pain after ingenol mebutate gel usage (Siller 2010). Depending on the study, patients could be asked to report any pain during or after treatment; this could be as an isolated assessment or could be done at intervals. Burning was the most common type of pain reported with PDT (Ezughah 2008; Arits 2013; Foley 2009a and Foley 2009b). Some authors reported supplying pre-treatment analgesia before PDT (Choi 2016, Haak 2015) or SE

(Rhodes 2004). Others reported that physical measures to induce analgesia during PDT were permitted (Morton 2018; Szeimies 2008; Wang 2001). Post-treatment analgesia was occasionally permitted after SE (Bath-Hextall 2014), imiquimod, radiotherapy (Garcia-Martin 2011) and sinecatechin applications (Kessels 2017). Pain and tenderness during treatment with imiquimod was expected, and participants were frequently allowed a rest period if needed in order to complete the treatment course (Bath-Hextall 2014; Ezughah 2008; Geisse 2002; Geisse 2004; Shumack 2002a; Shumack 2002b; Sterry 2002a and Sterry 2002b) with occasional participants unable to complete the treatment due to pain despite this (Ezughah 2008; Shumack 2002b). In total five patients discontinued treatment due to pain; four after imiquimod application (Ezughah 2008; Shumack 2002a; Shumack 2002b) and one after MAL-PDT (Rhodes 2004). For further details see Table 1 and Table 2.

Summary of adverse effects data

Patient-reported adverse effects did not always align with those reported by the observer (Eigentler 2007). The most commonly reported adverse effects were due to application site reactions seen in the non-surgical interventions. These manifested as localised inflammation resulting in: itching, weeping, crusting, scabbing, flaking, erythema, blistering, vesicles, eschar, erosions, burning, pain, purpura or swelling. Localised inflammation was reported in 13 of the 14 papers on imiquimod usage (Arits 2013; Bath-Hextall 2014; Eigentler 2007; Ezughah 2008; Garcia-Martin 2011; Geisse 2002; Geisse 2004; Marks 2001; Schulze 2005; Shumack 2002a; Shumack 2002b; Sterry 2002a;Sterry 2002b).

Other treatment modalities resulting in localised inflammation include AFXL-PDT (Haak 2015), intralesional 5-FU (Romagosa 2000), PDL (Eimpunth 2014; Karsai 2015; Tran 2012), radiotherapy (Garcia-Martin 2011), sinecatechins (Kessels 2017), laser/broadband light ALA-PDT (Soler 2000), tazarotene and valproic acid (2005-001474-27) and placebo/vehicle (Foley 2009a; Foley 2009b; Geisse 2002; Kessels 2017; Siller 2010).

Local wound infection or suppuration were reported after surgical treatments such as SE (Kuijpers 2007; Rhodes 2004; Smeets 2004; Szeimies 2008), cryosurgery (Basset-Seguin 2008; Kuijpers 2007; Wang 2001), cryosurgery and curettage (Kuijpers 2007) as well as non-surgical interventions: imiquimod (Arits 2013), 5-FU (Arits 2013), ALA-PDT (Mosterd 2008), but not after MAL-PDT (Rhodes 2004; Szeimies 2008).

Dyspigmentation was seen after treatment with PDL (Abd El-Naby 2019; Eimpunth 2014; Karsai 2015, Tran 2012), imiquimod (Eigentler 2007; Schulze 2005), AFXL-PDT, MAL-PDT (Haak 2015) and in 83% of treated with intralesional 5-FU (Miller 1997).

Reports of radiodystrophy and necrosis decreased over time after radiotherapy treatment (Avril 1997). Necrosis (of grafts) was also seen after SE (Smeets 2004). Scarring was seen after the use of PDL (Eimpunth 2014), AFXL-PDT, MAL-PDT (Haak 2015) and ingenol mebutate gel (Siller 2010). "Adverse" scarring was noted after SE (Avril 1997).

Headache was statistically more prevalent after treatment with certain imiquimod regimens (five times per week) than in placebo groups (Geisse 2004). Imiquimod also induced influenza-like symptoms (Bath-Hextall 2014; Schulze 2005; Shumack 2002a; Shumack 2002b; Sterry 2002a) and deranged haematology results

(Geisse 2004). Biochemical abnormalities were seen with ingenol mebutate gel usage (Siller 2010).

Withdrawal from study, discontinuation of therapy, interrupted therapy regimens or dose reduction due to treatment-related adverse effects occurred with imiquimod (Bath-Hextall 2014; Ezughah 2008; Geisse 2002, Geisse 2004; Marks 2001; Schulze 2005; Shumack 2002a; Shumack 2002b; Sterry 2002a; Sterry 2002b), diclofenac with or without calcipotriol (Brinkhuizen 2016), MAL-PDT (Foley 2009a; Foley 2009b; Morton 2018; Rhodes 2004), BF 200 ALA-PDT (Morton 2018), solasodine glycosides (Punjabi 2008) and ingenol mebutate gel with or without occlusion (Siller 2010; Spelman 2014).

Serious adverse effects requiring hospitalisation due to treatment were not specifically reported in any treatment group but the influenza-like symptoms and wound infections that were seen with small numbers treated with imiquimod and 5-FU in the Arits 2013 study were classed as suspected unexpected serious adverse reactions. More details regarding reaction severity, duration of adverse events and changes over treatment course can be found in Table 2.

DISCUSSION

Summary of main results

Basal cell carcinoma (BCC) is the most common skin cancer with several different interventions available for high- and low-risk histological subtypes. We aimed to assess the effectiveness of these interventions for primary BCC in immunocompetent individuals and found 52 randomised controlled trials (RCTs) (26 new to this review update) that randomised a total of 6690 participants. We synthesised the data into a total of 52 comparisons. All studies included a majority of BCCs of low-risk histological subtypes (nodular (nBCC), superficial (sBCC)), with only four studies including a minority of high-risk histological subtypes. No studies exclusively studied high-risk histological subtypes and we were unable to retrieve the raw data specific to the high-risk BCCs for full outcome assessment. Consequently, there was not enough information to draw any conclusions about the effects of interventions on histologically high-risk BCC.

Of the included studies, pooling of the data was feasible for only a very limited number of the reported outcomes, and the largest number of studies we were able to pool was four. Many comparisons were evaluated by only one study, preventing meta-analysis. We considered surgical excision (SE) versus Mohs micrographic surgery (MMS) as the main comparison in this review. However, only one study (Smeets 2004), which provided only low-certainty evidence, assessed MMS, even though this is often used as the gold-standard for high-risk facial BCC.

Broadly, non-surgical interventions were more commonly assessed than surgical interventions: more than double the number of trials assessed non-surgical compared to surgical interventions. The most assessed interventions were photodynamic therapy (PDT) (24 studies); topical imiquimod (14 studies); and surgical excision, which is often regarded as the gold-standard treatment for BCC (10 studies). Eleven studies assessed MAL-PDT; 6, ALA-PDT; 2, ablative fractional laser MAL-PDT, and single studies assessed HAL-PDT, laser and broadband ALA-PDT. Between two or four studies assessed radiotherapy, cryosurgery, fluorouracil,

intralesional interferon, pulsed dye laser, and ingenol mebutate. No more than one study assessed curettage and cautery, electrochemotherapy, solasodine glycosides, valproic acid and tazarotene gel, sinecatechins, calcitriol and diclofenac.

Safety was the most commonly-evaluated outcome, with 81% of the comparisons assessing adverse effects. Seventy-five per cent of comparisons assessed early treatment failure, 21% reported 3-year recurrence, 17% reported 5-year recurrence, 37% reported on cosmetic outcomes (27% had data for analysis), and 46% reported on pain (19% had data for analysis).

Surgical excision (SE)

Surgical interventions have the lowest rates of recurrence at three- and five- year follow-up.

We found that for high-risk facial BCC, there may be slightly fewer recurrences with MMS compared to SE at three years and five years (low-certainty evidence). However, the 95% confidence interval (CI) also includes the possibility of an increased risk of recurrence and no difference between treatments. There may be little to no difference regarding improvement of participant- and observer-rated cosmetic outcomes (low-certainty evidence) measured at 18 months post-operatively; however, no raw data were available for this outcome.

Smeets 2004 has been criticised for performing MMS with a standardised 3 mm margin as normally smaller margins are used and this larger margin may have diminished the tissue-preserving benefit of MMS, potentially worsening the cosmetic outcome (Muller 2009). The study included high-risk facial BCCs, defined as high-risk histological subtypes (infiltrative, micronodular, morphoeic, BCC with squamous differentiation) or BCCs located in the 'H-zone' of the face, or both.

The study followed up participants for over 10 years, and although our primary outcome was recurrence at three years and five years, it is important to note that during the five- to 10-year follow-up period there were an additional 14 recurrences (four in the MMS group and 10 in the SE group), which means that only 44% of BCC recurrences occurred during five years of follow-up. This is important as clinicians and patients should be aware that recurrences are possible up to 10 years following treatment.

For further details see Summary of findings 1.

Imiquimod

Evidence for low-risk sBCC and nBCC found that imiquimod probably results in more recurrences than SE at three years (10-fold increased risk, moderate-certainty evidence) and at five years (eight-fold increased risk, moderate-certainty evidence). This was a non-inferiority study and imiquimod was found to be inferior to SE as it failed to meet the study's pre-defined inferiority margin of 0.87. When measured at three years, there may be little to no difference between imiquimod and SE in the number of participant-rated good/excellent cosmetic outcomes (low-certainty evidence), but when this outcome is observer-rated, imiquimod may increase good/excellent cosmetic outcomes (low-certainty evidence). This discrepancy between participant- and observer-rated cosmetic outcomes may be important and should be highlighted to patients.

Although inferior to SE in terms of reducing recurrence rates, imiquimod's performance is still clinically acceptable to patients and clinicians and it is probably the best non-surgical treatment option for low-risk BCC. Another important benefit of imiquimod resides in the fact that it can be administered by patients at home, offering the opportunity to manage low-risk BCCs in the community. With the trend for patients presenting younger and with increasing numbers of BCCs, some now advocate the possibility of general practitioners diagnosing and managing low-risk BCCs with imiquimod cream and reserving SE for the approximate 1/5 BCCs that relapse, with the majority found to relapse within the first year following treatment (Kelleners-Smeets 2017).

Side effects of imiquimod cream comprise application site reactions including pain, weeping, itching, redness and swelling and were reported more often in the imiquimod group than in the SE group. The licensed treatment regimen is five days per week dosing for six weeks (sBCC) or 12 weeks (nBCC). Bath-Hextall 2014 used daily dosing (the discrepancy may have occurred as imiquimod was licensed for BCC after the study had commenced) and therefore more adverse effects may have been recorded during the study than would be expected in clinical practice. Recurrences recorded at five years compared with three years were small, with one additional recurrence for a sBCC treated with imiquimod and one after SE.

Out of 14 studies assessing imiquimod, 11 were funded by the science-based technology company 3M.

For further details see Summary of findings 2.

Radiotherapy

In comparison against SE with the option of frozen section margin control for facial BCCs (including high- and low-risk subtypes), radiotherapy may result in increased recurrences at three years (low-certainty evidence) and at four years (low-certainty evidence). When measured at four years, radiotherapy probably results in a lower number of good cosmetic outcomes (irrelevant of whether the outcome was participant- or observer-rated) compared to SE (moderate-certainty evidence), as dyspigmentation and telangiectasia can occur in people treated with radiotherapy.

Different radiation techniques exist (such as conventional X-ray therapy, interstitial brachytherapy and superficial contact therapy) with the choice of technique dependent on factors such as size and location of the lesion and performance status of the patient. In practice, radiotherapy is usually reserved for cases where lesions are not amenable to surgery. When deciding whether to choose radiotherapy or SE, patients need to consider that radiotherapy will probably involve numerous visits to the radiotherapy department up to five times a week, usually for several weeks. It should be noted that the RCTs for radiotherapy were all conducted decades ago. Since these studies were carried out, radiotherapy technology and protocols have improved and therefore these results may not be representative of modern radiotherapy outcomes. New studies comparing modern radiotherapy against other interventions are needed.

For further details see Summary of findings 3.

Photodynamic therapy (PDT)

PDT was studied in 16 RCTs against various surgical and non-surgical interventions. Out of 16 PDT studies, seven were industry-funded (five by PhotoCure/Galderma).

Based on participants with low-risk nBCC on the head and neck region, MAL-PDT may result in more recurrences than SE at three years (low-certainty evidence); there were no usable data for assessment at five years. MAL-PDT probably has slightly more participant- and observer-rated good/excellent cosmetic outcomes at one year compared to SE, based on participants with low-risk nBCC and sBCC (moderate-certainty evidence). For further details see Summary of findings 4.

Based on participants who each had a single low-risk sBCC, imiquimod probably results in fewer recurrences at three years and five years compared to MAL-PDT (moderate-certainty evidence), and there is probably little to no difference in observer-rated good/excellent cosmetic outcomes measured at one year between MAL-PDT and imiquimod (moderate-certainty evidence). This comparison did not measure participant-rated cosmetic outcomes. For further details see Summary of findings 5.

There is wide variation in PDT protocols with differences in photosensitising agent, use of prior debulking curettage, timing, source and amount of light irradiation and number of PDT cycles. MAL-PDT predominates in Europe and Australasia; physicians in the USA mainly use ALA-PDT. The standard European protocol defines one cycle as two PDT sessions separated by a one-week interval. MAL-PDT is significantly more expensive than ALA-PDT. 5-ALA, however is disadvantaged by the need to prepare the cream fresh prior to use whereas MAL is available in a standardised preparation which makes it easier to use. The newer, stable nanoemulsion ALA formulation (BF-200 ALA gel) is now licensed in the EU. HAL has been used for years in bladder cancer detection and its use in BCC treatment has now been investigated. Further studies are required to inform which protocol is most effective.

Arits 2013 identified that MAL-PDT probably leads to fewer recurrences compared to imiquimod for sBCC treatment, in one subgroup of patients only: older patients with sBCC on the lower extremities.

Adverse effects

Adverse effects with surgical interventions included wound infections, necrosis of grafts and post-operative bleeding. Local adverse effects such as itching, weeping, pain and redness occurred frequently with non-surgical interventions. Treatment-related adverse effects resulting in study modification or withdrawal occurred with imiquimod and MAL-PDT.

For further details see Table 4, Table 5, Table 8, Table 3, Table 7, and Table 6.

Overall completeness and applicability of evidence

This systematic review has included the full spectrum of interventions for primary BCC by including 52 RCTs (52 comparisons) of varying methodological quality. The evidence we have identified addressed our primary and secondary outcomes to varying degrees. Only 21% of the comparisons we included presented at least three-year recurrence data, and 17% of comparisons reported 5-year recurrence data. Given that the majority of recurrences are expected to occur by three years, this means that almost 80% of studies were not able to address our primary recurrence rate outcomes due to inadequate follow-up time. This threatens the applicability and external validity of the evidence presented. Histologically-confirmed early treatment failure data were available for all but 13 comparisons. This outcome benefits from not requiring a long follow-up period and was frequently used as a primary outcome in small, pilot phase 1/2 studies but is generally of limited use when informing decisions in clinical practice.

The finding in Smeets 2004 that 56% of recurrences of high-risk facial BCC occur between five and 10 years following surgery suggests that longer follow-up times are needed for studies on BCC and may represent a flaw in our review methodology. However, a large retrospective review of long-term BCC recurrence rates identified that only 18% of recurrences occurred between five and 10 years with 67% found to occur within the first three years (Rowe 1989). This study informed our original review's three-year time point. Further retrospective studies have reported that 18% to 20% of recurrences occur beyond five years (Griffiths 2005; Hruza 1994; Randle 1996).

Nineteen comparisons had cosmetic outcome data, of which 14 had data for analysis. There was heterogenous reporting of cosmetic outcomes, using different time points, scales and rater (e.g. participant, observer or both). Observers were generally medically trained (e.g. dermatologist, surgeon), but some studies used non-medical observers. Histologically-confirmed early treatment failure was available for all but 13 comparisons. Although 24 studies reported on pain, we were only able to perform analyses on pain data for 10 comparisons; the severity and analgesia required were not routinely reported, and the modes of assessment ranged from patient diaries to rating scales or visual analogue scores. Most studies presented this in their adverse effects data, and due to the heterogeneity, we have collated adverse effects and pain data into additional tables (Table 1 and Table 2).

The diversity of the outcome data generated by these trials impacted our ability to make direct comparisons between the studies; therefore, these data are occasionally not reported. The discrepancy in reported outcomes and the inconsistency in reported time points underscores the importance of the work being done to create core outcome sets based on the needs of the stakeholders for clinical trials in BCC (Schlessinger 2017).

Thirteen comparisons involved a placebo/vehicle/sham/no treatment arm, and imiquimod was over-represented in this group, with five studies comparing imiquimod against vehicle, involving 1145 participants. This allowed one of the few meta-analyses included in this review. It should also be noted that all of these imiquimod studies were industry-funded. BCC is a disease associated with significant local tissue destruction and therefore the harm of non-treatment is not insignificant. It is for this reason that most placebo-controlled studies had short follow-up periods and usually excised the treatment area at the end of the study. Twenty-six comparisons were head-to-head, and such studies are more applicable to clinical practice as they answer more pragmatic and clinically relevant questions.

We do not have sufficient evidence to determine the effects of treatment for histologically high-risk BCC, because only four of our included studies assessed this subtype and no studies

exclusively included high-risk histological subtypes. Only three studies exclusively assessed BCCs located at high-risk sites (H-zone of the face), and so there was insufficient evidence to determine the effects of treatment for these BCCs.

The vast majority of participants were elderly with a median age of 64.9 years old. Although participants as young as 20 were included, separate data on younger participants were not available and therefore we do not have sufficient evidence to determine if outcomes are different in younger participants.

Only one study provided evidence for our main comparison of surgical excision versus MMS. Non-surgical interventions were most widely evaluated by our included studies, which correlates with the inclusion of low-risk histological BCC subtypes by all of the studies.

Three types of treatment were disproportionately represented compared to the rest of the treatments considered: 48 trials assessed PDT, topical imiquimod, and surgical excision, whereas almost half of that number (26 studies), in total, assessed the following: radiotherapy, cryosurgery, fluorouracil, intralesional interferon, pulsed dye laser, ingenol mebutate, curettage and cautery, electrochemotherapy, solasodine glycosides, valproic acid and tazarotene gel, sinecatechins, and diclofenac.

Most of the evidence for the outcomes presented for each of the interventions has come from relatively small, single studies, which meant that meta-analysis was largely not possible (the exceptions being PDT versus SE, imiquimod versus vehicle and AFXL-PDT versus PDT). The majority of these single studies were multi-centre, but many were limited by small sample sizes, and consequently, many of the outcomes reported in this review have wide confidence intervals. This means there is a large amount of imprecision in the results, and therefore, several of our results have low-certainty evidence which threatens their external validity and reproducibility.

Despite these limitations, our study is the most up-to-date and extensive systematic review on interventions for BCC. It can be used globally to inform guidelines and to aid clinicians and patients in weighing up the risks and benefits of the various treatment options available for primary BCC.

Certainty of the evidence

The GRADE approach was used to rate the certainty of all the evidence in our review (as outlined in the Methods section). There was a wide variation in the certainty with most outcomes being rated as moderate to low certainty. A few outcomes were rated as very low-certainty, although these were assessed by comparisons not considered key. The main reasons for rating down the certainty of evidence related to serious risk of bias in the studies (for instance, high risk of selection bias) and serious imprecision with small sample sizes and wide confidence intervals. Where confidence intervals included important benefit and serious harm (i.e. > 1.25 and < 0.75), we rated down two levels for very serious imprecision. A few comparisons had such wide 95% CIs (including 1- and more than 100-fold difference) that we rated them down three levels for imprecision.

Only 19 studies were assessed as low risk of bias for blinding of the outcome assessor. For the studies that were unblinded we did not rate down the certainty of evidence for recurrence outcomes as it was unclear if being unblinded would bias the assessments. We did

rate down certainty of evidence for high risk of bias when there was unblinded assessment of cosmetic outcomes.

Only one study was identified as having a high risk of selection bias, but 22 studies were rated as unclear risk of bias due to the method of random sequence generation not being clearly stated by the study authors. Twenty-eight studies had unclear risk of bias due to the method of allocation concealment not being stated. All these studies stated that they randomised their participants, and therefore, we have had to assume that they did this correctly and we have not rated down the certainty of evidence for an unclear risk of selection bias assessment. Only six studies were deemed to be at low risk of selective outcome reporting bias, and only 11 studies prospectively registered. This number is very low, and selective outcome reporting may have occurred in studies rated as 'unclear' risk of bias, but we decided not to rate the certainty of evidence down for this. This stresses the importance of having pre-specified outcomes and prospectively registering studies.

The majority of included studies used participants as the unit of analysis; however, 27% of studies reported results based on lesions. Therefore, there is the potential of under-estimating the variation in the intervention effect from using results which are based on the same people contributing with multiple lesions. However, the majority of these studies included small numbers of people with multiple lesions; therefore, we anticipate that the likely impact on our results is minimal. Additionally, all of the latter studies aimed to treat the lesions individually, rather than using a systemic treatment.

Potential biases in the review process

We attempted to conduct a comprehensive search for studies. Review authors independently assessed eligibility of studies to minimise bias in the study selection process. As we were working from an old protocol, we did decide to make some changes to our methods that have been clearly described in the Differences between protocol and review section. Changes to our protocol were made at the start of the review process and were approved by Cochrane Skin editorial team. Bias may have been introduced by the time points chosen for some of our outcomes. For instance, when faced with cosmetic outcome data with a range of time points, we had to make a decision on which time point to include for the different comparisons. We attempted to minimise this bias by asking HW to decide on what should be the best time point to include. HW decided we should select a time point at least one year following treatment. The rationale being that scars often take around one year to heal and for the colour to settle. He was not aware of the included studies or any of the results when making this decision, so the risk of bias should be minimal, but ideally this should have been pre-specified in the protocol. For the SE versus radiotherapy study cosmetic outcome, we reported the time point with the biggest difference between interventions which was four years after treatment which may have introduced selective outcome reporting bias. The reason we reported this time point is because it is well documented that radiotherapy has deteriorating cosmetic outcomes over years and this would not be appreciated if we reported the one-year time point. Selective outcome reporting bias may also have been introduced by us selecting the maximum pain score recorded during treatment for interventions. We felt this was necessary as pain experienced during treatments is highly variable and depends on the treatment modality. For example, comparing pain on day one for a surgical treatment against a non-

surgical treatment like imiquimod would be meaningless as the surgical intervention will have produced a painful wound whereas imiquimod will likely not have had any effect on day one.

Agreements and disagreements with other studies or reviews

There have been a few systematic reviews assessing interventions for BCC published since our last update. Most recently, Drucker 2018 published a comprehensive systematic review and network meta-analysis (NMA) on treatments for primary BCC. This study only included English-language publications, and their search yielded fewer randomised controlled trials (RCTs) whilst also including non-randomised studies. This study also did not specify a time point for recurrence before performing the NMA. Despite these differences, our conclusion that surgical interventions have the lowest recurrence rates for BCC is consistent with theirs. Collier 2018 published a systematic review of PDT for BCC. This study included 15 RCTs and had similar outcome measures as our study, except recurrence at one year and five years were their chosen time points. Our review largely agrees with the results from this review. A systematic review and meta-analysis on PDT for BCC by Wang 2015 identified eight RCTs, of which seven are included in our review. This review pooled the results of all these studies regardless of PDT method including photosensitising agent (e.g. MAL versus ALA). We decided against pooling all types of PDT as the pharmacology for the photosensitising compounds is different and the evidence for their similar efficacy is of low quality. We disagree with the Wang study where they report that PDT is as effective as pharmacologic treatment (imiquimod and 5-FU creams). The Wang study combined both imiquimod and 5-FU in their analyses, and by doing so, they masked imiquimod's probable superior efficacy to PDT in terms of reducing recurrences.

Risk of transformation with non-invasive treatments?

We thought it was important to address the fairly recent literature that has suggested that topical therapies and PDT may cause non-aggressive sBCCs to "transform" to more aggressive subtypes (e.g. nodular, infiltrative or morphoeaform subtypes). This is an area of contention and others have argued that apparent transformation is more likely the result of sampling error from the diagnostic biopsies. The Arits 2013 study (MAL-PDT versus imiquimod versus 5-FU cream) data were used for a separate observational study to address the question of whether non-invasive therapies cause sBCCs to transform to higher risk subtypes (van Delft 2019). The study found that of 166 treatment failures (38.6%) were a non-superficial subtype and the proportion with a more aggressive subtype than the primary tumour were 51.3% (38.74) for early and 28.3% (26/92) for later treatment failures. The authors conclude that more aggressive treatment failure recurrences after noninvasive therapy for sBCC occur most often within the first three months following treatment, probably indicating sampling error and consequent under-diagnosis of more aggressive components in the primary tumour rather than transformation.

AUTHORS' CONCLUSIONS

Implications for practice

The overall quality of research on interventions for basal cell carcinoma (BCC) has improved since our 2007 review with the publication of several randomised controlled trials (RCTs) with long-term follow-up, but many of the included studies have

provided low- or moderate-certainty evidence that should be interpreted with caution.

The majority of studies have been performed on low-risk histological BCCs, located on low-risk sites, the results of which are probably not applicable to high-risk tumours. Only four studies have looked at high-risk histological subtypes, and three studies looked at BCCs at high-risk facial sites. More studies or subgroup analyses are required for morphoeic tumours.

Surgery remains the most effective treatment modality for BCC in terms of reducing recurrences, and there may be a slightly reduced recurrence rate with Mohs micrographic surgery (MMS) compared to surgical excision (SE); however, the 95% CI also includes the possibility of both increased risk and no difference between treatments (low-certainty evidence). With regard to improvement of participant- and observer-rated cosmetic outcomes, there may be little to no difference between MMS and SE (low-certainty evidence); however, no raw data were available for this outcome. Radiotherapy is effective but probably worse than surgery (under frozen section margin control) in terms of the number of good cosmetic outcomes (moderate-certainty evidence) and is therefore best reserved for tumours not amenable to surgery. Radiotherapy may also lead to increased recurrence compared to SE (low-certainty evidence).

Non-surgical treatments are less effective, but the evidence suggests that recurrence rates are acceptable and they are important options to offer patients. Imiquimod probably results in more recurrences than SE (moderate-certainty evidence) and there is probably little to no difference between groups in the number of participant-rated good/excellent cosmetic outcomes (low-certainty evidence). However, imiquimod may increase the number of observer-rated good/excellent cosmetic outcomes compared to SE (low-certainty evidence). Overall, imiquimod has the best evidence to support its efficacy out of the non-surgical treatments.

Moderate-certainty evidence indicates that imiquimod probably leads to fewer recurrences than MAL-PDT and there is probably little to no difference between these treatments in terms of observer-rated good/excellent cosmetic outcomes (participant-rated cosmetic outcomes were not measured in this comparison). MAL-PDT may result in more recurrences at three years than SE (low-certainty evidence; no useable data for measurement at five years), but probably increases the number of good/excellent cosmetic results (moderate-certainty evidence).

Adverse effects with surgical interventions include wound infections, graft necrosis and post-operative bleeding. Local adverse effects such as itching, weeping, pain and redness occur frequently with non-surgical interventions. Treatment-related adverse effects resulting in study modification or withdrawal occurred with imiquimod and MAL-PDT.

The six studies in Studies awaiting classification may alter the conclusions of the review once assessed.

Implications for research

Currently, there is only low-certainty evidence informing us on the efficacy of MMS against SE, with only one study assessing MMS against SE that met our inclusion criteria. Given this is the main comparison of our review, further studies assessing these treatments against each other are needed. Future studies

exclusively assessing interventions for high-risk BCC (high-risk histological subtypes and high-risk locations) are needed. As a minimum, future studies should present data on high-risk tumours in subgroup analyses.

Cost:benefit ratios have an important impact on clinical practice and guidelines and so future systematic reviews on interventions for BCC should also include cost-analyses as an outcome measure. This will allow us to answer important questions such as whether the higher operative costs and procedure times of MMS offset the potential higher number of recurrences seen with SE over time. It will also be important for imiquimod and 5-FU cream as there is a big cost difference between these treatments, which may offset the differences in efficacy so defining this further will be important in future research to impact clinical practice.

Given that the radiotherapy studies included were all conducted over 20 years ago, and based on the fact that radiotherapy techniques and protocols have changed a lot since then, up-to-date studies assessing the efficacy of radiotherapy using current methods are needed, as these older studies may not be reflective of modern radiotherapy outcomes.

One of the key problems with RCTs on interventions for BCC is the lack of an agreed set of core outcome measures and also the lack of longer-term outcomes for many of the studies which are now standard for most other cancer studies (for example, clinical recurrence at five years). An international group, in collaboration with the Core Outcome Measures in Effectiveness Trials (COMET) initiative and Cochrane Skin Group- Core Outcome Set Initiative (CSG-COUSIN) have begun the task of developing broad consensus for a core outcome set for BCC intervention trials, which will be essential to improve the evidence we have for BCC in the future (Schlessinger 2017). For example, core outcome sets would determine whose opinion should be sought for assessing cosmetic outcomes (dermatologist, participant, or both), and when or how best to report it. BCC research should benefit greatly from this initiative, but future studies must also ensure that all outcomes are pre-specified and registered prospectively to mitigate against the risk of selective outcome reporting bias.

Only a fifth of included RCTs followed participants up for at least three years and given that the majority of BCCs are likely to recur during the first three years after treatment, future studies should have follow-up periods of at least three years. Further research is needed into what the optimal length of follow-up should be as there is conflicting evidence documenting recurrences beyond five years. If at least 20% of recurrences occur beyond five years, then studies should follow up participants for up to 10 years. This will also impact the time points used for our primary outcome measures in future reviews.

Moreover, inadequate reporting of study methodology leads to biased estimates of treatment effects (Schulz 1995). Future studies on interventions for BCC must be well-designed RCTs and should include a power calculation to ensure that sufficient numbers of participants are recruited to avoid problems with imprecision. Studies must also be rigorously reported and conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz 2010). This will ensure a fair interpretation of the results and allow accurate appraisal and judgements to be made about the risk of bias and the overall certainty of evidence.

Given that curettage and cautery is commonly used in the treatment of low-risk BCC, more evidence is needed to assess its efficacy as currently we only have one small study with only two years follow-up that compared curettage and cautery with SE. Further RCTs with long-term follow-up are needed to assess its efficacy against other interventions including non-surgical interventions. Further RCTs with long-term follow-up are needed for solasodine glycosides, ingenol mebutate, topical valproic acid, tazarotene, diclofenac, calcitriol and sinecatechin. These non-surgical interventions should be compared against other non-surgical interventions with established efficacy in treating BCC, such as imiquimod.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

2005-001474-27

Study characteristics	
Methods	Single-centre, double-blinded, parallel-group, phase IIa RCT. ITT analysis.
Participants	Denmark. Inclusion criteria: adults with easily identifiable and treatable HP BCC with clearly defined borders measuring between 0.5 cm2 and 4 cm. Exclusion criteria: BCCs located on the eyelids, lips, nose, mucosa, or in the anogenital area. Age: not stated. Gender: not stated.
Interventions	Sample size: 50 participants. Period of inclusion: October 2005 to April 2008. T1: Week 1 – 8: placebo gel followed by tazarotene gel (n = 25), if not clear after 8 weeks, further 8 week treatment with Baceca® gel followed by tazarotene gel. T2: Week 1 – 8: Baceca® gel followed by Tazarotene gel (n = 25), if not clear after 8 weeks, further 8 week treatment with Baceca® gel followed by tazarotene gel.
Outcomes	Clinical evaluation at 8 weeks +/- histological assessment. Response rate at 12 weeks and histological assessment at 16 weeks. Patient-reported and safety measurements.
Notes	Sponsored by TopoTarget A/S

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.

2005-001474-27 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only two participants lost to follow-up.
Selective reporting (reporting bias)	High risk	Study prospectively registered. Complete remission (assessed histologically) 8 or 16 week time points (i.e. after each treatment cycle) were registered as the time points for the primary outcome but only reported data for response rate at 3-month follow-up which was not a registered outcome.

Abbade 2015

Study characteristics

Methods	Single-centre, randomised, parallel RCT - abstract only.
Participants	Brazil.
	Inclusion criteria: primary nodular HP BCC in the head and neck with a diameter up to two inches.
	Exclusion criteria: Gorlin syndrome, contraindication to surgical resection or PDT.
	Age: not stated.
	Gender: not stated.
Interventions	Sample size: 57 participants. 68 HP nodular BCC.
	Period of inclusion: not stated.
	T1: Standard protocol MAL-PDT (n = 33, two treatment sessions with 1-week interval, lesions shaved prior to treatment)
	T2: SE (n = 35, 4 mm margin)
Outcomes	Clinical response at 3 months, confirmed histologically if deemed necessary.
	Histologically-confirmed relapse at 6, 12 and 18+ months.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement

Abbade 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "treatment was decided by random drawing."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if blinded but we felt that unable to truly blind due to the nature of the interventions but not clear how this would affect outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively.

Abd El-Naby 2019

Study characteristics

Methods	Single-centre, randomised, parallel RCT.
Participants	Egypt. Inclusion criteria: HP BCC. Exclusion criteria: wound healing abnormalities, immunosuppressive or dermatological disease, undergoing chemical peel / dermabrasion / radiotherapy, cutaneous infection. Age: not stated. Gender: not stated.
Interventions	Sample size: 22 participants. Period of inclusion: May 2015 to May 2016. T1: One stacked PDL session (n = 11). T2: Two stacked PDL sessions, two weeks apart (n = 11).
Outcomes	Clinical and histological assessment for recurrence at 1 month. Safety and tolerability assessments. Recurrence at 6 months (unclear how assessment was made).
Notes	There are no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Low risk	Sequentially-numbered opaque-sealed envelopes.

Abd El-Naby 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Alpsoy 1996

Study characteristics	
Methods	Single-centre, parallel-group RCT. ITT analysis - abstract only.
Participants	Turkey. Inclusion criteria: HP BCC. Exclusion criteria: recurrent lesions, genetic or nevoid conditions, deep tissue involvement. Age range 38-74, (mean in years): T1 = 58.7, T2 = 63.6, T3 = 60.3 Gender: male = 23, female = 22
Interventions	Total: 45 participants, 45 BCCs. Period of inclusion: not stated. Intralesional interferon given three times weekly in all groups (10 injections): T1: IFN alfa-2a (n = 15) T2: IFN alfa 2b (n =15) T3: IFN alfa 2a and 2b (n = 15) (alfa 2a and alfa 2b injected alternately)
Outcomes	Clinical and histological clearance at 8 weeks. Weekly laboratory testing during treatment and at week 1 post-treatment. AEs.
Notes	No declarations of interest.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.

Alpsoy 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data given for outcomes.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively.

Arits 2013

Study characteristics	
Methods	Multi-centre, single-blinded, parallel group RCT. Modified ITT analysis.
Participants	The Netherlands.
	Inclusion criteria: primary, HP sBCC.
	Exclusion criteria: patient taking immunosuppressive drugs, genetic skin cancer disorders, breastfeeding or pregnant, tumour located at high-risk areas of the face, or on the scalp.
	Age (mean in years): T1 = 63, T2 = 62, T3 = 64
	Gender: male = 303, female = 298.
Interventions	Sample size: 601 participants, 601 sBCC.
	Period of inclusion: March 2008 to August 2010.
	T1: MAL-PDT (n = 202, two treatment sessions with 1-week interval, surface prepared atraumatically prior to treatment)
	T2: Imiquimod 5 days per week for 6 weeks (n = 198)
	T3: 5-FU twice daily for four weeks (n = 201)
Outcomes	Primary outcome measure
	Clinical clearance as assessed by blinded assessor at 3 and 12 months post-treatment, confirmed histologically if deemed necessary.
	Secondary outcome measures
	Aesthetic outcome assessed by blinded observer on a four-point scale at 12 months post-treatment.
	Compliance according to patient diary
	Weekly and during-treatment patient-reported pain and burning according to VAS.

Arits 2013 *(Continued)*

	Local adverse reactions according to a four-point scale.
	AEs.
Notes	Funded by a Grant of the Netherlands Organisation for Scientific Research.
	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Telephone randomisation.
Allocation concealment (selection bias)	Low risk	Computer-generated list using random permuted blocks of six to ensure concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Done by one physician blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data not balanced in numbers across intervention groups but unclear if missing outcome data related to the nature of the interventions.
Selective reporting (reporting bias)	Unclear risk	Retrospectively registered (ISRCTN 79701845). The trial registration stated cosmetic outcome would be measured by participants and observers at 3 and 12 months' follow-up using the "Patient and Observer scale" and a "5-point scale". However they reported an observer-rated 4-point scale at 12 months only. The study group showed the 4-point scale had better reproducibility for non-invasive scars in another study (Mosterd 2013) which may explain why they switched to this outcome measure.

Avril 1997

Study characteristics

Methods	Single-centre, single-blind, parallel-group RCT. ITT analysis.
Participants	France. Inclusion criteria: previously untreated BCC of the face, histologically confirmed, smaller than 4 cm in diameter. Exclusion criteria: BCC on scalp or neck. Participants who had total removal of BCC at biopsy, with five or more BCCs, life expectancy below three years. Age: mean 66 years (SD 12). Gender: male = "50%", female = "50%".
Interventions	Sample size: 347 patients, 347 BCC. Period of inclusion: February 1982 to November 1988

Avril 1997 *(Continued)*

T1: SE (n = 174, 2 mm margin, with or without frozen section margin control)

T2: radiotherapy (n = 173, interstitial brachytherapy, superficial contact therapy or conventional therapy)

Outcomes	Primary outcome measures: histological clearance at 4 years.
	Secondary outcome measures: cosmetic results at 3,6,12,24,36 and 48 months. Assessed by 1) patient using VAS 2) dermatologists rating scars using three-point scale, and 3) three blinded independent assessors rating appearance using three-point scale.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only stated that patients were randomly allocated.
Allocation concealment (selection bias)	Unclear risk	Quote: "sequential sealed envelopes opened by the trial data manager."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if participants or personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to truly blind due to nature of interventions but unclear if this would influence study outcomes. For cosmetic outcomes however it was felt there would be a high-risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Basset-Seguin 2008

Study characteristics

Methods	Multi-centre, open, parallel-group RCT. PP analysis.
Participants	Europe.
	Inclusion criteria: BCC size between 6 mm and 15 mm on face/scalp, < 20 mm on neck or < 30 mm on trunk
	Exclusion criteria: more than 10 lesions per patient, pigmented, morphoeaform or infiltrating, xeroderma pigmentosum, porphyria, Gorlin's syndrome, arsenic exposure, allergy to MAL/topical photosensitisers/excipients, participation in another trial within 30 days, pregnancy or breastfeeding, concomitant treatment with immunosuppressive medication.
	Age (mean in years): T1 = 62. T= 64.

Basset-Seguin 2008 *(Continued)*

Gender: male = 69, female = 46.

Interventions	Sample size: 118 participants with 219 sBCC.
	Period of inclusion: October 1999 to March 2000
	T1: MAL-PDT (n = 60, initially debrided, one treatment session only)
	T2: cryosurgery (n = 58, double freeze-thaw cycle, with freeze time of up to 20 seconds and thaw time of 2-3 x freeze time).
	Participants with an incomplete response at 3 months received further treatment (T1: 2 further MAL-PDT sessions; T2: repeat cryosurgery).
Outcomes	Clinical clearance at 3 months post-treatment, and at 1,2,3,4, and years, assessed as complete or incomplete resolution by assessor and confirmed histologically.
	Cosmetic appearance as assessed by patient (3 months, 1 and 2 years) and assessor (3 months, 1,2,3,4 and 5 years) using four-point scale.
	AEs at each follow-up visit up to 3 months post-treatment graded according to three-point severity scale.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded outcome assessor unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per protocol analysis.
Selective reporting (reporting bias)	High risk	Study prospectively registered (NCT00469417). Registration stated primary outcome "number of patients in whom 75% or more of the BCC lesions have responded completely at 3 months" but reported number of lesions with a complete response which was a registered secondary outcome.

Bath-Hextall 2014

Study characteristics

Bath-Hextall 2014 *(Continued)*

Methods	Multi-centre, non-inferiority, pragmatic parallel-group RCT. Modified ITT analysis.
Participants	UK.
	Inclusion criteria: HP, primary, previously untreated, nodular or superficial BCC at low-risk sites.
	Exclusion criteria: morphoeic or recurrent BCC, Gorlin's syndrome.
	Age (median in years): T1 = 69, T2 = 67.
	Gender: males = 278, females = 189.
Interventions	Sample size: 501 patients, 501 BCC
	Period of inclusion: June 2003 to Feb 2007
	T1: imiquimod 5 days per week for 6 weeks (n = 254)
	T2: SE (n = 247, 4 mm margin)
Outcomes	Primary outcome measure Clinical clearance at 3 years from start of treatment.
	Secondary outcome measures
	Clinical clearance at years 1,2 and 5.
	Time to first failure (stratified).
	Cosmetic appearance as rated by participant and dermatologist using six-point scale.
	Pain during treatment and at 16 weeks using six-point scale.
	Number of days of pain.
	Cost-effectiveness of imiquimod versus surgery.
Notes	Funded by Cancer Research UK.
	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation.
Allocation concealment (selection bias)	Low risk	Research nurse was required to telephone RDSU to obtain the allocated treatment for the next participant, which concealed the randomisation sequence from investigators.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to blind but unclear if this will affect judgement of BCC recurrence.

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Bath-Hextall 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	More losses to follow-up in the SE arm (70 vs 48 by 5 years). Modified ITT and sensitivity analysis were done which found no change to the results.
Selective reporting (reporting bias)	Low risk	Study protocol available and all expected outcomes reported.

Beutner 1999

Study characteristics

Methods	Single-centre, parallel RCT. ITT analysis
Participants	USA. Inclusion criteria: HP BCCs with clearly visible margins for nodular with area of 0.5 cm^2 to 1.5 cm^2 or superficial with an area of 0.5 cm^2 to 2 cm^2. Exclusion criteria: none described in paper. Age range (years): 37 to 81 Gender: not stated.
Interventions	Sample size: 35 participants (7 nBCC, 28 sBCC) Period of inclusion: not stated. Five treatment schedules with the imiquimod 5% cream or vehicle. All participants continued treatment until either 2 weeks after target tumour was clinically cleared or until 16 weeks. T1: twice per day (n = 7) T2: once per day (n = 4) T3: three times per week (n = 4) T4: twice per week (n = 5) T5: once per week (n = 4) T6: vehicle (n = 11)
Outcomes	Complete response rate (histologic clearance of BCC at 6 weeks following treatment), safety evaluations.
Notes	Funded by a grant from 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Double-blind" study.

Beutner 1999 *(Continued)*

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"Double-blind" study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Brinkhuizen 2016

Study characteristics	
Methods	Single-centre, single-blinded, parallel-group RCT. ITT analysis.
Participants	The Netherlands.
	Inclusion criteria: HP sBCC of 4 mm or larger.
	Exclusion criteria: tumours on the face or scalp, chronic NSAID use or Vitamin D supplementation in the preceding 30 days.
	Age (average in years): sBCC: T1 = 63, T2 = 65.5, T3 = 67.5, T4 = 61.5 ; nBCC: T1 = 78.5, T2 = 68.6, T3 = 71, T4 = 66.
	Gender: male = 89, female = 39.
Interventions	Sample size: total: 128 participants, 128 BCCs
	Period of inclusion: November 2011 to February 2013.
	Treatment applied twice daily under occlusion for 8 weeks:
	T1: diclofenac-3% gel (n = 32)
	T2: calcitriol 3ug/g ointment (n = 32)
	T3: diclofenac-3% gel and calcitriol 3ug/g ointment (n = 32)
	T4: no topical treatment (n = 32)
Outcomes	Primary outcome measure
	Post-treatment percentage of cells expressing Ki-67 and Bcl-2, determined by blinded assessor.
	Secondary outcome measures
	Histologic tumour regression at 8 weeks.
	Adverse events (including application site reactions, using VAS) and patient compliance at 8 weeks according to patient diary.
Notes	Funded by the Dutch Cancer Society.
	Calcipotriol supplied by Galderma.

Brinkhuizen 2016 *(Continued)*

No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation scheme was stratified for histologic tumour type.
Allocation concealment (selection bias)	Low risk	Random permuted blocks of 8 were used to ensure concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Pathologists who assessed histologic tumour regression were blinded. Unblinded for rest of the outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not clearly documented so unable to assess.
Selective reporting (reporting bias)	Low risk	Study prospectively registered (NCT01358045). Primary outcome reported in publication as stated in register. Secondary outcome reported in publication was "histologic tumor regression" but this was not a registered secondary outcome.

Choi 2016

Study characteristics

Methods	Single-centre, single-blinded, parallel-group RCT.
	ITT and PP analysis.
Participants	South Korea.
	Inclusion criteria: maximum tumour depth of 2 mm, contraindications for surgical excision.
	Exclusion criteria: greater than 5 eligible lesions or those located on the midface/nose/periorbital/ocular, greater than 15 mm, non-nodular subtype, allergy to trial agents, pregnancy or lactation, active systemic infectious disease, immunosuppressive medication, history of melanoma/melasma/keloid, indication of poor compliance.
	Age (mean in years): T1 = 66.9, T2 = 63.3.
	Gender: male = 21, female = 18
Interventions	Sample size: 39 patients, 42 nBCC
	Inclusion period: March 2011 to September 2012.
	T1: Er:YAG AFL MAL-PDT (n = 20)
	T2: MAL-PDT (n = 19)

Choi 2016 *(Continued)*

Outcomes	Primary outcome measures:
	Blinded investigator assessment of clinical response rate 3 and 12 months after final treatment.
	Recurrence rate at 12 months, based on clinical and histological findings.
	Secondary outcome measures:
	AEs immediately after treatment, at 1 week, 3 and 12 months.
	Investigator assessment of cosmetic outcome at 12 months using a four-point scale.
	Tertiary outcome measure:
	Patient-reported pain intensity during PDT according to 11-point VAS.
Notes	Funded in part by research funds from the Dong-A University.
	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The patients may have been able to differentiate between the two treatments because of the characteristics of Er:YAG pre-treatment". Unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups.
Selective reporting (reporting bias)	Unclear risk	Study retrospectively registered (NCT02018679). All expected outcomes from methods section reported.

Clover 2016

Study characteristics

Methods	Single-centre, parallel-group, non-inferiority RCT. PP analysis.
Participants	Ireland.
	Inclusion criteria: superficial, nodular, infiltrative and morphoeic subtypes
	Exclusion criteria: previously treated lesions, advanced BCC, SCC, bleomycin contraindication, chronic renal failure, coagulopathy, epilepsy, pacemaker, pregnancy or lactation.

Clover 2016 *(Continued)*

	Age (mean in years): T1: 66.8 ; T2: 63.8
	Gender: male = 49, female = 50
Interventions	Sample size: 86 participants; 105 BCCs
	Inclusion period: not stated.
	T1: electrochemotherapy (n = 45 patients, 60 lesions)
	T2: surgical excision (n = 41 participants, 45 lesions)
Outcomes	Recurrence rate at 1, 2, 3 and 4 years.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Shuffling of envelopes.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded but strict protocol and unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Theoretically blinded outcome assessors but scars may have led to unblinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Fairly balanced number of dropouts between groups (19 lesions ECT vs 15 lesions SE) but almost 1/5th lost in one group and small overall numbers.
Selective reporting (reporting bias)	Unclear risk	Study prospectively registered (EUDRACT 2010-019260-37). All expected outcomes reported but time-points and specific outcomes not stated in trial register.

Cornell 1990

Study characteristics

Methods	Multi-centre, double-blind, parallel-group RCT. PP analysis
Participants	USA. Inclusion criteria: HP BCC (superficial or nodular), in good health, between 32 to 70 years of age. Exclusion criteria: previously received therapy to test site, immunosuppressive or cytotoxic therapy (within prior 4 weeks), exogenous interferon/interferon alfa-2b (Intron A), lesion in perioral or central area of the face or penetrating to deep tissue, pregnancy. Age (mean in years): T1 = 56, T2 = 57

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Cornell 1990 *(Continued)*

		Gender: male = 136, female = 29.
Interventions		Sample size: 172 participants
		Inclusion period: not stated.
		Both given 3 days per week for 3 consecutive weeks:
		T1: Intralesional injections 1.5 million IU of interferon alfa-2b (n = 123)
		T2: placebo (vehicle for interferon preparation) (n = 42)
Outcomes		Clinical clearance by blinded assessor using a four-point scale weekly after each of the treatment weeks, then at 5, 9, 13 weeks after completion of treatment, then every 3 months up to 52 weeks.
		Adverse events weekly after each of the treatment weeks, then at 5, 9, 13 weeks after completion of treatment, then every 3 months up to 52 weeks.
		Assessor- and patient-reported cosmetic outcome at week 16.
		Histological assessment of efficacy by blinded assessor at 16 weeks.
Notes		Supported by a grant from the Chering Coporation and a grant from Matt and Barbara Browning.
		No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization quote: "by a computer-generated scheme".
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind". Use of injection of vehicle in placebo arm however patients treated with interferon developed systemic symptoms which would likely unblind them.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Total blinding of the examining physician was not possible because systemic symptoms developed in more patients who received interferon than in the placebo group. Unclear if this would influence study outcomes. Histopathologist blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per protocol analysis. 7/130 vs 0/42 interferon group vs placebo lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Edwards 1990

Study characteristics

Methods	Single-centre, parallel-group RCT. PP analysis.

Edwards 1990 *(Continued)*

Participants	USA.
	Inclusion criteria: nBCC or sBCC 0.5 cm to 1.5 cm diameter, with well-defined borders that could be easily excised.
	Exclusion criteria: serious or debilitating illness, history of thromboembolic or cardiovascular disease, radiation therapy to the test site area, history of arsenic ingestion, pregnancy, breast-feeding, immunosuppression as a result of medication or illness and receiving nonsteroidal anti-inflammatory medication. Morphoeic BCC, recurrent cancers, deeply invasive lesions, periorificial tumours and central facial BCC.
	Age range (years): 35 to 65
	Gender: not stated.
Interventions	Sample size: 65 participants
	Period of inclusion: not stated.
	T1: single injection of 10 million IU zinc chelate interferon alfa-2b (n = 33)
	T2: 1 dose of 10 million IU of zinc chelate interferon alfa-2b per week for 3 weeks (n = 32)
Outcomes	Clinical assessment at weeks 2, 8, 12 and 16.
	Histological assessment at 16 weeks.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not given. Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	No information given on allocation concealment. Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Paper does not mention that participants were blinded. Probably not done but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper does not mention that outcome assessors were blinded. Probably not done but unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2/65 (both from T2) did not complete the study (due to side effects).
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Eigentler 2007

Study characteristics

Eigentler 2007 *(Continued)*

Methods	Open-label phase III RCT. ITT analysis.
Participants	Germany.
	Inclusion criteria: at least one HP nBCC of maximum 1.5cm in diameter.
	Exclusion criteria: all micronodular, infiltrative, superficial, multicentric or morphoeic BCCs, those located within 0.5 cm of the eyes, pregnancy, skin disease/tattoo in the study area, clinically significant or unstable medical conditions, or immunomodulatory medication.
	Age: median 64 years (range 38 to 88)
	Gender: male = 63, female = 27.
Interventions	Sample size: 102 participants.
	Period of inclusion: November 2001 to May 2005.
	Imiquimod 5% applied thrice-weekly for:
	T1: 8 weeks
	T2: 12 weeks
Outcomes	Primary outcome measure:
	Histological and clinical clearance rate at 8 weeks post-treatment.
	Secondary outcome measure:
	Safety and cosmetic outcomes at 8 and 12 weeks.
Notes	Supported by 3M.
	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label, unblinded study but unlikely to influence outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label study but unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not balanced between groups. Missing outcome data addressed but unclear if related to true outcome.
Selective reporting (reporting bias)	Unclear risk	Study retrospectively registered (NCT00204555). All expected outcomes from methods section reported.

Eimpunth 2014

Study characteristics

Methods	Prospective RCT - pilot study, abstract only
Participants	USA.
	Inclusion criteria: HP BCC on trunk or extremities.
	Exclusion criteria: none described.
	Age range (years): 29 to 88.
	Gender: male = 16, female = 8.
Interventions	Sample size: 24 participants. 24 HP nodular BCC.
	Period of inclusion: not stated.
	T1: one session of double-stacked PDL, 10 mm spot-size, 7.5 J/cm2
	T2: no treatment
Outcomes	Histological clearance and immediate / delayed adverse events.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study retrospectively registered (NCT01245972).

Ezughah 2008

Study characteristics

Ezughah 2008 *(Continued)*

Methods	Single-centre, open-label, parallel RCT. ITT analysis.
Participants	UK. Inclusion criteria: adults with histologically-proven non-invasive and non-infected sBCC with a minimum area and maximum depth of 2 mm. Exclusion criteria: anogenital tumours, high-risk tumours, nodular/basosquamous/severe squamous metaplastic or infiltrative, Gorlin's syndrome, tumours within 1 cm of hairline, metastatic/recurrent tumours, involvement in other clinical trials, immunosuppressive treatment, corticosteroid therapy, cryosurgery/cutaneous surgery, pregnant/breastfeeding, other dermatological disorders at target site. Age: mean 68 (males) and 62 (females) Gender: male = 17, female = 13
Interventions	Sample size: 32 participants Period of inclusion: not stated. Imiquimod 5% applied: T1: for 8 weeks with once daily dose for alternate weeks (n = 15) T2: for 5 weeks, once daily dose fortnightly with 1-week interval (n = 16)
Outcomes	Primary outcome measure: Clinical clearance at weeks 19 and 52 Secondary outcome measures: Weekly patient-reported tolerability using VAS. Nurse-reported adverse events assessed using four-point severity scale at weeks 2, 4, 6 and 8. AEs also assessed by telephone at weeks 1, 3, 5 and 7.
Notes	Supported by 3M. No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated randomization schedule assigned patients to each dosing regimen."
Allocation concealment (selection bias)	Low risk	A unique identification number in numerical sequence was allocated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blinded but unclear if this would influence performance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"clinician assessing for clinical clearance at weeks 19 and 52 and the statistician were blinded to the dosing regimen."

Ezughah 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Foley 2009a

Study characteristics

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group prospective studies performed in Australia (study 308) and the USA (study 307). ITT analysis.
Participants	Australia. Inclusion criteria:aAdults with primary HP nodular BCC, suitable for simple excision. Exclusion criteria: periorbital/perioral/nasal lesions, < 6 mm, > 15 mm (face or scalp), > 20 mm (extremities or neck), > 30 mm (trunk), pigmented/morphoeaform/infiltrating. Patients with porphyria, xeroderma pigmentosum, arsenic exposure, allergy to study products, recent participation in a different trial, poorly compliant or pregnant/breastfeeding, immunosuppressive medications. Age (years): T1 = 66, T2 = 67. Gender: male = 99, female = 32.
Interventions	Sample size: 66 participants, 75 nBCCs. Period of inclusion: October 2000 to September2002. Lesion was prepared by gentle tumour surface debridement using a curette prior to application of MAL or placebo. Number of treatment cycles determined by response: T1: MAL-PDT (n = 66 participants, 75 lesions) T2: placebo prior to illumination (n = 65 participants, 75 lesions). Note these numbers are from both studies combined. Individual study data not presented.
Outcomes	Efficacy evaluated histologically by blinded assessor at 3 and 6 months. Clinical clearance according to a four-point scale. Safety assessments during treatment, at 2 and 4 weeks, and at 3 months after each treatment cycle. Assessor- and patient- rated cosmetic outcome according to four-point scale.
Notes	Funded byPhotoCure ASA, Oslo, Norway. The authors declare multiple conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme prepared by PAREXEL International. Randomisation was stratified by centre.

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Foley 2009a *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation by PAREXEL.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To ensure blinding to treatment, a study nurse was responsible for illumination and for monitoring adverse events during treatment sessions and at follow-up.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers between treatment groups.
Selective reporting (reporting bias)	Unclear risk	These studies were reported together in the final publication and although they were very similar in their design, they both had separate trial registrations (NCT00472043 and NCT00472108) and there was no mention of combining the results of the studies in the trial registers. However it is not clear how this would affect the overall results. Both studies were retrospectively registered.

Foley 2009b

Study characteristics	
Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group prospective studies performed in Australia (study 308) and the USA (study 307). ITT analysis.
Participants	USA. Inclusion criteria: adults with primary HP nodular BCC, suitable for simple excision. Exclusion criteria: periorbital/perioral/nasal lesions, < 6 mm, > 15 mm (face or scalp), > 20 mm (extremities or neck), > 30 mm (trunk), pigmented/morphoeaform/infiltrating. Patients with porphyria, xeroderma pigmentosum, arsenic exposure, allergy to study products, recent participation in a different trial, poorly compliant or pregnant/breastfeeding, immunosuppressive medications. Age (years): T1 = 66, T2 = 67. Gender: male = 99, female = 32.
Interventions	Sample size: 65 participants, 75 nBCCs. Period of inclusion: October 2000 to September 2002. Lesion was prepared by gentle tumour surface debridement using a curette prior to application of MAL or placebo. Number of treatment cycles determined by response: T1: MAL-PDT (n = 66 participants, 75 lesions) T2: placebo prior to illumination (n = 65 participants, 75 lesions). Note these numbers are from both studies combined. Individual study data not presented.
Outcomes	Efficacy evaluated histologically by blinded assessor at 3 and 6 months.

Foley 2009b *(Continued)*

Clinical clearance according to a four-point scale.

Safety assessments during treatment, at 2 and 4 weeks, and at 3 months after each treatment cycle.

Assessor- and patient- rated cosmetic outcome according to four-point scale.

Notes	Funded by PhotoCure ASA, Oslo, Norway.
	The authors declare multiple conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme prepared by PAREXEL International. Randomisation was stratified by centre.
Allocation concealment (selection bias)	Low risk	Central allocation by PAREXEL.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To ensure blinding to treatment, a study nurse was responsible for illumination and for monitoring adverse events during treatment sessions and at follow-up
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers between treatment groups.
Selective reporting (reporting bias)	Unclear risk	These studies were reported together in the final publication and although they were very similar in their design, they both had separate trial registrations (NCT00472043 and NCT00472108) and there was no mention of combining the results of the studies in the trial registers. However it is not clear how this would affect the overall results. Both studies were retrospectively registered.

Garcia-Martin 2011

Study characteristics

Methods	Single-centre, parallel-group RCT. ITT analysis.
Participants	Spain.
	Inclusion criteria: HP nBCC of the eyelid
	Exclusion criteria: previous BCC treatment, concomitant dermatological disease, immunocompromised.
	Age: mean 73.7 years (range 53-84) Gender: male = 16, female = 11.
Interventions	Sample size: 27 participants

Garcia-Martin 2011 *(Continued)*

Period of inclusion: not stated.

T1: 5% imiquimod applied once daily after initial curettage, five times per week for six weeks (n = 15)

T2: Radiotherapy, standard protocol (n = 12)

Outcomes	Efficacy evaluated histologically at six weeks post-treatment.
	Assessor and patient-evaluated cosmetic outcomes according to a three-point scale at six weeks post-treatment.
	Functional assessment.
	Adverse effects and overall tolerability according to three-point rating scale at 3, 6, 12 and 24 months post-treatment.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised to imiquimod if born on even day of month and randomised to RT if born on odd day of month.
Allocation concealment (selection bias)	High risk	Clear risk due to randomisation method.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not able to blind participants or personal but unclear if this would influence performance.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if ophthalmologist was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Geisse 2002

Study characteristics

Methods	Multi-centre phase II, double-blind, parallel-group vehicle-controlled RCT. ITT analysis.
Participants	USA.
	Inclusion criteria:aAdults with primary, HP sBCC measuring 0. 5 cm^2. to 2.0 cm^2.
	Exclusion criteria: recurrent tumour, within 1 cm of hairline, eyes, nose, mouth or ears, in the anogenital area or on hands and feet, or within 5 cm of another BCC tumour. Age: mean 59 years (range 35 to 85)

Geisse 2002 *(Continued)*

	Gender: male = 82, female = 46
Interventions	Sample size: 128 participants.
	Period of inclusion: not stated.
	Applied for 12 weeks:
	T1: Imiquimod twice daily (n = 10)
	T2: Imiquimod once daily (n = 31)
	T3: Imiquimod 5 consecutive days per week (n = 26)
	T4: Imiquimod 3 days per week (n = 29)
	T5: Vehicle (n = 32)
Outcomes	Clinical and histological clearance at six weeks post-treatment.
	Histological clearance as per two blinded assessors.
	Local skin reactions (descriptive and as per a four-point rating scale) and adverse events at each visit.
	Total amount of Imiquimod applied
	Number of patients taking rest periods.
Notes	Supported by 3M.
	Multiple authors received funding from or were employed by 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Compute- generated randomisation schedule.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. Quote: "Imiquimod cream and vehicle cream were in identical packaging...Both patients and investigators were blinded to the content of the treatment cream dispensed".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Biopsy specimens were...read by 2 independent, blinded dermatopathologists".
Incomplete outcome data (attrition bias) All outcomes	Low risk	125/128 patients completed study procedures and histological evaluations.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Geisse 2004 *(Continued)*

Study characteristics

Methods	Two identical multicentre phase III randomised, vehicle-controlled studies. ITT analysis.
Participants	USA. Inclusion criteria: adults with primary HP sBCC suitable for excision at least 0.5 cm^2 in size with a maximum diameter of 2 cm, located on limbs, trunk, neck or head. Exclusion criteria: lesions located on the facial H-zone or in the anogenital area, with no evidence of aggressive growth pattern, dermatological disease in the target site other than BCC and syndromes predisposing to BCCs. Age (years): T1 = 58.4, T2 = 59.9, T3 = 59.4, T4 = 57.6 Gender: male = 445, female = 279
Interventions	Sample size: 724 participants. Period of inclusion: not stated. For a six week period: T1: imiquimod 5% cream 5 days per week T2: vehicle 5 days per week T3: imiquimod 5% cream 7 days per week T4: vehicle 7 days per week
Outcomes	Clinical clearance at 12 weeks post-treatment using a four-point rating scale with histological correlation. Local skin reactions assessed using 4-point rating scale, and adverse reactions at weeks 1,3, and 6 and at post-treatment weeks 4 and 12.
Notes	Supported by 3M. Multiple authors received funding from or were employed by 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule.
Allocation concealment (selection bias)	Low risk	Blocks of four.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study personnel and subjects were blinded to the study cream identification until the database was completed."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information to make judgement.

Geisse 2004 *(Continued)*

All outcomes

Selective reporting (re-porting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Haak 2015

Study characteristics

Methods	Single-centre, parallel-group RCT.
Participants	Denmark.
	Inclusion criteria: adult with previously untreated HP nBCC with 1) diameter > 15 mm 2) high-risk facial zones and/or 3) located on sun-damaged site.
	Exclusion criteria: lactation/pregnancy, porphyria, known allergy to MAL cream, Gorlin syndrome, immunosuppressive treatment, Fitzpatrick skin type IV-VI, history of keloid and poor compliance.
	Age: median 66 years (range 37-88).
	Gender: male = 15, female = 17.
Interventions	Sample size: 32 participants, 32 BCCs.
	Period of inclusion: December 2010 to September 2011.
	Preceded by debulking curettage:
	T1: AFXL-PDT (n = 16)
	T2: MAL-PDT (n = 16).
Outcomes	Primary outcome measures:
	Clinical response according to blinded assessor at 3,6,9 and 12 months, confirmed histologically if deemed necessary.
	Secondary outcome measures:
	Pain scores during treatment rated on VAS scale. Assessor-rated cosmesis according to a three-point scale at 3,6,9 and 12 months.
	Assessor-rated adverse events according to a four-point scale at 3,6,9 and 12 months.
	PpIX fluorescence measures (Methyl-amonolevulinate uptake) before and directly after treatment.
Notes	The authors received multiple grants from Galderma International.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Low risk	Allocations contained in opaque, sequentially-numbered, sealed envelopes.

Haak 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel not blinded but unclear if this would influence performance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded clinical and histological assessments.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear reasons for lost to follow-up.
Selective reporting (reporting bias)	Low risk	Study prospectively registered (EudraCT 2010-020179-22). All expected outcomes reported.

Hall 1986

Study characteristics	
Methods	Single-centre, parallel-group RCT. PP analysis.
Participants	UK.
	Inclusion criteria: HP BCC, considered suitable candidate for treatment with radiotherapy. Exclusion criteria: recurrent tumours, lesions on nose or pinna, lesion near eye and vision in eye less than 6/18.
	Age: not stated.
	Gender: not stated.
Interventions	Sample size: 105 participants.
	Period of inclusion: not stated.
	T1: cryosurgery (Cry-Owen, two freeze thaw cycles, except periocular lesions treated with thermocouple-regulated Brymil cryospray) (n = 44)
	T2: Radiotherapy, duration dictated by lesion thickness (n = 49)
Outcomes	Investigator-assessed clinical evaluation of efficacy and cosmesis according to a three point scale at 1, 6, 12, 24 months.
	Patient-evaluated pain and adverse event evaluation from 0 to 4 weeks.
Notes	No declarations of interest.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.

Hall 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Selective reporting (reporting bias)	Unclear risk	Study not registered prospectively. All expected outcomes from methods section reported.

Karsai 2015

Study characteristics	
Methods	Multi-centre, parallel-group, double-blinded RCT.
Participants	Germany. Inclusion criteria: HP, unpigmented BCC on trunk and extremities, maximum diameter 30 mm. Exclusion criteria: Fitzpatrick skin type >III, pregnancy, previous BCC treatment within 4 weeks, coagulation disorders or anticoagulant therapy, photosensitising medications, poor compliance. Age (mean in years): T1 = 75.3, T2 = 68.4. Gender: male = 27, female = 12.
Interventions	Sample size: 39 participants, 100 sBCCs. Period of inclusion: November 2012 to October 2013. T1: PDL (n = 56) T2: sham treatment (n = 44).
Outcomes	Primary outcome measure: Clinical and histological remission at 6 months post-treatment. Secondary outcome measures: Patient-recorded adverse events and pain intensity graded according to a VAS at 6 weeks and 6 months post-treatment. Patient satisfaction according to a 3 point scale at 6 weeks and 6 months post-treatment.
Notes	Cynosure Multiplex-brand pulsed dye laser provided by Cynosure Inc. No other conflicts of interests or funding declared.

Risk of bias

Karsai 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list was generated via a web-based program.
Allocation concealment (selection bias)	Low risk	Allocation concealed by using sequentially numbered envelopes by the study nurse.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All blinded except laser practitioner.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinded outcome assessor but residual dyspigmentation after laser treatment persisted up to 6 months following treatment so likely to have become unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patients dropped out or lost to follow-up".
Selective reporting (reporting bias)	Unclear risk	Study retrospectively registered (NCT02125669). All expected outcomes from methods section reported.

Kessels 2017

Study characteristics	
Methods	Single-centre, double-blinded, parallel-group, placebo controlled RCT. ITT and PP analysis.
Participants	The Netherlands.
	Inclusion criteria: adults with primary HP sBCC with a diameter between 4 mm and 20 mm, without co-morbidities interfering with study treatment, and ability to understand instructions.
	Exclusion criteria: recurrent BCC, breastfeeding/pregnant, serious co-morbidities, immunosuppression, genetic skin cancer disorders, high-risk tumour site.
	Age: not stated.
	Gender: not stated.
Interventions	Sample size: 42 participants
	Period of inclusion: November 2014 to September 2015.
	Applied twice daily for 6 weeks:
	T1: topical sinecatechins ointment 10% (n = 21)
	T2: placebo ointment (n = 21).
Outcomes	Primary outcome measure:
	Histological regression as assessed by two blinded investigators at 8 weeks.
	Secondary outcome measures:
	Patient-reported adverse events at weeks 1,4, and 6.

Kessels 2017 *(Continued)*

		Decrease in expression of Ki-67 and Bcl-2 from baseline to week 8 according to immunohistochemistry analyses
Notes		Supported in part by Willpharma BV, the Netherlands, which supplied study medication.
		No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a generated randomization list using random permuted blocks of four". An independent statistician prepared the randomisation list.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization list will not be available to investigators or the project team."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and investigators, including the assessing pathologists, blinded to treatment assignment until the end of the study. Placebo was of identical colour and consistency as sinecatechins ointment to ensure blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers lost to follow-up balanced between groups.
Selective reporting (reporting bias)	Low risk	Study prospectively registered (NCT02029352). All expected outcomes reported.

Kessels 2018

Study characteristics

Methods	Multi-centre, single-blind, parallel-group RCT. ITT and PP analysis.
Participants	The Netherlands.
	Inclusion criteria: adults with primary HP sBCC.
	Exclusion criteria: immunosuppressive drugs, genetic skin cancer disorder, previous treatment, porphyria, pregnancy/breastfeeding, known allergy to study materials, tumours located on H-zone on the face, hairy scalp and convex or concave areas such as the ears/fingers.
	Age (mean in years): T1 = 63.6, T2 = 65.9.
	Gender: male = 75, female = 87.
Interventions	Sample size: 162 participants
	Period of inclusion: September 2013 to May 2015.
	T1: MAL-PDT (n = 80, standard treatment repeated after 1 week)
	T2: two-fold fractionated ALA-PDT (n = 82).

Kessels 2018 *(Continued)*

Outcomes	Primary outcome measure:
	Clinical clearance at 12 months, confirmed histologically if deemed necessary.
	Secondary outcome measures:
	Aesthetic outcome measured on a 4-point scale and independently scored by two blinded investigators at 3 and 12 months.
	Patient-reported adverse events on a 4-point scale 1 week after treatment.
	Patient-reported pain on a VAS scale immediately and 1 week after treatment.
Notes	Funded by a grant from the Health Foundation Limburg, the Netherlands.
	No conflicts of interests declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated lists in permuted blocks of six"
Allocation concealment (selection bias)	Low risk	Quote:"The research physicians did not have access to the randomization lists".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:"The patients could not be blinded for treatment allocation". Unclear if this would influence performance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"All study visits... were performed by two investigators who were blinded to treatment allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers lost to follow-up fairly balanced between both groups.
Selective reporting (reporting bias)	Low risk	Study registered prospectively (NCT01491711). Primary outcome reported as described in registration. Secondary outcomes in registration different from publication (cosmetic outcome and adverse effects reported in publication; registration reported patient preferences and health care costs as secondary outcomes).

Kuijpers 2006

Study characteristics

Methods	Single-centre, parallel RCT - pilot study.
Participants	The Netherlands.
	Inclusion criteria:nNodular, primary BCC anywhere except periocular/hairy scalp areas, measuring < 20 mm.

Kuijpers 2006 *(Continued)*

Exclusion criteria: pigmented BCC, contraindications to surgery, hypersensitivity to daylight, known allergy to study materials, porphyria, more than 5 BCCs per patient.

Age: mean 68.4 years (range 39-87).

Gender: male = 24, female = 15

Interventions	Sample size: 39 patients, 43 HP nBCC.
	Period of inclusion: not stated.
	In each group, half of the tumours were debulked using curettage prior to PDT:
	T1: ALA-PDT (n = 22)
	T2: MAL-PDT (n = 21)
Outcomes	Histological clearance accorded to blinded assessor at 8 weeks post-treatment.
	Pain reported using visual analogue scale and descriptive terms, during and after treatment.
Notes	No declarations of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pathologist examining the sections was blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients dropped out or lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Kuijpers 2007

Study characteristics

Methods	Single-centre, parallel-group RCT. PP analysis.
Participants	The Netherlands.

Kuijpers 2007 *(Continued)*

	Inclusion criteria: adults with HP primary BCC (nodular or superficial) in the head and neck area, < 20 mm.
	Exclusion criteria: recurrent BCC, other histological subtypes, > 20 mm, contraindications to surgery or cryosurgery, > 5 BCCs.
	Age: mean 67 years (range 34-92).
	Gender: male = 50, female = 38.
Interventions	Sample size: 88 participants, 100 HP BCCs.
	Period of inclusion: March 1996 and January 1999.
	T1: SE (n = 49, 3 mm margin)
	T2: cryosurgery (n = 51, after debulking with curette, using two cycles and cone-spray technique).
Outcomes	Histological evidence of recurrence within 5 mm of the scar at 5 years.
	Adverse events.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Performed by telephone via uninvolved party
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessors but unclear if this would influence study outcomes. For cosmetic outcomes however it was felt there would be a high-risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Difference in numbers lost to follow-up but unclear if due to allocated treatments.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Landthaler 1989

Study characteristics

Methods	Single-centre, parallel RCT.
Participants	Germany.

Landthaler 1989 *(Continued)*

	Inclusion criteria: HP BCC and SCC
	Exclusion criteria: not stated.
	Age: median age 71-75 for both T1 and T2.
	Gender: T1: 93 = males, 71 = female; T2: 94 = male, 61 = female.
Interventions	Sample size: 319 participants (BCC and SCC)
	Period of inclusion: 1980-1983
	T1: 60 Gy total (n = 142 BCCs, 24 SCC, sGy on 20 consecutive days)
	T2 48 Gy total (n = 148 BCCs, 20 SCCs, 4Gy 3 x/week for 12 sessions).
Outcomes	Recurrence rate at 3 years.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low numbers lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study not registered. Insufficient information to make judgement.

Marks 2001

Study characteristics

Methods	Multi-centre, open-label, parallel-group RCT. ITT and PP analysis.
Participants	Australia and New Zealand.
	Inclusion criteria: adults with primary HP sBCC on the head, neck, trunk of limbs, with a surface area of between 5 mm^2 to 20 mm^2.

Marks 2001 *(Continued)*

	Exclusion criteria: recurrent, previously treated, within 1 cm of the hairline/anogenital/facial orifices/distal extremities. Age: mean 61 years (range 23 to 83). Gender: male = 72, female = 27.
Interventions	Sample size: 99 participants. Period of inclusion: Not stated. All groups treated with 5% imiquimod for six weeks: T1: twice per day (n = 3) T2: once per day (n = 33) T3: twice per day for 3 days each week (n = 30) T4: once per day for 2 days each week (n = 33)
Outcomes	Histological assessment of efficacy at 6 weeks, and patient-reported adverse events on a three-point scale including characterisation of local reactions.
Notes	Supported by 3M Pharmaceuticals, by whom some authors were employed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information given to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information given to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information given to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers between treatment groups.
Selective reporting (reporting bias)	Unclear risk	Study not registered. Insufficient information to make judgement.

Miller 1997

Study characteristics

Methods	Multi-centre, open-label, parallel-group RCT. ITT and PP analysis.
Participants	USA.

Miller 1997 *(Continued)*

Inclusion criteria: Single HP BCCs, 6 mm to 15 mm in diameter, with well-defined margins, at least 50 mm away from another malignancy.

Exclusion criteria: lesions that had already received treatment, those at high-risk sites (e.g. eyelids, nose, ears and central part of the face), tumours considered to be more appropriately treated with Mohs micrographic surgery, lesions with deep tissue involvement, morphoeic lesions, basal cell nevus syndrome, hypersensitivities or allergies to 5-FU, sulphites, epinephrine, bovine collagen, history of autoimmune disease or immunosuppression, pregnant or lactating women.

Age: Mean 61 yrs (range 29 - 86).

Gender: male = 97 male and female = 25.

Interventions	Sample size: 122 participants.
	Period of inclusion: Not stated.
	Intralesional sustained-release 6fluorouracil/epinephrine injectable gel (5FU/epi gel)
	T1: 1.0 ml 5 FU/epi gel once weekly for 6 weeks (n = 20)
	T2: 0.5 ml 5-FU/epi gel once weekly for 6 weeks (n = 21)
	T3: 1.0 ml 5-FU/epi gel twice weekly for 3 weeks (n = 18)
	T4: 0.5ml 5-FU/epi gel twice weekly for 3 weeks (n = 19)
	T5: 0.5 ml 5-FU/epi gel twice weekly for 4 weeks (n = 21)
	T6: 0.5 ml 5-FU/epi gel 3 times weekly for 2 weeks (n = 17)
Outcomes	Clinical investigator-led examinations at 1, 4, 8 and 12 weeks. Patient-reported assessment of adverse effects at 1, 4, 8 and 12 weeks. Participant- and investigator-reported evaluation of cosmetic appearance according to a five-point scale. Clinical and histological regression assessed at 12 weeks.
Notes	No declarations of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information given to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information given to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study does not mention blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study does not mention blinding of participants and personnel during the study but unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Most participants completed the study (116/122).

Miller 1997 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Morton 2018

Study characteristics

Methods	Randmonised, multinational, multi-centre, non-inferiority RCT. PP analysis.
Participants	Germany, UK.
	Inclusion criteria: One to three non-aggressive BCC with less than or equal to 2 mm thickness, 0.5 cm to 2 cm diameter, on face/scalp, neck/trunk or extremities.
	Exclusion criteria: patients with porphyria, photodermatoses, intolerances to ingredients, recent treatments potentially influencing the ocutome.
	Age: 66.5 in MAL group (+/- 11.5 SD), 67.3 in ALA group (+/- 11.6 SD).
	Gender: male = 131, female = 100.
Interventions	Sample size: 281 participants
	Period of inclusion: January 2014 to November 2015
	One obligatory PDT cycle with 2 PDT sessions 1 week apart, and a second PDT cycle in case of partial or no response 12 weeks after the first cycle:
	T1: BF-200 ALA PDT (n = 121)
	T2: MAL PDT (n = 110)
Outcomes	Primary outcome measure: overall complete clinical repose of all lesions in each patient at 12 weeks
	Secondary outcome measures: clinical clearance rate of individual lesions at weeks 4 and 12. Cosmetic outcome as rated by patient satisfaction on a four-point scale. Patient-reported local adverse reactions as rated on a three-point scale, pain as rated on a ten-point scale and adverse events on a four-point scale.
Notes	Supported by Biofrontera.
	Multiple conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a validated program that automates the random assignment of treatments to randomizations numbers."
Allocation concealment (selection bias)	Low risk	Randomization schedule was generated by Accovion GmbH (Eschborn, Germany). Specific details not given but likely to have been concealed adequately.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants not blinded but unclear if this would influence study outcomes.

Morton 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observer-blinded. Quote: "To guarantee the blind status of investigators assessing efficacy and safety, a second investigator or delegated person was to perform the PDT treatment and all safety evaluations at all visits where PDT was performed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers lost to follow-up relatively small and balanced between groups.
Selective reporting (reporting bias)	Low risk	Study prospectively registered (EudraCT 2013-003241-42-DE). All expected outcomes reported.

Mosterd 2008

Study characteristics

Methods	Single-centre, parallel group RCT. ITT analysis.
Participants	The Netherlands.
	Inclusion criteria: adults with previously untreated HP nBCC with a largest diameter of 20 mm
	Exclusion criteria: pregnancy, life expectancy of < 5 years, known skin cancer syndromes, phototoxic/photosensitive drugs, hypersensitivity to light or ALA cream, recurrent or pigmented BCC, histological subtypes other than nodular BCC, localisation on concave areas or hairy skin.
	Age: mean 64.7 years +/- 13
	Gender: male = 75, female = 74
Interventions	Sample size: 149 participants with 173 BCC
	Period of inclusion: August 2002 and February 2006.
	3 weeks prior to PDT lesions underwent partial debulking curettage under local anaesthesia:
	T1: ALA-PDT (n = 83)
	T2: SE (n = 88, 3mm margin)
Outcomes	Clinical recurrence at 3,6,12,18 months and 2,3,4, and 5 years (confirmed histologically as no recurrence within 5 mm of the scar).
Notes	No declarations of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation per tumour using a computer-generated random allocation scheme.
Allocation concealment (selection bias)	Low risk	Quote: "A person who was not involved in the trial performed randomization per tumour."
Blinding of participants and personnel (performance bias)	Unclear risk	Patients and treating physicians unblinded but unclear if this would influence performance.

Mosterd 2008 *(Continued)*

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Dermatologists other than the research physician conducted the oncological follow-up in most cases." An "independent investigator" looked at the histopathology.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data presented. Fairly large dropouts over the study- unclear if related to true outcomes.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Punjabi 2008

Study characteristics

Methods	Multi-centre, parallel, double-blinded RCT. ITT analysis.
Participants	UK. Inclusion criteria: adults with HP BCC of any type except morphoeic, measuring at least 0.5cm diameter. Exclusion criteria: pregnant or lactating patients, those with known sensitivities, immunosuppression, recent 5-FU or topical tretinoin treatments, history of recurrent BCC after surgery/cryosurgery/radiotherapy. Age: Range 32-95 years. Gender: male = 50, female = 44.
Interventions	Sample size: 94 participants. Period of inclusion: not stated. T1: Zycure cream, containing 0.005% of solasodine glycosides every 12 hours for 8 weeks (n = 62) T2: Vehicle (control) every 12 hours for 8 weeks (n = 32)
Outcomes	Primary outcome measure: histologically-confirmed clearance of test lesion BCC at 8 weeks. Secondary outcome measures: physician's global evaluation of response to treatment, assessment of local irritation and cosmetic outcome on a four-point scale, and adverse events at screening and end of treatment.
Notes	Sponsored by GlycoMed Sciences Lt

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.

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Punjabi 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigator, pharmacist, and the patients were blinded to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Large difference in proportion of patients withdrawing between groups. Quote: "For participants who withdrew and missing data, we carried forward the last observation."
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Rhodes 2004

Study characteristics

Methods	Multi-centre RCT. PP analysis.
Participants	UK.
	Inclusion criteria: previously untreated nodular BCC in adults
	Exclusion criteria: more than 10 lesions, midface region/orbital/ears, lesions < 6 mm or > 15 mm on the face/scalp, > 20 mm on limbs/neck or > 30 mm on trunk, pigmented/morpheaform BCC, porphyria, Gorlin syndrome, arsenic exposure, involved in other study, poor compliance, immunosuppression, pregnancy or breastfeeding.
	Age: Mean 69 in T1 (40-95) and 67 in T2 (38-82)
	Gender: male = 61, female = 40
Interventions	Sample size: 103 participants, 105 BCC
	Period of inclusion: October 1999 to September 2000
	T1: MAL-PDT (n = 52, 75J/cm^2 red light, 570 nm to 670 nm)
	T2: SE (n = 49, with 5 mm margin)
Outcomes	Primary outcome measure: clinical clearance at 3 months.
	Secondary outcome measures: sustained response rate at 12 and 24 months. Patient and assessor-reported cosmetic outcome at 3, 12 and 24 months on a four-point rated scale.
Notes	Supported by PhotoCure ASA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation

Rhodes 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The randomization list was kept centrally, and investigators called or faxed to the monitor when a new patient was included to find out the treatment allocated to that patient."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unable to blind due to nature of interventions but unclear if this would influence study outcomes. For cosmetic outcomes however it was felt there would be a high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to blind due to nature of interventions but unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large number of dropouts but unclear if related to study interventions.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Rogozinski 1997

Study characteristics	
Methods	Single-centre, parallel RCT. ITT analysis.
Participants	Poland. Inclusion criteria: unclear. Exclusion criteria: unclear. Total: 35 participants. Age: unclear. Gender: unclear.
Interventions	T1: recombinant IFN-beta T2: placebo T1: 1 MU three times a week.
Outcomes	Early treatment failure at 16 weeks and recurrence at 2 years.
Notes	Translated for 2007 review. No declarations of interest.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.

Rogozinski 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Selective reporting (reporting bias)	Unclear risk	Study not registered. Insufficient information to make judgement.

Romagosa 2000

Study characteristics

Methods	Single-centre, double-blind parallel-group RCT. ITT analysis. Pilot study.
Participants	USA. Inclusion criteria: at least one HP, non-superficial BCC measuring at least 0.7 cm in diameter, in a healthy individual. Exclusion criteria: systemic disease, women of childbearing age, facial BCCs. Age: not stated Gender: not stated.
Interventions	Sample size: 13 participants, 17 BCCs. Period of inclusion: not stated. Applied twice daily for 4 consecutive weeks: T1: 5% 5-FU in PC vehicle (n = not stated) T2: 5% 5-FU in a petrolatum base (n = not stated)
Outcomes	Clinical assessment on four-point scale by blinded investigator, cosmetic appearance, AEs and laboratory assessments at 4, 8, 12 and 16 weeks. Histological assessment by blinded assessor at week 16.
Notes	No declarations of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information given to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information given to make judgement.

Romagosa 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "lesions were evaluated by a blinded investigator","specimens were evaluated by a dermatopathologist who was blinded with respect to whether the biopsy specimens were from treatment or control groups". Probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Study not registered. Insufficient information to make judgement.

Salmanpoor 2012

Study characteristics		
Methods	Single-centre, parallel group. ITT analysis.	
Participants	Iran. Inclusion criteria: HP BCC. Exclusion criteria: indication for Mohs surgery Age: mean 57.3 years (range 21 - 84 years) Gender: male = 31, female = 24	
Interventions	Sample size: 55 participants, (69 lesions) Period of inclusion: not stated. T1: SE (n = 24, 4 mm margin) T2: curettage (n = 20) T3: curettage and cautery (n = 25)	
Outcomes	Recurrence rate at 28 months	
Notes	No declarations of interest	
Risk of bias		

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation" but no further details given.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement

Salmanpoor 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make judgement
Selective reporting (reporting bias)	Unclear risk	Study not registered. Insufficient information to make judgement.

Salmivuori 2019

Study characteristics

Methods	Multi-centre, parallel, double-blinded RCT
Participants	Finland. Inclusion criteria: HP sBCC. Exclusion criteria: pigmented, morpheaform, infiltrative or nodular basal cell carcinomas; lesions that are in face and scalp area; pregnancy; breast feeding; allergy to photosensitiser; porphyria or photosensitivity. Age (mean (range)) T1: 71 (47–91); T2: 74 (51–91); T3: 74 (57–91). Gender: unclear from numbers presented.
Interventions	Sample size: 98 HP BCC from 57 participants. Period of inclusion: March 2015-ongoing T1: MAL-PDT T2: BF-200 ALA-PDT T3: HAL-PDT
Outcomes	Histological clearance at three months. Pain, post-treatment reactions and cosmetic outcomes (including photobleaching).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Salmivuori 2019 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Selective reporting (reporting bias)	Unclear risk	Prospectively registered (NCT02367547). Only abstract with interim results so unable to assess.

Schulze 2005

Study characteristics	
Methods	Multi-centre, phase III, parallel-group, double-blind, vehicle-controlled RCT. ITT analysis.
Participants	Finland, France, Germany, Italy, Spain. Inclusion criteria: adults with HP sBCC on limbs, trunk, neck or head. Minimum area 0.5 cm^2 and maximum diameter 2 cm.
	Exclusion criteria: clinically significant, unstable medical conditions, pregnancy, metastatic tumours or high probability thereof, tumours located within 1 cm of the hairline, nose, mouth, ears and eyes, with no evidence of morphoeic, metaplastic, infiltrative or desmoplastic features, participants with dermatological disease in target tumour site. Age (median): T1 = 67, T2 = 68
	Gender: male = 101, female = 65
Interventions	Sample size: 166 participants
	Period of inclusion: not stated.
	Once daily application for six weeks:
	T1: imiquimod 5% (n = 84)
	T2: vehicle (n = 82)
Outcomes	Clinical clearance at 12 weeks post-treatment, confirmed by blinded histopathological assessment. Investigator-reported skin quality assessment at week 12 post-treatment.
	Adverse events at weeks 2, 4 and 6 and post-treatment weeks 4 and 12.
	LSR at all post-treatment visits, assessed according to four-point scale.
Notes	Supported by 3M.

Schulze 2005 *(Continued)*

Multiple authors received funding from or were employed by 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated randomisation schedule"
Allocation concealment (selection bias)	Low risk	Quote: "Subjects, study personnel and the sponsor's clinical research team were blinded to study cream identity and treatment assignment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded investigators including dermatopathologists.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Shumack 2002a

Study characteristics

Methods	Mult-icentre, open-label, dose-response RCT. ITT analysis. First of two studies included in the paper (see Shumack 2002b for 12-week study).
Participants	Australia and New Zealand
	Inclusion criteria: adult with single, primary, HP, nBCC (measuring 0.5 cm^2 to 1.5 cm^2), greater than 1 cm from eyes, nose, mouth, ear and hairline. Exclusion criteria: BCC with morphoeic infiltrating and micronodular patterns. Age (mean in years): T1 = 72, T2 = 66, T3 = 69, T4 = 63
	Gender: male = 81, female = 18
Interventions	Sample size: 99 participants
	Period of inclusion: Not stated
	Topical 5% imiquimod applied for six weeks:
	T1: twice daily, seven days per week (n = 1)
	T2: once daily, seven days per week (n = 35)
	T3: twice daily, three alternating days per week (n = 31)
	T4: once daily, three alternating days per week (n = 32)

Shumack 2002a *(Continued)*

Outcomes	Clinical and histological clearance at six weeks post-treatment.
	Safety and efficacy evaluations at 1, 2, 4 and 6 weeks.
	Local skin reactions according to four-point scale at all visits.
Notes	Supported by 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label but unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15/92 discontinued study but unclear in which treatment arms.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Shumack 2002b

Study characteristics

Methods	Multi-centre, open-label, dose-response RCT. ITT analysis. Second of two studies included in the paper (see Shumack 2002a for 6-week study).
Participants	USA.
	Inclusion criteria: adult with single, primary, HP, nBCC (measuring 0.5 cm2 to 1.5 cm2), greater than 1 cm from eyes, nose, mouth, ear and hairline.
	Exclusion criteria: BCC with morphoeic infiltrating and micronodular patterns.
	Age (mean in years): T1 = 53, T2 = 63, T3 = 63, T4 = 58, T5 = 62
	Gender: male = 63, female = 29
Interventions	Sample size: 92 participants
	Period of inclusion: Not stated.
	Imiquimod or vehicle for 12 weeks:
	T1: imiquimod twice daily, seven days per week (n = 4)

Shumack 2002b *(Continued)*

T2: imiquimod once daily, seven days per week (n = 21)

T3: imiquimod once daily for 5 consecutive days per week (n = 23)

T4: imiquimod once daily for 3 alternating days per week (n = 20)

T5: Vehicle (n = 24)

Outcomes	Clinical and histological clearance at six weeks post-treatment.
	Safety and efficacy evaluations at 1, 2, 4, 6, 8, 10 and 12 weeks.
	Local skin reactions according to four-point scale at all visits.
Notes	Supported by 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label but unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 patients discontinued study.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Siller 2010

Study characteristics

Methods	Multi-entre RCT. Modified ITT analysis.
Participants	Australia.
	Inclusion criteria: adults with HP sBCC, 4 mm to 15 mm diameter, maximum thickness 4 mm.
	Exclusion criteria: recurrent or atypical lesions, immunosuppression, and prior, concomitant or anticipated therapy with the potential to confound the study results. women of childbearing potential were also excluded.
	Mean age years 59 (34 to 86)

Siller 2010 *(Continued)*

	Gender: male = 88, female = 32
Interventions	Sample size: 60 participants
	Period of inclusion: April to December 2005
	Topical application by investigator using micro-pipette
	T1: ingenol mebutate gel 0.0025% (n = 16)
	T2: ingenol mebutate gel 0.01% (n = 16)
	T3: ingenol mebutate gel 0.05% (n = 16)
	T4: identical vehicle (n = 12)
Outcomes	Clinical response (according to a six-point scale), and histological response at day 85. Local skin reactions on a three-point scale and with descriptive analysis.
Notes	Supported by Peplin Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent clinical research organisation used a computer-generated randomisation schedule with a block size of eight. Participants assigned to treatment or vehicle in a ratio of 1:2
Allocation concealment (selection bias)	Low risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Both the investigator and the participants were blinded. The authors state that complete blinding could not be guaranteed because of the skin responses expected with active treatment. The active and vehicle gels were physically indistinguishable, and identical packaging used to maintain blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The post-treatment excision specimen at day 85 looked at by central pathologist blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 60 patients completed follow-up.
Selective reporting (reporting bias)	Unclear risk	Study retrospectively registered. All expected outcomes from methods section reported.

Smeets 2004

Study characteristics

Methods	Multi-centre, unblinded, parallel-group RCT. ITT analysis.
Participants	The Netherlands.
	Inclusion criteria: HP primary or recurrent BCC located on the face, at least 1cm diameter, located in the H-zone or high-risk/aggressive histopathological subtype.

Smeets 2004 *(Continued)*

	Exclusion: life expectancy less than 3 years.
	Age: mean 67.7 years (SD 12.65)
	Gender: male (n = 224), female (n = 150)
Interventions	Sample size: primary BCC 374 participants (408 lesions) and recurrent BCCs 191 participants (204 lesions).
	Period of inclusion: October 1999 to January 2001
	T1: MMS (n = 204)
	T2: SE (n = 204, 3 mm margin)
Outcomes	Recurrence at 30 months and 5 years and incomplete excision rate. Cost-effectiveness after 5 years. Participant assessment of cosmetic outcome at 6 and 18 months, some lesions also retrospectively assessed by investigators and laymen.
Notes	Supported by the Dutch Fund for Investigative Medicine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using computer programme.
Allocation concealment (selection bias)	Low risk	Secretary not involved in trial undertook the randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not possible but unclear if this would influence performance.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "For practical reasons, the research physician was not blinded to the treatment, nor was the patients' own dermatologist" but unclear if this would influence detection.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants lost to follow-up clearly documented and fairly even between groups.
Selective reporting (reporting bias)	Unclear risk	Study retrospectively registered (ISRCTN65009900). All expected outcomes reported.

Soler 2000

Study characteristics

Methods	Single-centre parallel RCT. ITT analysis.
Participants	Norway.
	Inclusion criteria: HP BCC, clinical thickness less than 1mm, diameter less than 3 cm, fewer than six lesions per patient

Soler 2000 *(Continued)*

Exclusion criteria: not stated.

Age (mean, in years): T1 = 62.4, T2 = 62

Gender: male = 39, female = 44

Interventions	Sample size: 83 participants and 245 lesions.
	Inclusion period: study dates not reported.
	All lesions in both groups were treated with the same drug (topical application of 20% ALA). Three hours later the cream was removed and light source applied. Two different light sources used:
	T1: laser light (n = 41 participants, 111 lesions, 630 nm)
	T2: broadband light (n = 42 participants, 134 lesions, 570 nm to 740 nm)
Outcomes	Clinical response at 3 and 6 months after treatment according to a three-point scale. Adverse events at one week, patient-reported pain during and throughout follow-up. Cosmetic outcome according to a four-point scale.
Notes	No declarations of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not given.
Allocation concealment (selection bias)	Low risk	Quote: "The primary investigator was provided with the randomization numbers in locked envelopes, one envelope for each patient." Allocation in blocks of 4. Locked envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigator and patients unblinded but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigator and patients unblinded but unclear if this would influence study outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data for outcomes of interest.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Spelman 2014

Study characteristics

Methods	RCT. Conference abstract.
Participants	Australia

Spelman 2014 *(Continued)*

	Inclusion criteria: HP sBCC in adults, 4 mm to 15 mm diameter and < 1 mm thick on trunk/extremities
	Exclusion criteria:
	Age: 60.8 (mean)
	Gender: male = 35; female = 40
Interventions	Sample size: 75 participants
	Period of inclusion: April 2011- March 2012
	Ingenol mebutate 0.05% gel applied for three consecutive days with:
	T1: full occlusive aluminium disk (n = 27)
	T2: semi-occlusive dressing with OpsiteTM (n = 24)
	T3: no occlusion (n = 24)
Outcomes	Complete histological clearance at day 120. AEs and local skin responses.
Notes	No declarations of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make judgement.
Selective reporting (reporting bias)	Unclear risk	Study prospectively registered (NCT01325688). All expected outcomes reported.

Sterry 2002a

Study characteristics

Methods	Multi-centre (two studies), parallel, open-label. ITT analysis.
Participants	Two studies in Europe.

Sterry 2002a *(Continued)*

	Inclusion criteria: adults with HP primary sBCC on limbs, trunk, neck or head, measuring 0.25 cm^2 to 1.5 cm^2 if sBCC
	Exclusion criteria: previous treatment to target tumour, dermatological conditions interfering with local assessments, tumours located on hands and feet, anogenital area. High-risk areas within 1 cm of hairline, eyes, nose, mouth or ears were excluded if sBCC but included if nBCC.
	Age: mean 63 years (+/- 13.8 SD)
	Gender: male = 59, female = 34
Interventions	Sample size: 93 with sBCC
	Period of inclusion: not stated
	All treated with imiquimod 5% for 6 weeks:
	T1: 3 times per week with occlusion (n = 23)
	T2 3 times per week without occlusion (n = 25)
	T3: twice per week with occlusion (n = 21)
	T4: twice per week without occlusion (n = 24)
Outcomes	Primary outcome measure: histological confirmation of response at 6 weeks.
	Secondary outcome measures: safety and efficacy at 1, 2, 4, 6 and 6 weeks post-treatment. AEs rated on four-point scale Clinical evaluation at 6 weeks.
Notes	Funded by 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule assigned patients in blocks of four to each dosing regimen.
Allocation concealment (selection bias)	Unclear risk	Quote: "Study personnel were blinded to this randomization schedule until after subject treatment assignments had been made".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel not blinded but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Does not state that the dermatopathologists were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for withdrawals detailed and balanced between groups.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Sterry 2002b

Study characteristics

Methods	Multi-centre (two studies), parallel, open-label. ITT analysis.
Participants	Two studies in Europe.
	Inclusion criteria: adults with HP primary nBCC on limbs, trunk, neck or head, measuring 0.5 cm^2 to 2 cm^2
	Exclusion criteria: previous treatment to target tumour, dermatological conditions interfering with local assessments, tumours located on hands and feet, anogenital area. High-risk areas within 1 cm of hairline, eyes, nose, mouth or ears were excluded if sBCC but included if nBCC.
	Age: mean 63 years (+/- 13.8 SD)
	Gender: male = 59, female = 34
Interventions	Sample size: 90 with nBCC
	Period of inclusion: not stated
	All treated with imiquimod 5% for 6 weeks:
	T1: 3 times per week with occlusion (n = 23)
	T2 3 times per week without occlusion (n = 24)
	T3: twice per week with occlusion (n = 22)
	T4: twice per week without occlusion (n = 21)
Outcomes	Primary outcome measure: histological confirmation of response at 6 weeks.
	Secondary outcome measures: Safety and efficacy at 1, 2, 4, 6 and 6 weeks post-treatment. AEs rated on four-point scale Clinical evaluation at 6 weeks.
Notes	Funded by 3M.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule assigned patients in blocks of four to each dosing regimen.
Allocation concealment (selection bias)	Unclear risk	Quote: "Study personnel were blinded to this randomization schedule until after subject treatment assignments had been made".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel not blinded but unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Does not state that the dermatopathologists were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for withdrawals detailed and balanced between groups.

Sterry 2002b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Szeimies 2008

Study characteristics

Methods	Multi-centre, parallel-group RCT. PP analysis.
Participants	UK, Germany, Switzerland and Australia
	Inclusion criteria: adults with HP sBCC, suitable for excision, with no evidence of aggressive growth patterns.
	Exclusion criteria: more than 5 lesions, lesions in mid-face region, lesions with a largest diameter < 8 mm or > 20 mm, recurrent lesions, lesions in areas of severe sun damage, lesions proximal to current/previous SCC, pigmented/morphoeaform/infiltrating lesions, pregnancy or breastfeeding, contraindications to MAL-PDT.
	Age: mean 63.8 years (range 31 to 92)
	Gender: male = 194, female = 132
Interventions	Sample size: 196 participants, 246 sBCC(1.4 lesions per participant).
	Period of investigation: not stated.
	T1: MAL-PDT (n = 100)
	T2: SE (n = 96)
Outcomes	Primary outcome measures: Clinical response at 3 months and investigator-assessed cosmetic outcome according to a four-point scale at 12 months.
	Secondary outcome measures: Clinical response at 12 months, investigator-assessed cosmetic outcome according to a four-point scale at 3, 6 and 12 months.
	Other outcomes: AEs at each visit.
Notes	Funded by Galderma R&D, Sophia Antipolis, France.
	The investigating authors received payments for the project, and two are Galderma employees.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A block of numbered randomisation cards were provided to each site. Whenever a patient was considered eligible, the investigator had to scratch a randomisation card, following an ascending number order, to disclose the procedure assigned to the patient.
Allocation concealment (selection bias)	Low risk	see above.
Blinding of participants and personnel (performance bias)	Unclear risk	Unable to blind due to nature of treatments but unclear if this would influence performance.

Szeimies 2008 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to blind due to nature of treatments but unclear if this would influence detection. For cosmetic outcomes however it was felt there would be a high-risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome unlikely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

Tran 2012

Study characteristics

Methods	Single-centre, parallel, pilot RCT.
Participants	USA. Inclusion criteria: HP superficial, nodular, multicentric BCC measuring 0.4 cm to 3 cm on trunk and extremities in Caucasian patients with Fitzpatrick skin types I and II. Exclusion criteria: morphoeaform, infiltrating and recurrent BCCs or those on the head and neck, feet or genitals. Age: range 46 to 84 years, median age 62 (SD +/- 12 years). Gender: Male = 10, female = 10.
Interventions	Sample size: 17 participants with 20 HP BCC. Period of inclusion: not stated. T1: PDL 7 mm spot-size, single pulses, 15 J/cm2 (n = 8). T2: PDL 10 mm spot-size, stacked pulses, 7.5 J/cm2 (n = 8). T3: Control group (no treatment) (n = 7).
Outcomes	Histological clearance and adverse events at 0 to 157 days.
Notes	No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to treatment allocation.
Blinding of outcome assessment (detection bias)	Low risk	No mention of blinding but unlikely to have affected interpretation of histology for primary outcome.

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Tran 2012 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study not prospectively registered. All expected outcomes from the methods section reported.

Wang 2001

Study characteristics

Methods	Single-centre parallel-group RCT. PP analysis.
Participants	Sweden.
	Inclusion criteria: non-morphoeic HP BCC suitable for PDT or cryosurgery, in patients aged 20 to 90 years.
	Exclusion criteria: pregnancy and lactation, severe malignancies, daily intake of vitamins E or C, beta carotene, iron preparations, non-steroidal anti-inflammatory agents or strong analgesics in higher than specified doses. BCC on nose, morphoeic growth, porphyria, abdominal pain of unknown aetiology, photosensitivity, treatment of BCC with topical steroids within the last month.
	Age: Range 42 to 88 years
	Gender: male = 44, female = 44
Interventions	Sample size: 88 participants
	Period of inclusion: not stated
	T1: ALA-PDT (n = 47, 20% weight-based ALA/water in oil cream applied, irradiation 6 hours later)
	T2: cryosurgery (n = 41, liquid nitrogen using a spray technique. Two freeze thaw cycles of 25 to 30 seconds with 2 to 4 minutes thaw time)
Outcomes	Histological resolution at three months.
	Clinical and histopathological resolution at 12 months. Blinded-assessor rated cosmetic outcome according to two three-point scales.
	Tolerability as assessed by discomfort according to a VAS and self-reporting of analgesia used.
Notes	Supported by Johnson & Johnson Medical GmbH, Norderstedt, Germany, and the Swedishand the Norwegian Cancer Societies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised according to a stratified randomisation pattern in blocks of 10 participants.
Allocation concealment (selection bias)	Low risk	Allocation concealed by regional cancer registry.

Wang 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "No blinding regimen was possible due to the nature of the treatment procedures". Unclear if this would influence study outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "No blinding regimen was possible due to the nature of the treatment procedures." For cosmetic outcomes however it was felt there would be a high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Study not registered. All expected outcomes from methods section reported.

AEs: advere events;**ALA:** aminolevulinic acid; **BCC:** basal cell carcinoma; **nBCC:** nodular BCC; **sBCC:** superficial BCC; **HP:** histologically proven; **IFN:** interferons; **ITT:** intention-to-treat; **IU:** international unit; **MAL:** methyl aminolevulinate; **MMS:** Mohs micrographic surgery; **NSAIDs:** non-steroidal anti-inflammatories; **MU:** megaunits; **PC:** phosphatidyl choline;**PDL:** pulsed dye laser; **PDT**: photodynamic therapy; **PP:** per protocol;**RCT:** randomised controlled trial; **SCC:** squamous cell carcinoma; **SE:** surgical excision; **T1:** treatment group 1; **T2:** treatment group 2; **T3**: treatment group 3; **5-FU:** 5-fluorouracil; **5-FU/epi:** 5-fluorouracil/epinephrine; **VAS:** visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Niaimi 2015	No outcomes of interest measured - study measured outcomes relating to number of sections and stages.
Arits 2014	No outcomes of interest measured - study addressed cost-effectiveness. Arits 2013 study is included which measured outcomes of interest.
Berroeta 2007	Not clear if biopsy-proven BCC.
Butler 2009	No outcomes of interest measured, study addressed stages and defect size.
Čarija 2016	Not an RCT, intra-patient study.
Cho 2013	Not an RCT.
de Haas 2006	Not all BCCs histologically proven.
Dessinioti 2014	Not an RCT.
EudraCT 2013-000092-33	Not all BCCs histologically proven.
Genouw 2018	Not an RCT, intra-patient randomised study.
Groselj 2018	Not an RCT.
Huang 2004	No outcomes of interest measured. This study was about the utility of preoperative tumour curettage in Mohs micrographic surgery for primary or recurrent BCC. The end points were per cent surface area increase from tumour surface area to wound surface area; actual surface area increase from tumour surface area to wound surface area; and number of layers removed to clear tumour.

Study	Reason for exclusion
Ibbotson 2018	Not all BCCs histologically proven.
Lippert 2013	Included previously treated lesions.
Lu 2017	Included several tumour types. Data related to BCC alone not available.
Lui 2004	Included Gorlin syndrome patients.
Migden 2015	Included previously treated lesions.
NCT01033019	No outcomes of interest measured.
Nguyen 2018	No outcomes of interest measured.
Quirk 2010	Not an RCT.
Radiotis 2014	Not an RCT.
Schleier 2007	Included participants with Gorlin syndrome.
Sekulic 2012	Not an RCT
Spencer 2006	Adjuvant therapy study.
Tang 2012	Included participants with Gorlin syndrome.
van der Geer 2012	No outcomes of interest measured.
Vijlder 2012	Not all lesions histologically proven.
Wettstein 2013	Not all lesions histologically proven.
Zane 2017	Not all lesions histologically proven.

BCC: basal cell carcinoma;**RCT:** randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Bunker 2000

Methods	Unknown
Participants	Unknown
Interventions	5- Fluorouracil/adrenaline injectable gel.
Outcomes	Unknown
Notes	This trial was identified from the National Research Register in our old review searches but no more details of the study have been found and we are uncertain if this is an RCT despite attempts to contact the author.

IRCT 2017 030732933N1

Methods	Single-centre, randomised, parallel RCT.
Participants	Iran.
	Inclusion criteria: pathologically documented BCC; maximum tumour diameter of 30 mm.
	Exclusion criteria: skins with Fitzpatrick type of higher than 3; coagulation disorders or recent receiving of anticoagulant agents; consumption of light-sensitive drugs.
Interventions	T1: 585-nanometer PDL laser with power of 9 joules, in 450 microseconds, for 2 treatment sessions with 3-week intervals ; T2 585-nanometer PDL laser with power of 9 joules, in 450 microseconds, followed by cryosurgery with one unit of liquid nitrogen (CRY-ACW) using spray method during two freeze cycles each of which being 4 ± 2 minutes, for 2 sessions with intervals of 3 weeks.
Outcomes	Primary: tumour remission 6 months after the last treatment session.
Notes	Recruitment completed in 2017. Results not published and author not responded to email.

ISRCTN 92678315

Methods	Single-centre, randomised, parallel RCT.
Participants	UK.
	Participant inclusion criteria 1. Patients referred for PDT as judged appropriate by dermatologists in local area 2. Patients will have BCCs, Bowen's disease or actinic keratoses and will be randomised depending on diagnosis.
Interventions	Two treatment arms in the study, randomised in double-blind fashion to receive either topical 20% ALA or 20% ALA, 2% EDTA cream. Both groups will then receive light treatment to the areas to which the cream has been applied. Comparison of the two groups will be by change in size of skin lesion by any tolerance of procedure.
Outcomes	Response of skin lesion clinically by size change at 3-month follow-up.
Notes	Recruitment completed in 2003. Results not published and author not responded to email.

Kang 2018

Methods	Single-centre, randomised, parallel RCT - abstract only.
Participants	China.
	Unclear inclusion criteria
	Age: not stated.
	Gender: not stated.
Interventions	72 participants. Unclear BCC subtype. Unclear if HP.
	T1: 635 nm Ella light once a week for 4 weeks.
	T2: imiquimod pre-treatment and 635 nm Ella light once a week for 4 weeks.

Kang 2018 *(Continued)*

Outcomes	Immune index changes, clinical efficacy, cosmetic effect and adverse reactions.
Notes	Chinese study. Only translated English abstract obtained. Unable to access full paper or contact authors.

Ma 2018

Methods	Randomised, parallel RCT - abstract only.
Participants	China. Unclear inclusion criteria Age: not stated. Gender: not stated.
Interventions	40 participants. T1: adriamycin combined with cisplatin. T2: cisplatin.
Outcomes	Quote: "Observe and compare the clinical effects, adverse reactions, serum VEGF level, pain score and self-efficacy of two groups."
Notes	Chinese study. Only translated English abstract obtained. Unable to access full paper or contact authors.

RPCEC00000147

Methods	Multi-centre, randomised, parallel RCT.
Participants	Cuba. Inclusion criteria 1. Clinical and histological diagnosis of BCC 2. > 18 years of age. 3. Lesions between 1.5 cm^2 to 10.0 cm^2. 4.Lesions of any subtype, localisation and size 5. Non recurrent lesion. 6. Without previous specific treatments.
Interventions	Study group (CIGB-128-A). Perilesional treatment with CIGB-128-A (dose of 10.5 MIU) 2 times per week for 4 weeks Study group (CIGB-128-A). Perilesional treatment with CIGB-128-A (dose of 10.5 MIU) 2 times per week for 6 weeks Study group (CIGB-128-A). Perilesional treatment with CIGB-128-A (dose of 10.5 MIU) 2 times per week for 8 weeks Control group (CIGB-128-A). Perilesional treatment with CIGB-128-A (dose of 10.5 MIU) 3 times per week for 4 weeks Study group (CIGB-128-A). Perilesional treatment with CIGB-128-A (dose of 10.5 MIU) 3 times per week for 6 weeks Study group (CIGB-128-A). Perilesional treatment with CIGB-128-A (dose of 10.5 MIU) 3 times per week for 8 weeks.
Outcomes	Primary outcomes

RPCEC00000147 *(Continued)*

Clinical response (Size of the lesion. RECIST criteria. Complete Response (CR); Partial Response (PR); Stable Disease (SD) and Progression Disease (PD)). Measuring time: at baseline and at week 16 after starting the treatment.

Secondary outcomes
Clinical response time (time to reach partial or complete response). Measuring time: weeks 1, 4, 8, 12 and 16. Quality of scarring; Will be evaluated since the clinical standpoint, in patients that respond completely to treatment. Measuring time: at a week 16 and annually for 10 years. Time to recurrence (time elapsing from the first day provided the absence of neoplastic cells according to the evaluation histological or clinical (patient refusal to biopsy end or biopsy no useful), until appears an injury histologically demonstrated in the treated site). Measuring time: annually for 10 years. Presence of clinical adverse effects. Anti-IFN alpha and gamma antibodies.

Notes	Date of first enrolment: 01/02/2013. Recruitment status: Pending. No reply to email to trial registration contact.

ALA: aminolevulinic acid; **BCC:** basal cell carcinoma; **EDTA:** Ethylenediaminetetraacetic acid; **HP:** histologically proven; **PDL:** pulsed dye laser; **PDT**: photodynamic therapy; **RCT:** randomised controlled trial; **VEGF:** Vascular endothelial growth factor.

Characteristics of ongoing studies *[ordered by study ID]*

EudraCT 2016-002255-25

Study name	Electrochemotherapy versus standard radiotherapy for the treatment of basal cell carcinoma.
Methods	Single-centre, randomised, parallel RCT.
Participants	Denmark.
	Age > 18 with HP BCC.
	Aiming for 52 participants.
Interventions	T1: bleomycin electrochemotherapy.
	T2: standard radiotherapy (no further detail given).
Outcomes	Primary: evaluate tumour response and compare efficacy of electrochemotherapy versus standard radiotherapy (time point: 3 months).
	Secondary: adverse effects (up to 5 years after treatment).
Starting date	2016.
Contact information	camilla.kjaer.loenkvist@regionh.dk
Notes	

NCT02242929

Study name	Surgical excision versus combined treatment with curettage and imiquimod for nodular basal cell carcinoma: an open, non-inferiority, randomized controlled trial
Methods	Single-centre, randomised, parallel RCT
Participants	Netherlands.
	Age:18-90.

	Primary HP nBCC ≥ 4 mm and ≤ 20 mm in diameter.
	Aiming for 145 participants.
Interventions	T1: Standard surgical excision (including a 3-mm clinically tumour-free margin)
	T2: Imiquimod 5% cream with prior curettage
Outcomes	Primary: proportion of participants tumour-free [Time Frame: At 1 year after end of treatment]
	Secondary: 5-year cumulative probability of recurrence-free survival after end of treatment [Time Frame: At 5 years after end of treatment]. Compliance [Time Frame: At 3 months after end of treatment]. Cosmetic appearance [Time Frame: At 1 and 5-year after end of treatment]. Patient satisfaction [Time Frame: At 1 and 5-year after end of treatment]. Level of Pain [Time Frame: 2 weeks after end of treatment]. Cost-effectiveness [Time Frame: At 5-year after end of treatment]. Adverse events [Time Frame: Up to 3 months after end of treatment].
Starting date	January 2016.
Contact information	Principal Investigator: Klara Mosterd, MD, PhD Maastricht University Medical Centre.
Notes	Ongoing study, results expected 2022.

NCT03573401

Study name	A randomized, double blind, vehicle-controlled multicenter phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the treatment of superficial basal cell carcinoma (sBCC) With photodynamic therapy (PDT).
Methods	Multi-centre, randomised, parallel RCT.
Participants	USA.
	Aiming for 186 participants (over 18 years old) across 15 centres.
Interventions	Experimental: BF-200 ALA Topical application of BF-200 ALA containing 7.8% 5-ALA (5-aminolevulinic acid).
	Placebo comparator: vehicle Topical application of vehicle to BF-200 ALA containing no active ingredient.
Outcomes	Primary: Composite clinical and histological response of the participant's Main Target Lesion as assessed 12 weeks after the start of the last PDT cycle that included treatment of the main target lesion. [Time Frame: 12 weeks after the start of the last PDT cycle that included treatment of the main target lesion] The composite clinical and histological response rate of the participant's main target lesion is the percentage of participants with clinically and histologically cleared main target lesion 12 weeks after the start of the last PDT cycle that included treatment of the main target lesion (Visit 5 or Visit 8).
Starting date	2018.
Contact information	b.schmitz@biofrontera.com
Notes	Study aiming to complete 2024.
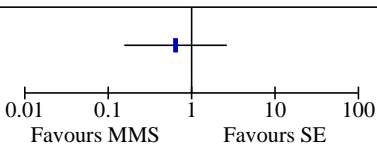
ALA: aminolevulinic acid; **BCC:** basal cell carcinoma; **nBCC:** nodular basal cell carcinoma; **HP:** histologically proven; **PDT**: photodynamic therapy; **RCT:** randomised controlled trial.

DATA AND ANALYSES
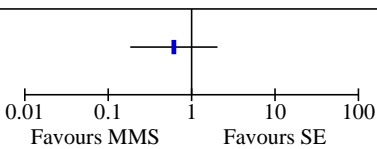
Comparison 1. Mohs micrographic surgery vs surgical excision

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Recurrence at 3 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2 Recurrence at 5 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Mohs micrographic surgery vs surgical excision, Outcome 1: Recurrence at 3 years (lesions)

	MMS		SE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Smeets 2004	3	160	5	171	0.64 [0.16 , 2.64]	

0.01 0.1 1 10 100
Favours MMS   Favours SE

Analysis 1.2. Comparison 1: Mohs micrographic surgery vs surgical excision, Outcome 2: Recurrence at 5 years (lesions)

	MMS		SE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Smeets 2004	4	125	7	134	0.61 [0.18 , 2.04]	

0.01 0.1 1 10 100
Favours MMS   Favours SE

Comparison 2. Imiquimod vs surgical excision

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Recurrence at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.2 Recurrence at 5 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Cosmetic outcome (good/excellent)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.3.1 Observer rated at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.3.2 Participant rated at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.4 Pain (moderate/severe)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.4.1 During treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.4.2 During follow-up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Imiquimod vs surgical excision, Outcome 1: Recurrence at 3 years

Study or Subgroup	Imiquimod cream Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bath-Hextall 2014	35	213	3	188	10.30 [3.22 , 32.94]	

0.01   0.1   1   10   100
Favours imiquimod cream   Favours SE
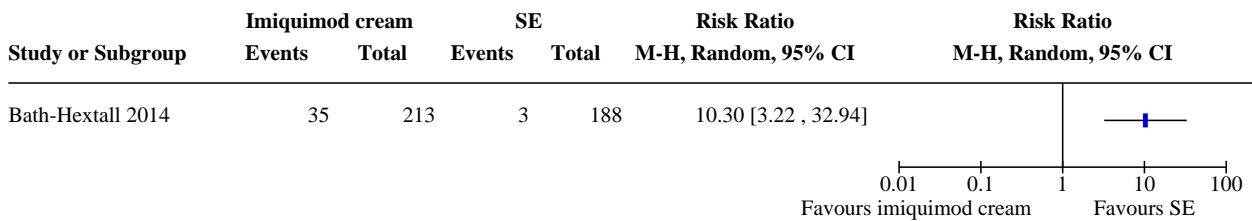
Analysis 2.2. Comparison 2: Imiquimod vs surgical excision, Outcome 2: Recurrence at 5 years

Study or Subgroup	Imiquimod cream Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bath-Hextall 2014	36	206	4	177	7.73 [2.81 , 21.30]	

0.01   0.1   1   10   100
Favours imiquimod cream   Favours SE
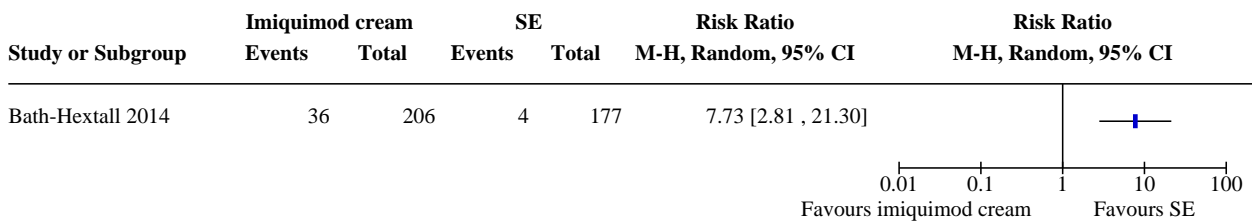
Analysis 2.3. Comparison 2: Imiquimod vs surgical excision, Outcome 3: Cosmetic outcome (good/excellent)

Study or Subgroup	Imiquimod cream Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.3.1 Observer rated at 3 years						
Bath-Hextall 2014	103	170	62	174	1.70 [1.35 , 2.15]	
2.3.2 Participant rated at 3 years						
Bath-Hextall 2014	147	160	153	166	1.00 [0.94 , 1.06]	

0.1   0.2   0.5   1   2   5   10
Favours SE   Favours imiquimod
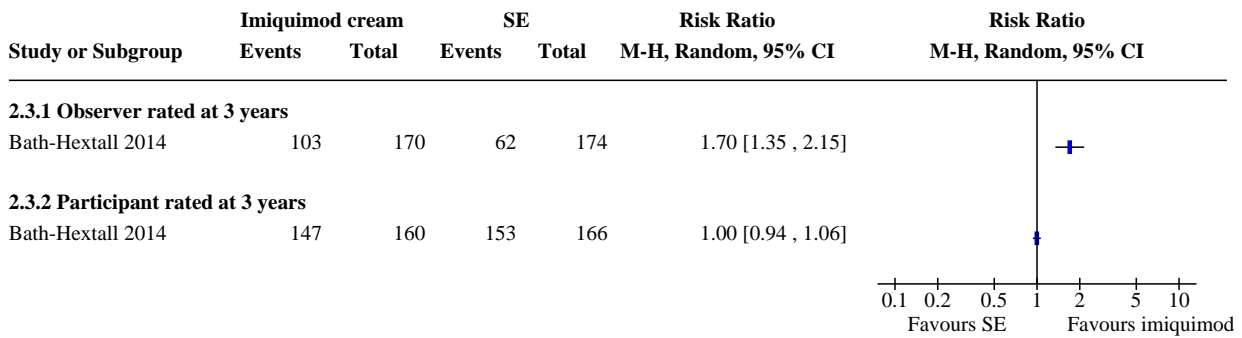
Analysis 2.4. Comparison 2: Imiquimod vs surgical excision, Outcome 4: Pain (moderate/severe)
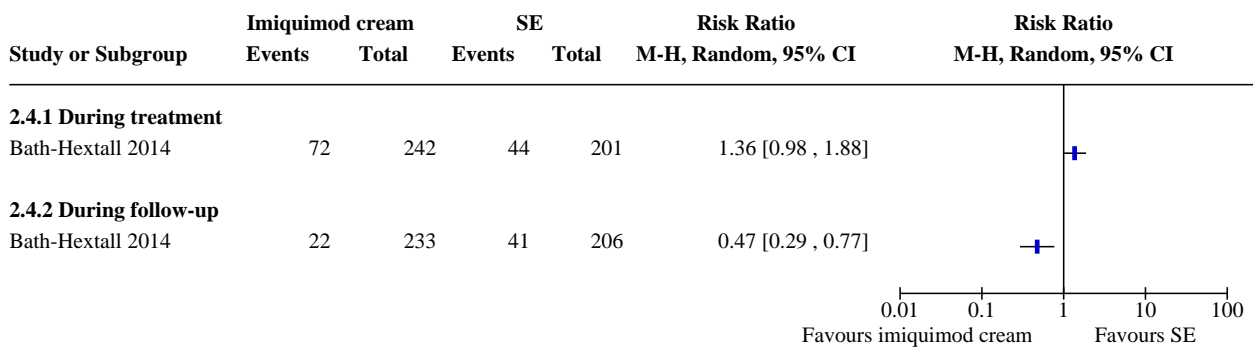
Study or Subgroup	Imiquimod cream Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.4.1 During treatment						
Bath-Hextall 2014	72	242	44	201	1.36 [0.98 , 1.88]	
2.4.2 During follow-up						
Bath-Hextall 2014	22	233	41	206	0.47 [0.29 , 0.77]	

0.01   0.1   1   10   100
Favours imiquimod cream   Favours SE

Comparison 3.   Radiotherapy vs surgical excision (with or without frozen section margin control)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Recurrence at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.2 Recurrence at 4 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.3 Cosmetic outcome (good)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.3.1 Participant rated at 4 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.3.2 Observer rated at 4 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Radiotherapy vs surgical excision (with or without frozen section margin control), Outcome 1: Recurrence at 3 years

Study or Subgroup	Radiotherapy Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Avril 1997	9	173	0	174	19.11 [1.12 , 325.78]	

0.001 0.1 1 10 1000
Favours radiotherapy   Favours SE
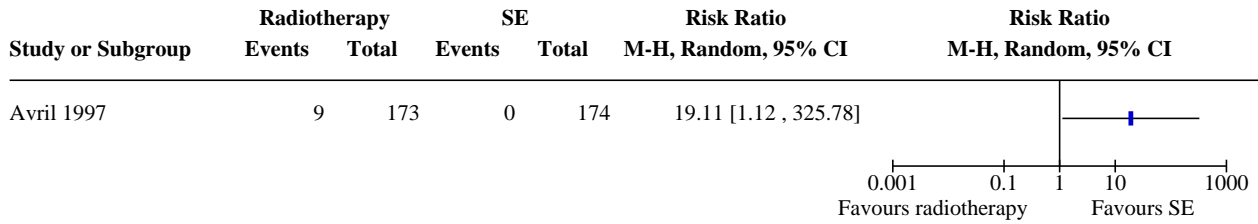
Analysis 3.2. Comparison 3: Radiotherapy vs surgical excision (with or without frozen section margin control), Outcome 2: Recurrence at 4 years

Study or Subgroup	Radiotherapy Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Avril 1997	11	173	1	174	11.06 [1.44 , 84.77]	

0.01 0.1 1 10 100
Favours radiotherapy   Favours SE
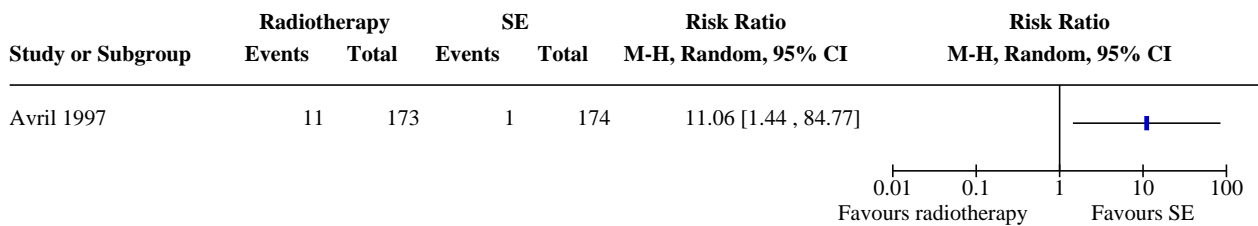
Analysis 3.3. Comparison 3: Radiotherapy vs surgical excision (with or without frozen section margin control), Outcome 3: Cosmetic outcome (good)

Study or Subgroup	Radiotherapy Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.3.1 Participant rated at 4 years						
Avril 1997	87	173	115	174	0.76 [0.63 , 0.91]	
3.3.2 Observer rated at 4 years						
Avril 1997	50	173	105	174	0.48 [0.37 , 0.62]	

0.2 0.5 1 2 5
Favours SE   Favours radiotherapy

Comparison 4. Curettage vs surgical excision

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Recurrence at 2 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Curettage vs surgical excision, Outcome 1: Recurrence at 2 years (lesions)

Study or Subgroup	Curettage Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Salmanpoor 2012	4	20	2	24	2.40 [0.49 , 11.77]	

0.01 0.1 1 10 100
Favours curettage   Favours SE

Comparison 5. Curettage and cautery vs surgical excision

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Recurrence at 2 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Curettage and cautery vs surgical excision, Outcome 1: Recurrence at 2 years (lesions)

Study or Subgroup	C&C Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Salmanpoor 2012	2	25	2	24	0.96 [0.15 , 6.28]	

0.002 0.1 1 10 500
Favours C&C   Favours SE

Comparison 6. Curettage and cautery vs curettage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Recurrence at 2 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
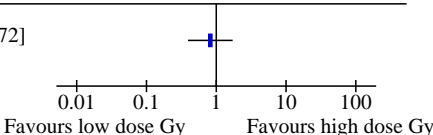
Analysis 6.1. Comparison 6: Curettage and cautery vs curettage, Outcome 1: Recurrence at 2 years (lesions)

Study or Subgroup	C&C Events	Total	Curettage Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Salmanpoor 2012	2	25	4	20	0.40 [0.08 , 1.97]	

0.005 0.1 1 10 200
Favours C&C   Favours curettage

Comparison 7.   Low dose radiotherapy vs high dose radiotherapy

Outcome or subgroup title	No. of studies	No. of par-ticipants	Statistical method	Effect size
7.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
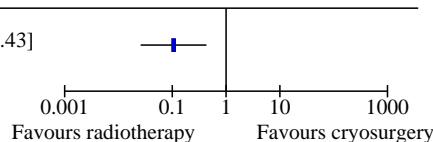
Analysis 7.1. Comparison 7: Low dose radiotherapy vs high dose radiotherapy, Outcome 1: Early treatment failure

Study or Subgroup	Low Gy Events	Total	High Gy Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Landthaler 1989	12	148	14	142	0.82 [0.39 , 1.72]	

0.01   0.1   1   10   100
Favours low dose Gy   Favours high dose Gy

Comparison 8.   Radiotherapy vs cryosurgery

Outcome or subgroup title	No. of studies	No. of par-ticipants	Statistical method	Effect size
8.1 Recurrence at 2 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Radiotherapy vs cryosurgery, Outcome 1: Recurrence at 2 years

Study or Subgroup	Radiotherapy Events	Total	Cryosurgery Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hall 1986	2	49	17	44	0.11 [0.03 , 0.43]	

0.001   0.1   1   10   1000
Favours radiotherapy   Favours cryosurgery

Comparison 9.   Curettage and cryosurgery vs surgical excision

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9.1 Recurrence at 3 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2 Recurrence at 5 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.3 Cosmetic outcome (good)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.3.1 Participant rated at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
9.3.2 Obsever rated at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Curettage and cryosurgery vs surgical excision, Outcome 1: Recurrence at 3 years (lesions)

	Curettage/cryosurgery		SE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Kuijpers 2007	7	51	2	49	3.36 [0.73 , 15.40]	

0.01 0.1 1 10 100
Favours curettage/cryo   Favours SE

Analysis 9.2. Comparison 9: Curettage and cryosurgery vs surgical excision, Outcome 2: Recurrence at 5 years (lesions)

	Curettage/cryosurgery		SE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Kuijpers 2007	9	38	4	47	2.78 [0.93 , 8.34]	

0.01 0.1 1 10 100
Favours curettage/cryo   Favours SE

Analysis 9.3. Comparison 9: Curettage and cryosurgery vs surgical excision, Outcome 3: Cosmetic outcome (good)

	Curettage/cryosurgery		SE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
9.3.1 Participant rated at 1 year						
Kuijpers 2007	42	48	48	48	0.88 [0.78 , 0.98]	
9.3.2 Obsever rated at 1 year						
Kuijpers 2007	11	48	40	48	0.28 [0.16 , 0.47]	

0.1 0.2 0.5 1 2 5 10
Favours SE   Favours curettage/cryo

Comparison 10. MAL-PDT vs surgical excision

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
10.1 Recurrence at 3 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
10.2 Cosmetic outcome (good/excel-lent)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.2.1 Participant rated at 1 year	2	309	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.09, 1.27]
10.2.2 Observer rated 1 year	2	256	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.54, 2.26]
10.3 Pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.4 Early treatment failure (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10: MAL-PDT vs surgical excision, Outcome 1: Recurrence at 3 years (lesions)

Study or Subgroup	MAL-PDT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Abbade 2015	12	33	0	35	26.47 [1.63 , 429.92]	

0.001 0.1 1 10 1000
Favours MAL-PDT   Favours SE

Analysis 10.2. Comparison 10: MAL-PDT vs surgical excision, Outcome 2: Cosmetic outcome (good/excellent)

Study or Subgroup	MAL-PDT Events	Total	SE Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.2.1 Participant rated at 1 year							
Rhodes 2004	41	42	36	43	29.5%	1.17 [1.01 , 1.34]	
Szeimies 2008	104	107	96	117	70.5%	1.18 [1.08 , 1.30]	
Subtotal (95% CI)		**149**		**160**	**100.0%**	**1.18 [1.09 , 1.27]**	
Total events:	145		132				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%							
Test for overall effect: Z = 4.24 (P < 0.0001)							
10.2.2 Observer rated 1 year							
Rhodes 2004	33	42	17	45	21.8%	2.08 [1.38 , 3.12]	
Szeimies 2008	77	83	44	86	78.2%	1.81 [1.46 , 2.25]	
Subtotal (95% CI)		**125**		**131**	**100.0%**	**1.87 [1.54 , 2.26]**	
Total events:	110		61				
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%							
Test for overall effect: Z = 6.44 (P < 0.00001)							

0.5 0.7 1 1.5 2
Favours surgery   Favours MAL-PDT

Analysis 10.3.   Comparison 10: MAL-PDT vs surgical excision, Outcome 3: Pain

Study or Subgroup	MAL-PDT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rhodes 2004	7	52	3	49	2.20 [0.60 , 8.03]	

0.01 0.1 1 10 100
Favours MAL-PDT   Favours SE

Analysis 10.4.   Comparison 10: MAL-PDT vs surgical excision, Outcome 4: Early treatment failure (lesions)
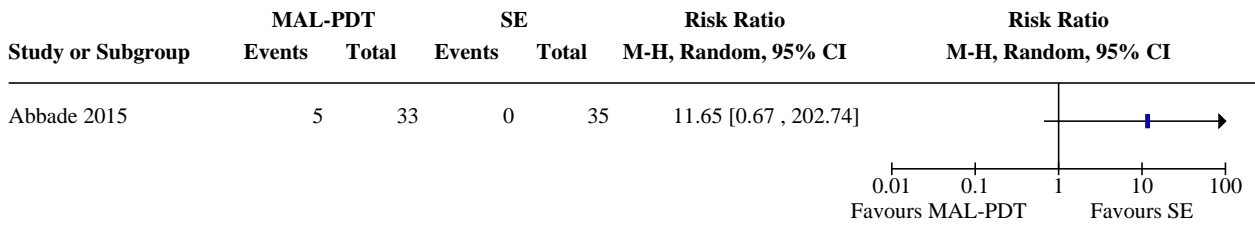
Study or Subgroup	MAL-PDT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Abbade 2015	5	33	0	35	11.65 [0.67 , 202.74]	

0.01 0.1 1 10 100
Favours MAL-PDT   Favours SE

Comparison 11.   ALA-PDT vs surgical excision

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Recurrence at 3 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.2 Recurrence at 5 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.3 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 11.1.   Comparison 11: ALA-PDT vs surgical excision, Outcome 1: Recurrence at 3 years (lesions)

Study or Subgroup	ALA-PDT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mosterd 2008	21	85	2	88	10.87 [2.63 , 44.95]	

0.001 0.1 1 10 1000
Favours ALA-PDT   Favours SE
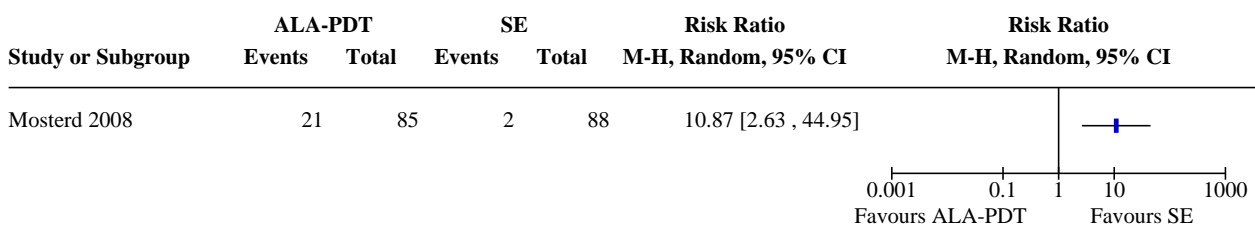
Analysis 11.2. Comparison 11: ALA-PDT vs surgical excision, Outcome 2: Recurrence at 5 years (lesions)

Study or Subgroup	ALA-PDT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mosterd 2008	23	85	2	88	11.91 [2.90 , 48.95]	

0.01   0.1   1   10   100
Favours ALA-PDT   Favours SE
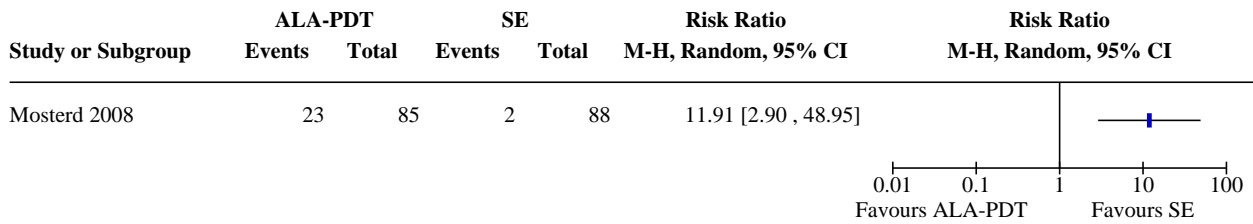
Analysis 11.3. Comparison 11: ALA-PDT vs surgical excision, Outcome 3: Early treatment failure
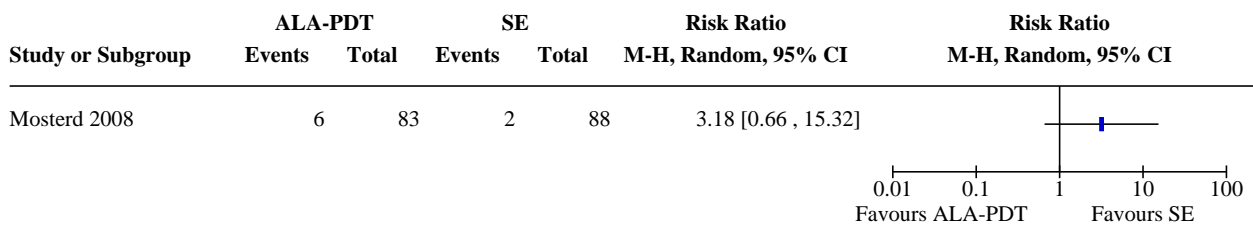
Study or Subgroup	ALA-PDT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mosterd 2008	6	83	2	88	3.18 [0.66 , 15.32]	

0.01   0.1   1   10   100
Favours ALA-PDT   Favours SE

Comparison 12. ALA-PDT vs MAL-PDT

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.1 Cosmetic outcome (good/very good)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.2 Pain (visual analogue score)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.2.1 Cycle 1	2	313	Mean Difference (IV, Random, 95% CI)	0.56 [-0.76, 1.88]
12.2.2 Cycle 2	2	300	Mean Difference (IV, Random, 95% CI)	0.43 [-0.18, 1.05]
12.3 Pain (numerical rating scale)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.3.1 Cycle 1	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.3.2 Cycle 2	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.4 Early treatment failure	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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Analysis 12.1. Comparison 12: ALA-PDT vs MAL-PDT, Outcome 1: Cosmetic outcome (good/very good)

Study or Subgroup	ALA-PDT Events	Total	MAL-PDT Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kessels 2018	58	73	48	72	1.19 [0.98 , 1.46]	
Morton 2018	41	56	39	57	1.07 [0.84 , 1.36]	

0.5　0.7　1　1.5　2
Favours MAL-PDT　　Favours ALA-PDT
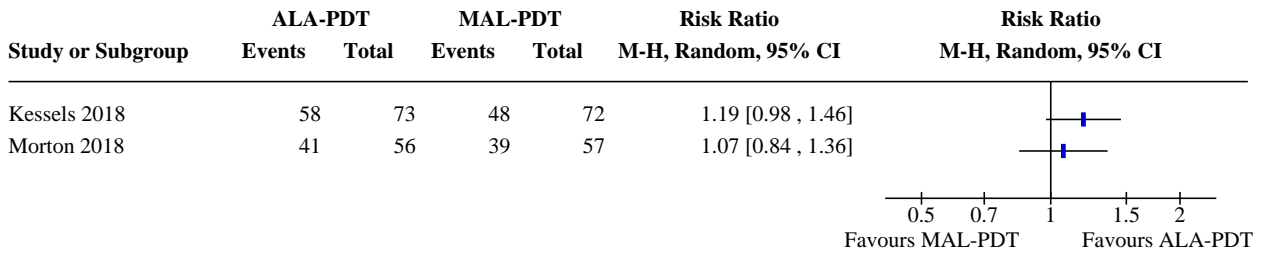
Analysis 12.2. Comparison 12: ALA-PDT vs MAL-PDT, Outcome 2: Pain (visual analogue score)

Study or Subgroup	ALA-PDT Mean	SD	Total	MAL-PDT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
12.2.1 Cycle 1									
Kuijpers 2006	4.38	2.57	13	2.84	2.41	19	32.2%	1.54 [-0.23 , 3.31]	
Morton 2018	3.7	2.4	138	3.6	2.2	143	67.8%	0.10 [-0.44 , 0.64]	
Subtotal (95% CI)			151			162	100.0%	0.56 [-0.76 , 1.88]	
Heterogeneity: Tau² = 0.59; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%									
Test for overall effect: Z = 0.84 (P = 0.40)									
12.2.2 Cycle 2									
Kuijpers 2006	4.83	3.21	12	3.89	2.83	12	6.5%	0.94 [-1.48 , 3.36]	
Morton 2018	4.5	2.7	138	4.1	2.7	138	93.5%	0.40 [-0.24 , 1.04]	
Subtotal (95% CI)			150			150	100.0%	0.43 [-0.18 , 1.05]	
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%									
Test for overall effect: Z = 1.38 (P = 0.17)									

-2　-1　0　1　2
Favours MAL-PDT　　Favours ALA-PDT

Analysis 12.3. Comparison 12: ALA-PDT vs MAL-PDT, Outcome 3: Pain (numerical rating scale)

Study or Subgroup	ALA-PDT Mean	SD	Total	MAL-PDT Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
12.3.1 Cycle 1								
Kessels 2018	1.88	2.36	82	2.25	2.54	79	-0.37 [-1.13 , 0.39]	
12.3.2 Cycle 2								
Kessels 2018	3.36	2.57	82	2.48	2.57	79	0.88 [0.09 , 1.67]	

-10　-5　0　5　10
Favours ALA-PDT　　Favours MAL-PDT
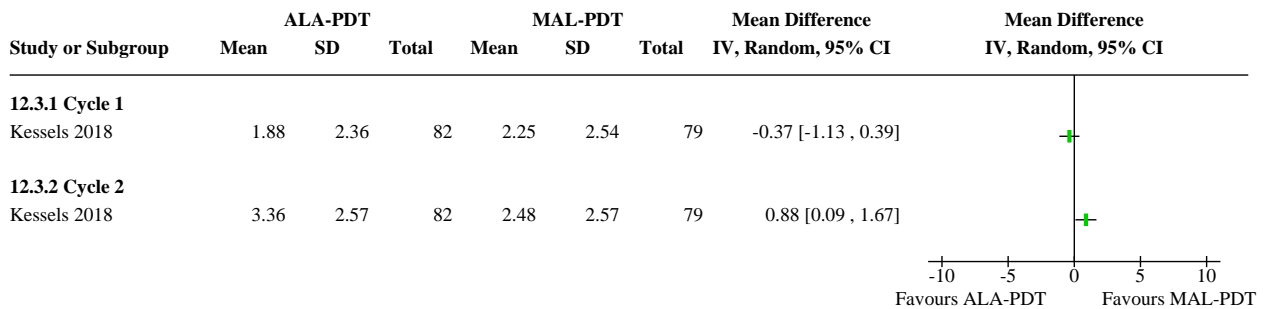
Analysis 12.4. Comparison 12: ALA-PDT vs MAL-PDT, Outcome 4: Early treatment failure
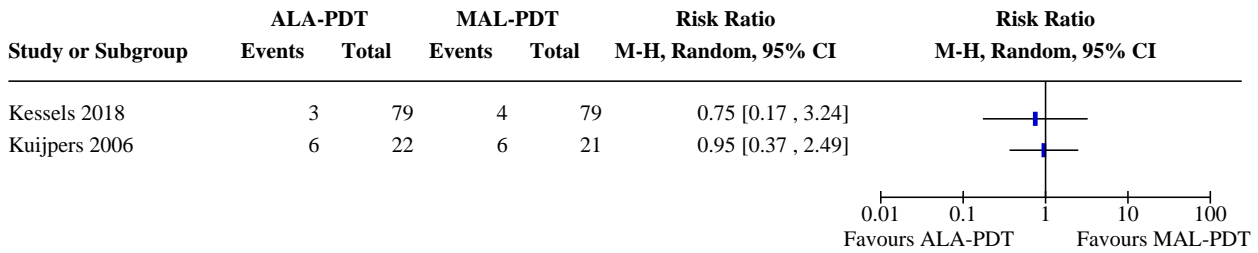
Study or Subgroup	ALA-PDT Events	ALA-PDT Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kessels 2018	3	79	4	79	0.75 [0.17 , 3.24]	
Kuijpers 2006	6	22	6	21	0.95 [0.37 , 2.49]	

0.01 0.1 1 10 100
Favours ALA-PDT   Favours MAL-PDT

Comparison 13. BF-200 ALA-PDT vs MAL-PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13: BF-200 ALA-PDT vs MAL-PDT, Outcome 1: Early treatment failure
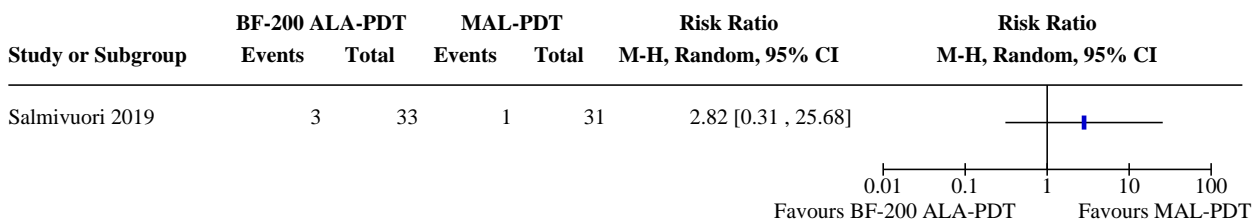
Study or Subgroup	BF-200 ALA-PDT Events	BF-200 ALA-PDT Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Salmivuori 2019	3	33	1	31	2.82 [0.31 , 25.68]	

0.01 0.1 1 10 100
Favours BF-200 ALA-PDT   Favours MAL-PDT

Comparison 14. HAL-PDT vs MAL-PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 14.1. Comparison 14: HAL-PDT vs MAL-PDT, Outcome 1: Early treatment failure

Study or Subgroup	HAL-PDT Events	HAL-PDT Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Salmivuori 2019	2	31	1	31	2.00 [0.19 , 20.93]	

0.01 0.1 1 10 100
Favours HAL-PDT   Favours MAL-PDT
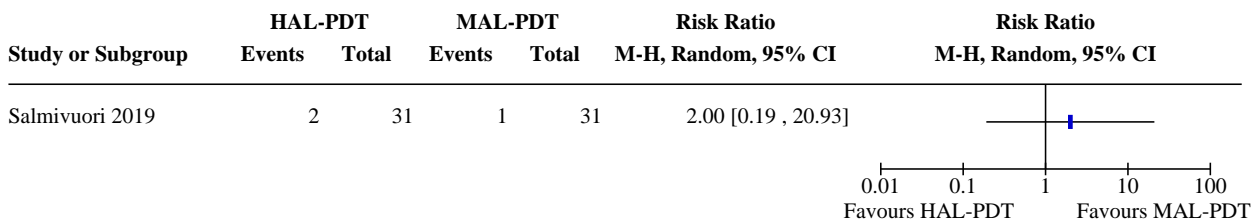
Comparison 15. HAL-PDT vs BF-200 ALA-PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 15.1. Comparison 15: HAL-PDT vs BF-200 ALA-PDT, Outcome 1: Early treatment failure
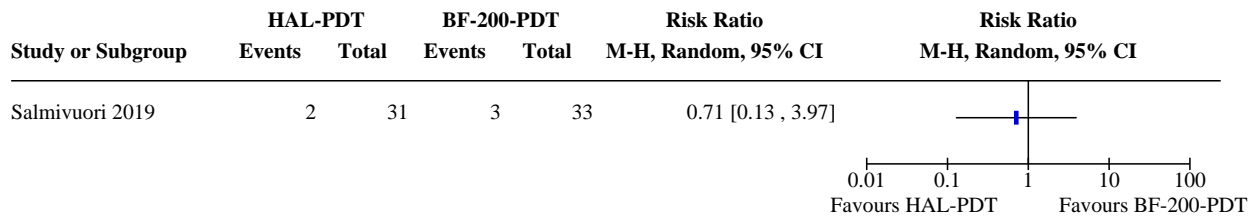
	HAL-PDT		BF-200-PDT		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Salmivuori 2019	2	31	3	33	0.71 [0.13 , 3.97]	

```
         0.01    0.1      1      10     100
        Favours HAL-PDT      Favours BF-200-PDT
```

Comparison 16. MAL-PDT vs cryosurgery

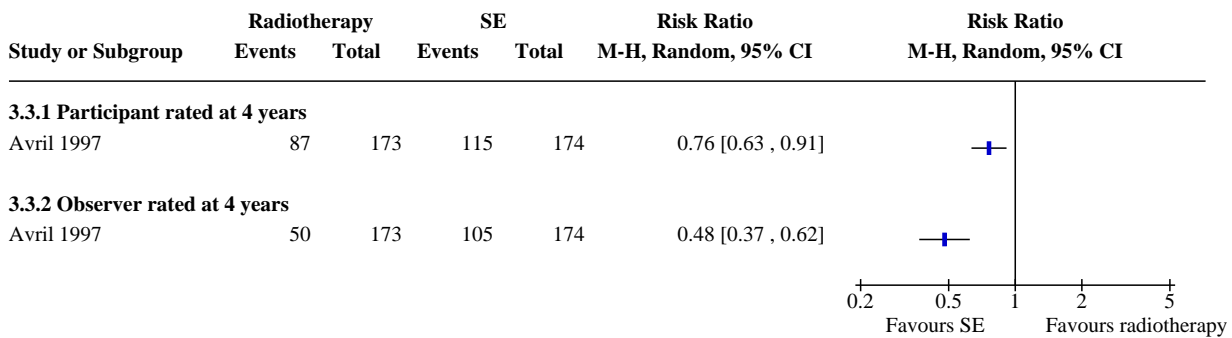| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Recurrence at 3 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.2 Recurrence at 5 years (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.3 Cosmetic outcome (good/excellent)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.3.1 Participant rated at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.3.2 Observer rated at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.4 Pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.5 Early treatment failure (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 16.1. Comparison 16: MAL-PDT vs cryosurgery, Outcome 1: Recurrence at 3 years (lesions)

Study or Subgroup	MAL-PDT Events	Total	Cryosurgery Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Basset-Seguin 2008	22	100	18	93	1.14 [0.65 , 1.98]	

0.01   0.1   1   10   100
Favours MAL-PDT   Favours cryosurgery
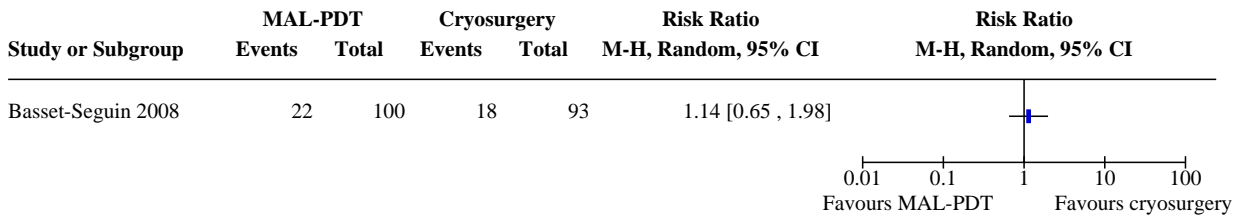
Analysis 16.2. Comparison 16: MAL-PDT vs cryosurgery, Outcome 2: Recurrence at 5 years (lesions)

Study or Subgroup	MAL-PDT Events	Total	cryosurgery Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Basset-Seguin 2008	22	100	19	93	1.08 [0.62 , 1.86]	

0.1   0.2   0.5   1   2   5   10
Favours MAL PDT   Favours cryosurgery
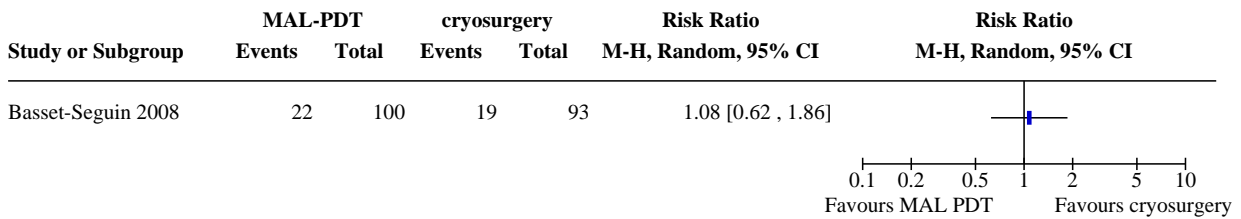
Analysis 16.3. Comparison 16: MAL-PDT vs cryosurgery, Outcome 3: Cosmetic outcome (good/excellent)

Study or Subgroup	PDT Events	Total	cryosurgery Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
16.3.1 Participant rated at 1 year						
Basset-Seguin 2008	51	51	39	48	1.23 [1.07 , 1.41]	
16.3.2 Observer rated at 1 year						
Basset-Seguin 2008	45	51	29	48	1.46 [1.14 , 1.88]	

0.01   0.1   1   10   100
Favours cryosurgery   Favours MAL-PDT

Analysis 16.4. Comparison 16: MAL-PDT vs cryosurgery, Outcome 4: Pain

Study or Subgroup	MAL-PDT Events	Total	cryosurgery Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Basset-Seguin 2008	22	60	19	58	1.12 [0.68 , 1.84]	

0.01   0.1   1   10   100
Favours MAL-PDT   Favours cryosurgery
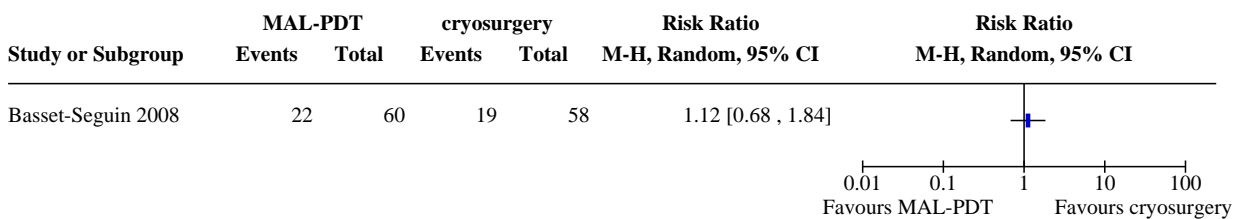
Analysis 16.5. Comparison 16: MAL-PDT vs cryosurgery, Outcome 5: Early treatment failure (lesions)

Study or Subgroup	MAL PDT Events	MAL PDT Total	cryosurgery Events	cryosurgery Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Basset-Seguin 2008	3	103	5	98	0.57 [0.14 , 2.33]	

```
        0.01   0.1    1    10   100
         Favours PDT    Favours cryosurgery
```

Comparison 17. ALA-PDT vs cryosurgery

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
17.1 Cosmetic outcome (good/excellent)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17.2 Pain	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 17.1. Comparison 17: ALA-PDT vs cryosurgery, Outcome 1: Cosmetic outcome (good/excellent)

Study or Subgroup	PDT Events	PDT Total	cryosurgery Events	cryosurgery Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wang 2001	39	42	20	37	1.72 [1.26 , 2.34]	

```
        0.01    0.1     1     10    100
      Favours cryosurgery   Favours MAL-PDT
```

Analysis 17.2. Comparison 17: ALA-PDT vs cryosurgery, Outcome 2: Pain

Study or Subgroup	ALA-PDT Mean	ALA-PDT SD	ALA-PDT Total	cryosurgery Mean	cryosurgery SD	cryosurgery Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Wang 2001	43	31	47	32	27	41	11.00 [-1.12 , 23.12]	

```
      -100    -50     0     50    100
      Favours ALA-PDT    Favours cryosurgery
```

Comparison 18. Imiquimod cream vs MAL-PDT

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
18.1 Recurrence at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2 Recurrence at 5 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

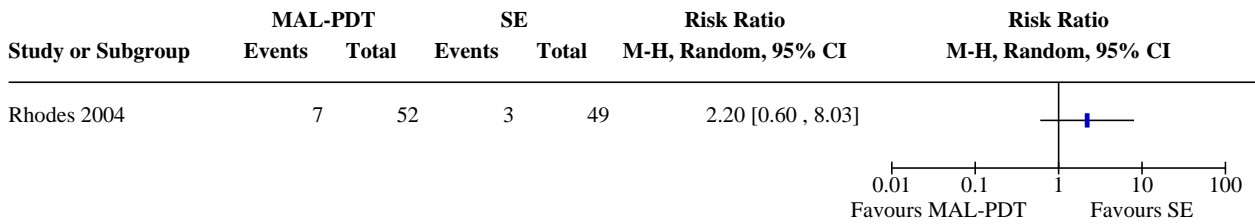| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.3 Cosmetic outcome (good/excellent, observer rated at 1 year)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.4 Pain (moderate/severe)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.5 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18: Imiquimod cream vs MAL-PDT, Outcome 1: Recurrence at 3 years

Study or Subgroup	Imiquimod Events	Total	MAL-PDT Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	34	149	66	128	0.44 [0.32 , 0.62]	

0.01　0.1　1　10　100
Favours imiquimod　　　Favours MAL-PDT

Analysis 18.2. Comparison 18: Imiquimod cream vs MAL-PDT, Outcome 2: Recurrence at 5 years

Study or Subgroup	Imiquimod Events	Total	MAL-PDT Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	36	126	70	102	0.42 [0.31 , 0.57]	

0.01　0.1　1　10　100
Favours imiquimod　　　Favours MAL-PDT

Analysis 18.3. Comparison 18: Imiquimod cream vs MAL-PDT, Outcome 3: Cosmetic outcome (good/excellent, observer rated at 1 year)

Study or Subgroup	Imiquimod Events	Total	MAL-PDT Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	113	184	116	186	0.98 [0.84 , 1.16]	

0.2　0.5　1　2　5
Favours MAL-PDT　　　Favours imiquimod

Analysis 18.4. Comparison 18: Imiquimod cream vs MAL-PDT, Outcome 4: Pain (moderate/severe)

Study or Subgroup	Imiquimod Events	Imiquimod Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	33	181	58	190	0.60 [0.41 , 0.87]	

0.01   0.1   1   10   100
Favours imiquimod   Favours MAL-PDT
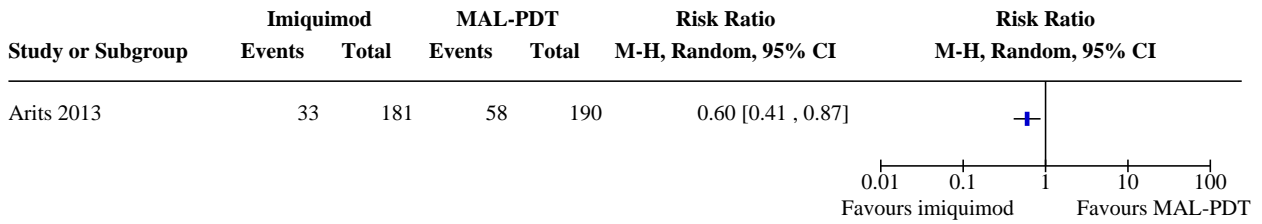
Analysis 18.5. Comparison 18: Imiquimod cream vs MAL-PDT, Outcome 5: Early treatment failure

Study or Subgroup	Imiquimod Events	Imiquimod Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	19	189	31	196	0.64 [0.37 , 1.09]	

0.01   0.1   1   10   100
Favours imiquimod   Favours MAL-PDT

Comparison 19. 5-FU cream vs MAL-PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Recurrence at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.2 Recurrence at 5 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.3 Cosmetic outcome (good/excellent, observer rated at 1 year)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.4 Pain (moderate/severe)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.5 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 19.1. Comparison 19: 5-FU cream vs MAL-PDT, Outcome 1: Recurrence at 3 years

Study or Subgroup	5-FU cream Events	5-FU cream Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	50	146	66	126	0.65 [0.49 , 0.86]	

0.1   0.2   0.5   1   2   5   10
Favours 5-FU cream   Favours MAL-PDT
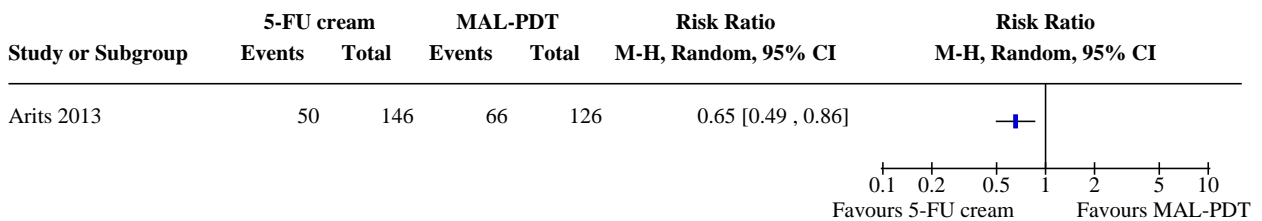
Analysis 19.2. Comparison 19: 5-FU cream vs MAL-PDT, Outcome 2: Recurrence at 5 years

Study or Subgroup	5-FU cream Events	5-FU cream Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	57	124	70	102	0.67 [0.53 , 0.84]	

Favours 5-FU cream Favours MAL-PDT
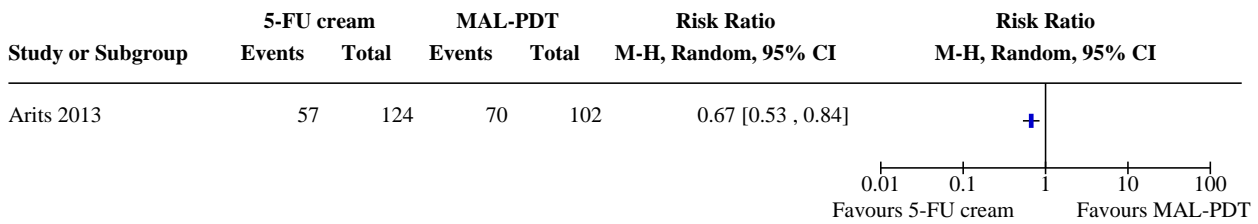
Analysis 19.3. Comparison 19: 5-FU cream vs MAL-PDT, Outcome 3: Cosmetic outcome (good/excellent, observer rated at 1 year)

Study or Subgroup	5-FU cream Events	5-FU cream Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	111	193	116	186	0.92 [0.78 , 1.09]	

Favours MAL-PDT Favours 5-FU cream
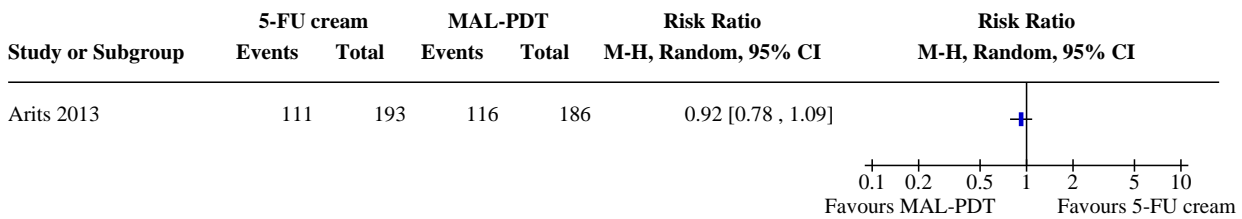
Analysis 19.4. Comparison 19: 5-FU cream vs MAL-PDT, Outcome 4: Pain (moderate/severe)

Study or Subgroup	5-FU cream Events	5-FU cream Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	23	184	58	190	0.41 [0.26 , 0.63]	

Favours 5-FU cream Favours MAL-PDT
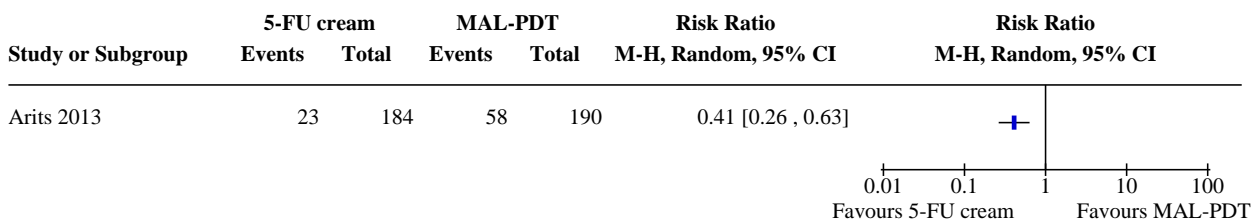
Analysis 19.5. Comparison 19: 5-FU cream vs MAL-PDT, Outcome 5: Early treatment failure

Study or Subgroup	5-FU cream Events	5-FU cream Total	MAL-PDT Events	MAL-PDT Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	24	198	31	196	0.77 [0.47 , 1.26]	

Favours 5-FU cream Favours MAL-PDT
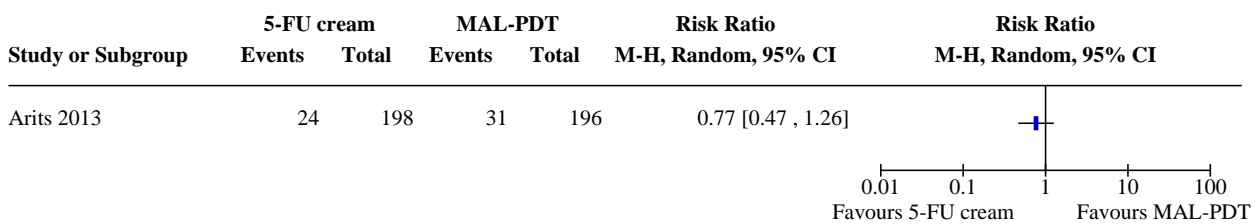
Comparison 20. Laser ALA-PDT vs broadband light ALA-PDT

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
20.1 Cosmetic outcome (good/excellent, observer rated at 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
20.2 Pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.2.1 Discomfort during/after illumina- tion	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.2.2 Discomfort during 1st week after treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 20.1. Comparison 20: Laser ALA-PDT vs broadband light ALA-PDT, Outcome 1: Cosmetic outcome (good/excellent, observer rated at 6 months)

Study or Subgroup	Laser Events	Total	Broad band Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Soler 2000	80	95	102	110	0.91 [0.82 , 1.01]	

0.5 0.7 1 1.5 2
Favours Broad band   Favours laser

Analysis 20.2. Comparison 20: Laser ALA-PDT vs broadband light ALA-PDT, Outcome 2: Pain

Study or Subgroup	Laser Events	Total	Broad band Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
20.2.1 Discomfort during/after illumination						
Soler 2000	34	41	32	42	1.09 [0.87 , 1.35]	
20.2.2 Discomfort during 1st week after treatment						
Soler 2000	28	41	31	42	0.93 [0.70 , 1.22]	

0.01 0.1 1 10 100
Favours LL   Favours BL

Comparison 21. AFXL MAL-PDT vs MAL-PDT

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
21.1 Cosmetic outcome (good/excel- lent)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1.1 Observer rated at 1 year	2	57	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.54, 2.31]
21.1.2 Participant rated at 1 year	1	23	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.17]

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
21.2 Early treatment failure	2	71	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.17, 0.84]

Analysis 21.1. Comparison 21: AFXL MAL-PDT vs MAL-PDT, Outcome 1: Cosmetic outcome (good/excellent)

Study or Subgroup	AFXL MAL-PDT Events	Total	MAL-PDT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
21.1.1 Observer rated at 1 year							
Choi 2016	17	18	16	16	65.8%	0.95 [0.81 , 1.11]	
Haak 2015	8	13	4	10	34.2%	1.54 [0.64 , 3.68]	
Subtotal (95% CI)		31		26	100.0%	**1.12 [0.54 , 2.31]**	
Total events:	25		20				
Heterogeneity: Tau² = 0.20; Chi² = 2.97, df = 1 (P = 0.08); I² = 66%							
Test for overall effect: Z = 0.31 (P = 0.76)							
21.1.2 Participant rated at 1 year							
Haak 2015	12	13	10	10	100.0%	0.94 [0.75 , 1.17]	
Subtotal (95% CI)		13		10	100.0%	**0.94 [0.75 , 1.17]**	
Total events:	12		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.59 (P = 0.56)							

Favours MAL-PDT 0.01 0.1 1 10 100 Favours AFXL MAL-PDT

Analysis 21.2. Comparison 21: AFXL MAL-PDT vs MAL-PDT, Outcome 2: Early treatment failure
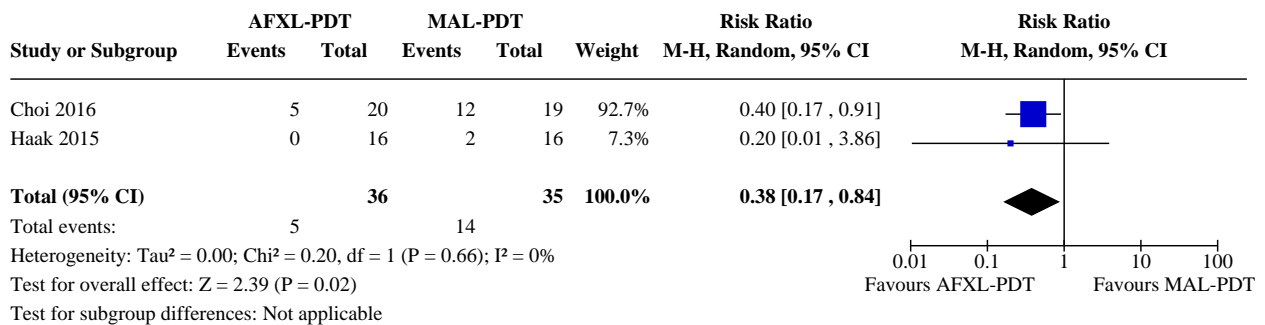
Study or Subgroup	AFXL-PDT Events	Total	MAL-PDT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Choi 2016	5	20	12	19	92.7%	0.40 [0.17 , 0.91]	
Haak 2015	0	16	2	16	7.3%	0.20 [0.01 , 3.86]	
Total (95% CI)		36		35	100.0%	**0.38 [0.17 , 0.84]**	
Total events:	5		14				
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%							
Test for overall effect: Z = 2.39 (P = 0.02)							
Test for subgroup differences: Not applicable							

Favours AFXL-PDT 0.01 0.1 1 10 100 Favours MAL-PDT

Comparison 22. MAL-PDT vs placebo

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
22.1 Cosmetic outcome (good/excellent, ob- server rated at 6 months))	1		Risk Ratio (M-H, Random, 95% CI)	Totals not select- ed

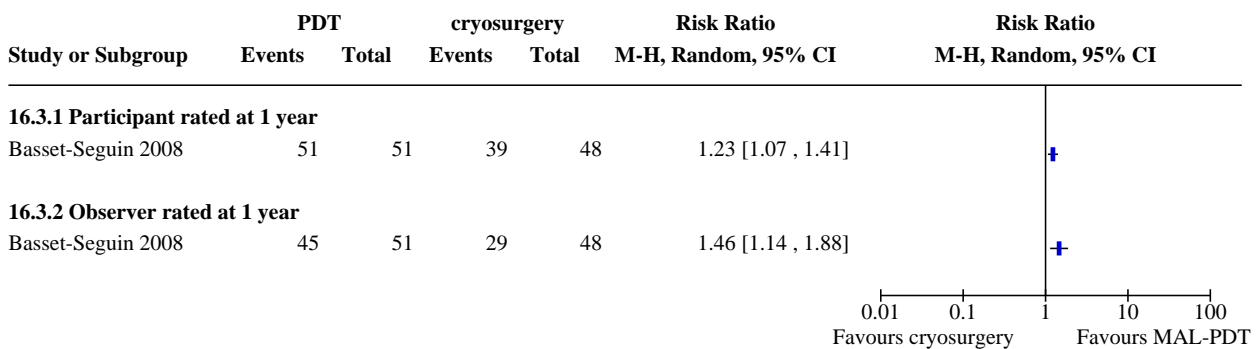| Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
22.2 Pain (frequency reported as local AE)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not select- ed
22.3 Early treatment failure (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not select- ed

Analysis 22.1. Comparison 22: MAL-PDT vs placebo, Outcome 1: Cosmetic outcome (good/excellent, observer rated at 6 months))

	MAL-PDT		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Foley 2009a	42	43	14	15	1.05 [0.91 , 1.21]	

0.01   0.1   1   10   100
Favours Placebo   Favours MAL-PDT

Analysis 22.2. Comparison 22: MAL-PDT vs placebo, Outcome 2: Pain (frequency reported as local AE)

	MAL-PDT		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Foley 2009a	12	66	3	65	3.94 [1.17 , 13.32]	

0.01   0.1   1   10   100
Favours MAL-PDT   Favours Placebo

Analysis 22.3. Comparison 22: MAL-PDT vs placebo, Outcome 3: Early treatment failure (lesions)

	MAL-PDT		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Foley 2009a	20	75	55	75	0.36 [0.24 , 0.54]	

0.02   0.1   1   10   50
Favours MAL-PDT   Favours Placebo

Comparison 23. Imiquimod cream vs 5-FU cream

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
23.1 Recurrence at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.2 Recurrence at 5 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.3 Cosmetic outcome (good/excellent, observer rated at 1 year)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.4 Pain (moderate/severe)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.5 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 23.1. Comparison 23: Imiquimod cream vs 5-FU cream, Outcome 1: Recurrence at 3 years

Study or Subgroup	Imiquimod cream Events	Total	5-FU cream Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	34	145	50	146	0.68 [0.47 , 0.99]	

0.2 0.5 1 2 5
Favours imiquimod cream   Favours 5-FU cream
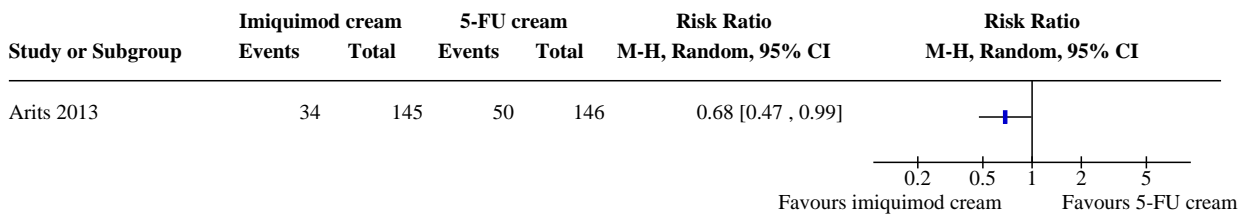
Analysis 23.2. Comparison 23: Imiquimod cream vs 5-FU cream, Outcome 2: Recurrence at 5 years

Study or Subgroup	Imiquimod cream Events	Total	5-FU cream Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	36	126	57	124	0.62 [0.44 , 0.87]	

0.05 0.2 1 5 20
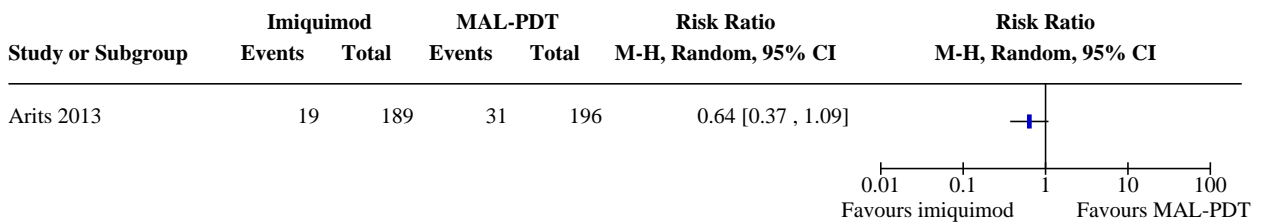Favours imiquimod cream   Favours 5-FU cream
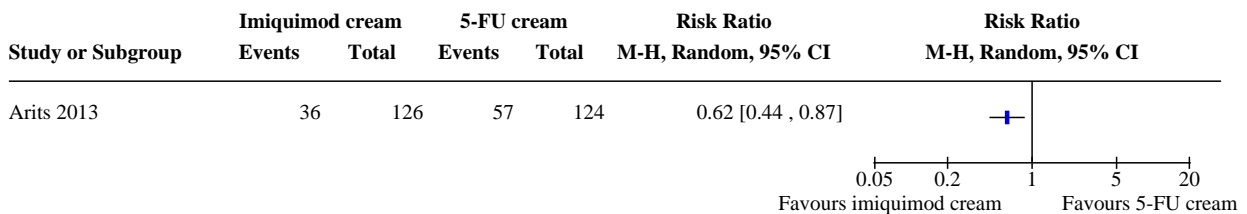
Analysis 23.3. Comparison 23: Imiquimod cream vs 5-FU cream, Outcome 3: Cosmetic outcome (good/excellent, observer rated at 1 year)

Study or Subgroup	Imiquimod cream Events	Total	5-FU cream Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	113	184	111	193	1.07 [0.90 , 1.26]	

0.1 0.2 0.5 1 2 5 10
Favours 5-cream   Favours imiquimod cream
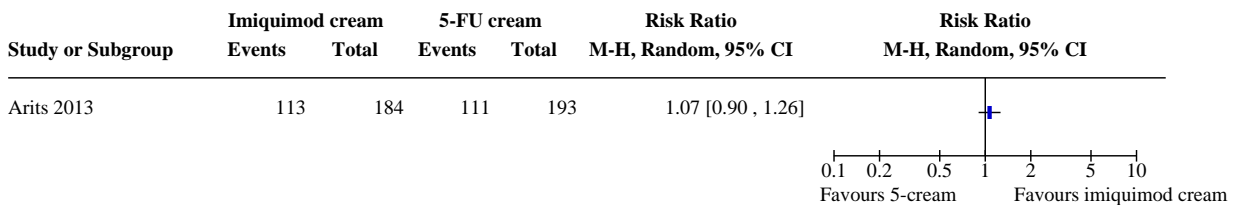
Analysis 23.4. Comparison 23: Imiquimod cream vs 5-FU cream, Outcome 4: Pain (moderate/severe)

Study or Subgroup	Imiquimod cream Events	Total	5-FU cream Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	33	181	23	184	1.46 [0.89 , 2.38]	

0.01 0.1 1 10 100
Favours imiquimod cream   Favours 5-FU cream
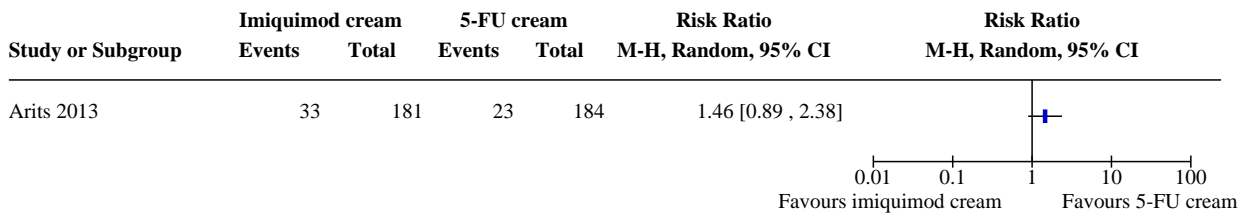
Analysis 23.5. Comparison 23: Imiquimod cream vs 5-FU cream, Outcome 5: Early treatment failure
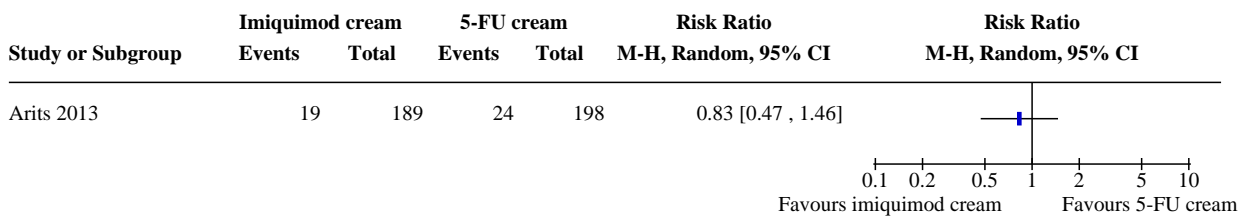
Study or Subgroup	Imiquimod cream Events	Total	5-FU cream Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arits 2013	19	189	24	198	0.83 [0.47 , 1.46]	

0.1 0.2 0.5 1 2 5 10
Favours imiquimod cream   Favours 5-FU cream

Comparison 24. Imiquimod vs radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Cosmetic outcome (excellent, participant rated at 6 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 24.1. Comparison 24: Imiquimod vs radiotherapy, Outcome 1: Cosmetic outcome (excellent, participant rated at 6 weeks)
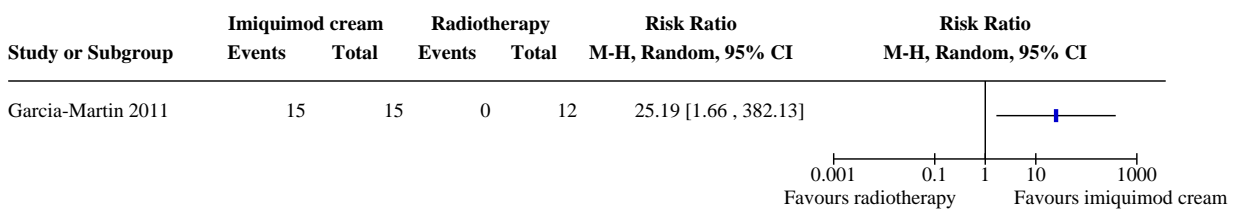
Study or Subgroup	Imiquimod cream Events	Total	Radiotherapy Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Garcia-Martin 2011	15	15	0	12	25.19 [1.66 , 382.13]	

0.001 0.1 1 10 1000
Favours radiotherapy   Favours imiquimod cream

Comparison 25. Imiquimod cream under occlusion vs no occlusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Early treatment failure	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1.1 sBCC	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
25.1.2 nBCC	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 25.1. Comparison 25: Imiquimod cream under occlusion vs no occlusion, Outcome 1: Early treatment failure

	With occlusion		Without occlusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
25.1.1 sBCC						
Sterry 2002a	15	44	18	49	0.93 [0.53 , 1.61]	
25.1.2 nBCC						
Sterry 2002b	19	45	21	45	0.90 [0.57 , 1.44]	

0.1 0.2 0.5 1 2 5 10
Favours occlussion   Favours no occlusion
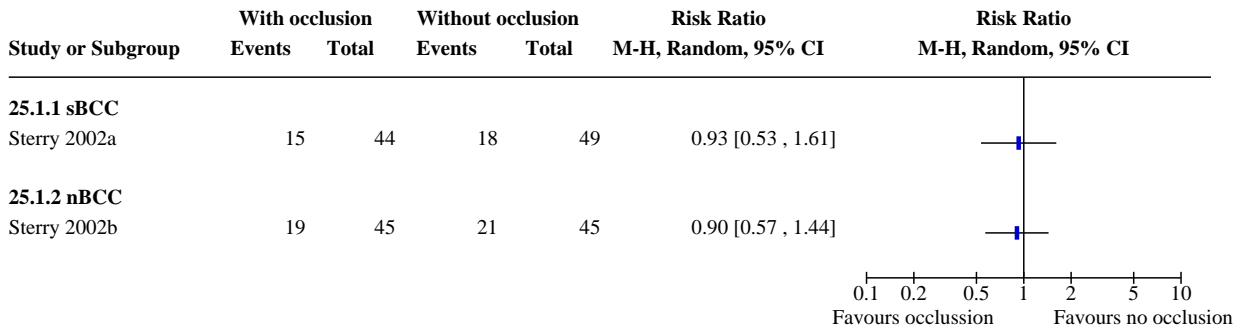
Comparison 26. Imiquimod cream vs vehicle

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
26.1 Early treatment failure	5	1145	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.19, 0.32]

Analysis 26.1. Comparison 26: Imiquimod cream vs vehicle, Outcome 1: Early treatment failure

	Imiquimod cream		Vehicle			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Beutner 1999	4	24	10	11	7.1%	0.18 [0.07 , 0.46]	
Geisse 2002	23	96	26	32	21.1%	0.29 [0.20 , 0.44]	
Geisse 2004	70	364	349	360	31.0%	0.20 [0.16 , 0.25]	
Schulze 2005	17	84	77	82	19.5%	0.22 [0.14 , 0.33]	
Shumack 2002b	21	68	21	24	21.4%	0.35 [0.24 , 0.52]	
Total (95% CI)		**636**		**509**	**100.0%**	**0.25 [0.19 , 0.32]**	
Total events:	135		483				

Heterogeneity: Tau² = 0.05; Chi² = 9.22, df = 4 (P = 0.06); I² = 57%
Test for overall effect: Z = 10.19 (P < 0.00001)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours imiquimod cream   Favours vehicle

Comparison 27.   Imiquimod 5 weeks vs 8 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 Recurrence at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 27.1.   Comparison 27: Imiquimod 5 weeks vs 8 weeks, Outcome 1: Recurrence at 1 year

Study or Subgroup	Imiquimod 5 weeks Events	Total	Imiquimod 8 weeks Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ezughah 2008	8	14	2	16	4.57 [1.16 , 18.05]	

0.01   0.1   1   10   100
Favours 5 weeks   Favours 8 weeks

Comparison 28.   Imiquimod 8 weeks vs 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 28.1.   Comparison 28: Imiquimod 8 weeks vs 12 weeks, Outcome 1: Early treatment failure

Study or Subgroup	8 weeks Events	Total	12 weeks Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Eigentler 2007	16	45	17	45	0.94 [0.55 , 1.62]	

0.01   0.1   1   10   100
Favours 8 weeks   Favours 12 weeks

Comparison 29.   5-FU in PC vs 5-FU in petrolatum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 Early treatment failure (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 29.1. Comparison 29: 5-FU in PC vs 5-FU in petrolatum, Outcome 1: Early treatment failure (lesions)
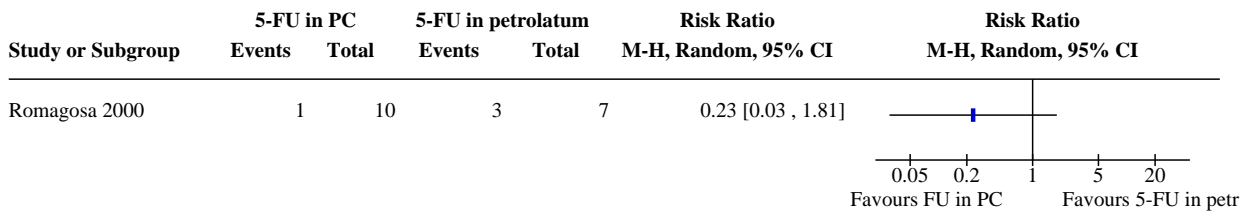
Study or Subgroup	5-FU in PC		5-FU in petrolatum		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Romagosa 2000	1	10	3	7	0.23 [0.03 , 1.81]	

0.05   0.2   1   5   20
Favours FU in PC   Favours 5-FU in petr

Comparison 30. 5-FU/epinephrine gel (1.0 mL once a week for 6 weeks vs 0.5 mL once a week for 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 30.1. Comparison 30: 5-FU/epinephrine gel (1.0 mL once a week for 6 weeks vs 0.5 mL once a week for 6 weeks, Outcome 1: Early treatment failure
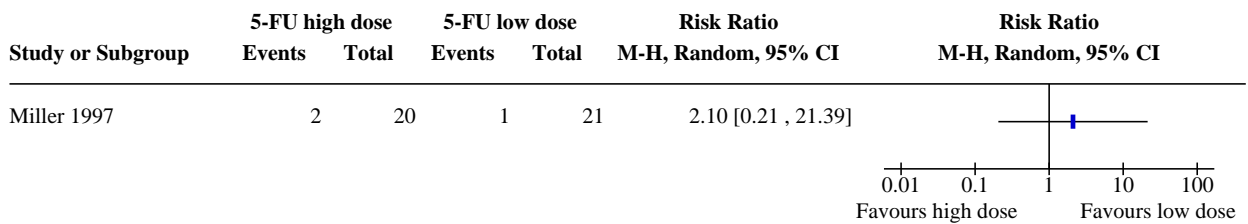
Study or Subgroup	5-FU high dose		5-FU low dose		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Miller 1997	2	20	1	21	2.10 [0.21 , 21.39]	

0.01   0.1   1   10   100
Favours high dose   Favours low dose

Comparison 31. 5-FU/epinephrine gel(1.0 mL twice a week for 3 weeks vs 0.5 mL twice a week for 3 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 31.1. Comparison 31: 5-FU/epinephrine gel(1.0 mL twice a week for 3 weeks vs 0.5 mL twice a week for 3 weeks), Outcome 1: Early treatment failure
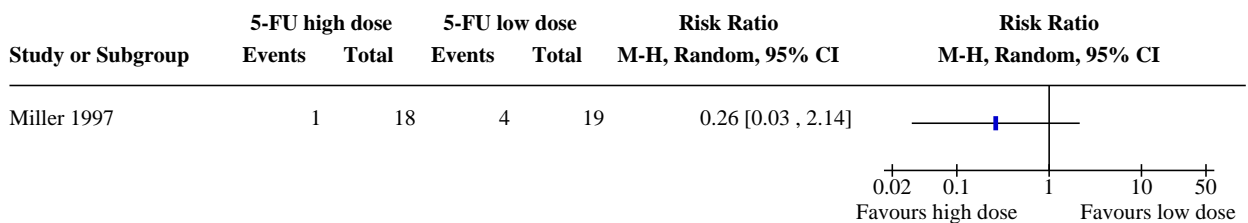
Study or Subgroup	5-FU high dose		5-FU low dose		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Miller 1997	1	18	4	19	0.26 [0.03 , 2.14]	

0.02   0.1   1   10   50
Favours high dose   Favours low dose

Comparison 32. 5-FU/epinephrine gel(0.5ml twice a week for 4 weeks vs 0.5 mL three times a week for 2 weeks.

Outcome or subgroup title	No. of studies	No. of par-ticipants	Statistical method	Effect size
32.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 32.1. Comparison 32: 5-FU/epinephrine gel(0.5ml twice a week for 4 weeks vs 0.5 mL three times a week for 2 weeks., Outcome 1: Early treatment failure

Study or Subgroup	0.5 , 2x/wk for 4 wk Events	Total	0.5, 3x/wk for 2 wk Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Miller 1997	2	21	0	17	4.09 [0.21 , 79.88]	

0.01 0.1 1 10 100
Favours 2x/wk for 4w   Favours 3xwk for 3 w

Comparison 33. Electrochemotherapy vs surgical excision

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
33.1 Recurrence at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
33.2 Recurrence at 5 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 33.1. Comparison 33: Electrochemotherapy vs surgical excision, Outcome 1: Recurrence at 3 years

Study or Subgroup	ECT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Clover 2016	4	38	1	36	3.79 [0.44 , 32.32]	

0.001 0.1 1 10 1000
Favours ECT   Favours SE

Analysis 33.2. Comparison 33: Electrochemotherapy vs surgical excision, Outcome 2: Recurrence at 5 years

Study or Subgroup	ECT Events	Total	SE Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Clover 2016	5	37	1	36	4.86 [0.60 , 39.63]	

0.002 0.1 1 10 500
Favours ECT   Favours SE

Comparison 34. Ingenol vs vehicle (day 1+2)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
34.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
34.1.1 Ingenol 0.05% vs vehicle	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
34.1.2 Ingenol 0.01% vs vehicle	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
34.1.3 Ingenol 0.0025% vs vehicle	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 34.1. Comparison 34: Ingenol vs vehicle (day 1+2), Outcome 1: Early treatment failure

Study or Subgroup	Ingenol Events	Total	Vehicle Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
34.1.1 Ingenol 0.05% vs vehicle						
Siller 2010	3	8	6	6	0.42 [0.18 , 0.97]	
34.1.2 Ingenol 0.01% vs vehicle						
Siller 2010	6	8	6	6	0.78 [0.49 , 1.23]	
34.1.3 Ingenol 0.0025% vs vehicle						
Siller 2010	8	8	6	6	1.00 [0.77 , 1.30]	

0.01 0.1 1 10 100
Favours ingenol   Favours vehicle
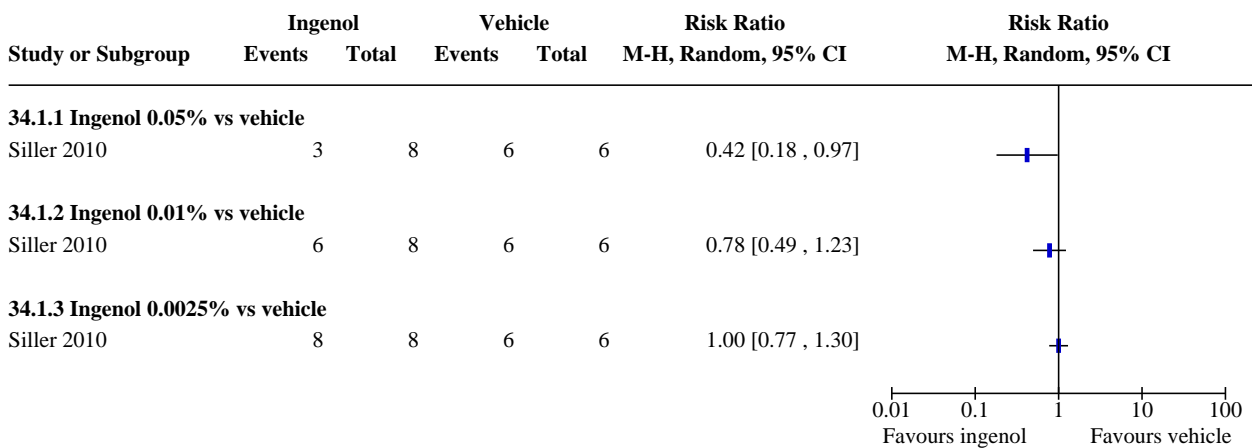
Comparison 35. Ingenol vs vehicle (day 1+8)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
35.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.1.1 Ingenol 0.05% vs vehicle	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.1.2 Ingenol 0.01% vs vehicle	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.1.3 Ingenol 0.0025% vs vehicle	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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Analysis 35.1. Comparison 35: Ingenol vs vehicle (day 1+8), Outcome 1: Early treatment failure
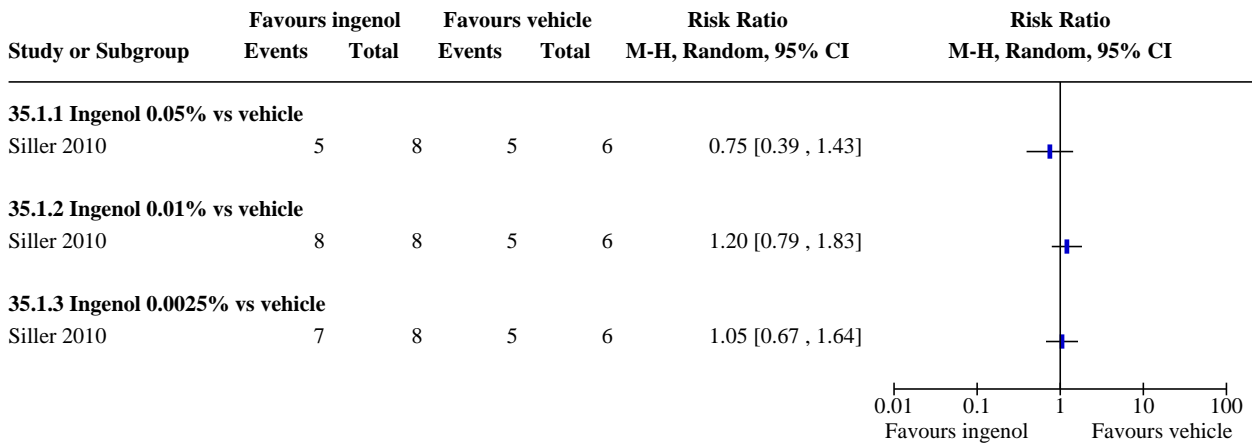
| Study or Subgroup | Favours ingenol | | Favours vehicle | | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
35.1.1 Ingenol 0.05% vs vehicle						
Siller 2010	5	8	5	6	0.75 [0.39 , 1.43]	
35.1.2 Ingenol 0.01% vs vehicle						
Siller 2010	8	8	5	6	1.20 [0.79 , 1.83]	
35.1.3 Ingenol 0.0025% vs vehicle						
Siller 2010	7	8	5	6	1.05 [0.67 , 1.64]	

0.01   0.1   1   10   100
Favours ingenol   Favours vehicle

Comparison 36. Ingenol under occlusion vs no occlusion

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
36.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
36.1.1 Full occlusion vs no occlusion	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
36.1.2 Semi-occlusion vs no occlusion	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 36.1. Comparison 36: Ingenol under occlusion vs no occlusion, Outcome 1: Early treatment failure
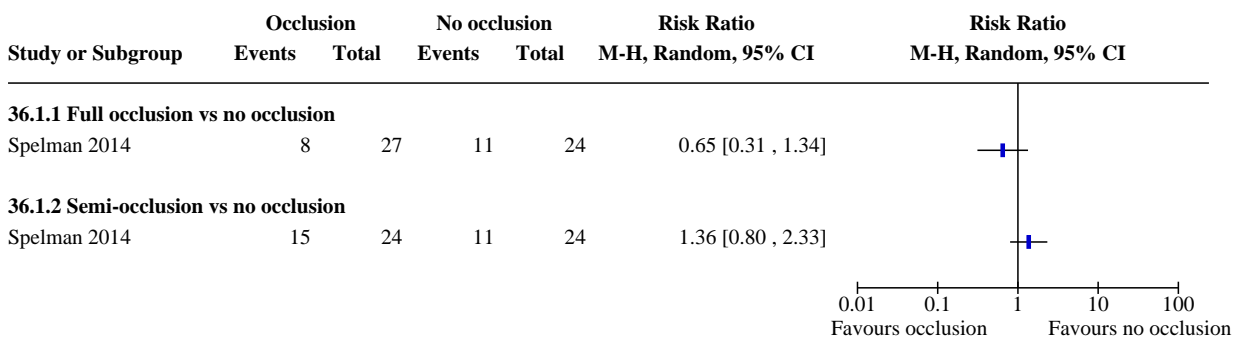
| Study or Subgroup | Occlusion | | No occlusion | | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
36.1.1 Full occlusion vs no occlusion						
Spelman 2014	8	27	11	24	0.65 [0.31 , 1.34]	
36.1.2 Semi-occlusion vs no occlusion						
Spelman 2014	15	24	11	24	1.36 [0.80 , 2.33]	

0.01   0.1   1   10   100
Favours occlusion   Favours no occlusion

Comparison 37. Solasodine glycoside cream vs vehicle

Outcome or subgroup title	No. of studies	No. of par-ticipants	Statistical method	Effect size
37.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 37.1. Comparison 37: Solasodine glycoside cream vs vehicle, Outcome 1: Early treatment failure

Study or Subgroup	BEC-5 cream Events	BEC-5 cream Total	Vehicle Events	Vehicle Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Punjabi 2008	21	62	24	32	0.45 [0.30 , 0.67]	

0.1 0.2 0.5 1 2 5 10
Favours BEC-5 cream   Favours vehicle
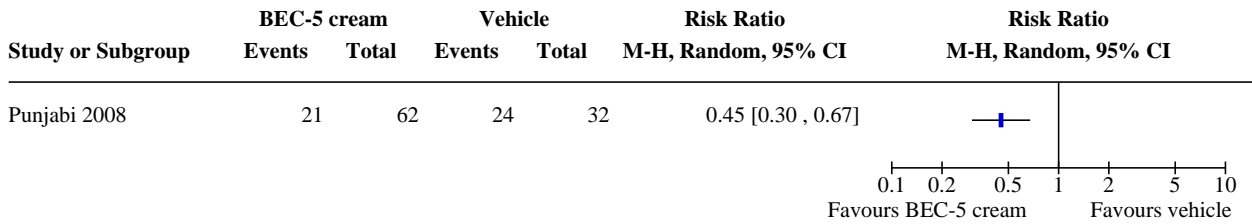
Comparison 38. Valproic acid gel + Tazarotene gel vs placebo + Tazarotene

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 38.1. Comparison 38: Valproic acid gel + Tazarotene gel vs placebo + Tazarotene, Outcome 1: Early treatment failure

Study or Subgroup	Baceca + Tazarotene Events	Baceca + Tazarotene Total	Placebo + Tazarotene Events	Placebo + Tazarotene Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2005-001474-27	8	25	13	25	0.62 [0.31 , 1.22]	

0.01 0.1 1 10 100
Favours Baceca + Tazarotene   Favours placebo + Tazarotene
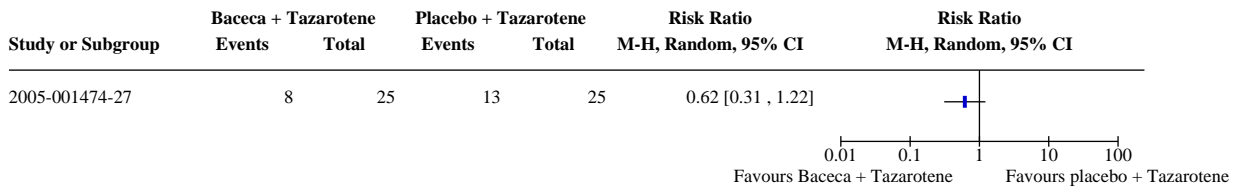
Comparison 39. Diclofenac gel vs calcitriol ointment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 39.1. Comparison 39: Diclofenac gel vs calcitriol ointment, Outcome 1: Early treatment failure

Study or Subgroup	Diclofenac gel Events	Diclofenac gel Total	Calcitriol oint Events	Calcitriol oint Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Brinkhuizen 2016	16	30	31	32	0.55 [0.39 , 0.77]	

0.5 0.7 1 1.5 2
Favours diclofenac   Favours calcitriol
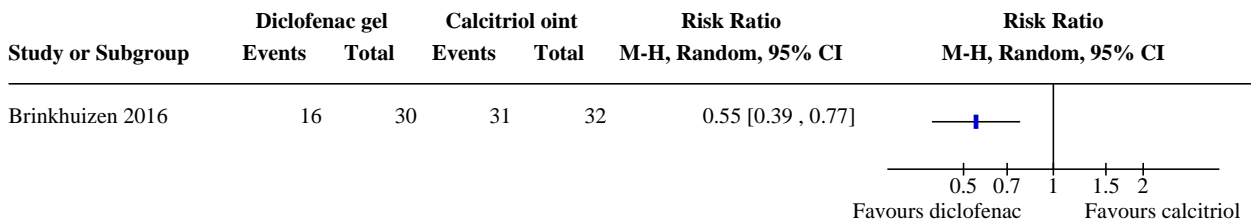
Comparison 40. Diclofenac gel vs diclofenac+calcitriol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 40.1. Comparison 40: Diclofenac gel vs diclofenac+calcitriol, Outcome 1: Early treatment failure

Study or Subgroup	Diclofenac Events	Total	Diclofenac+calcitriol Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Brinkhuizen 2016	16	30	19	31	0.87 [0.56 , 1.35]	

0.01   0.1   1   10   100
Favours diclofenac   Favours diclofen+calcitri
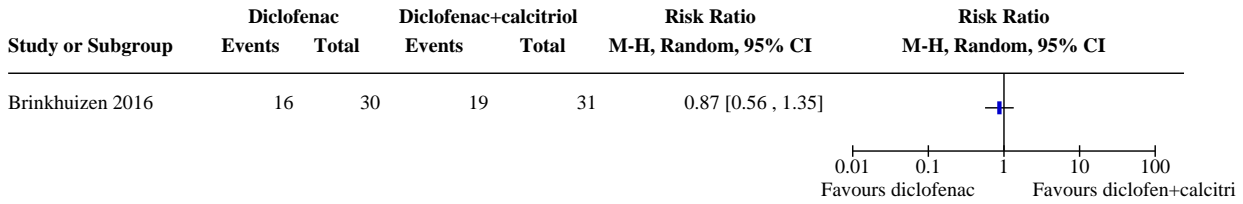
Comparison 41. Calcitriol ointment vs calcitriol+diclofenac

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 41.1. Comparison 41: Calcitriol ointment vs calcitriol+diclofenac, Outcome 1: Early treatment failure

Study or Subgroup	Calcitriol oint Events	Total	Diclofenac+calcitriol Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Brinkhuizen 2016	31	32	19	31	1.58 [1.19 , 2.11]	

0.5   0.7   1   1.5   2
Favours calcitriol   Favours diclofen+calcitri
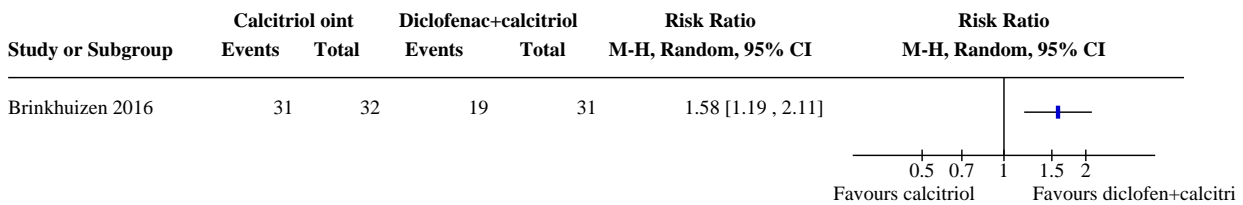
Comparison 42. PDL one session vs PDL two sessions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
42.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 42.1. Comparison 42: PDL one session vs PDL two sessions, Outcome 1: Early treatment failure

Study or Subgroup	Two sessions Events	Two sessions Total	One session Events	One session Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Abd El-Naby 2019	9	11	11	11	0.83 [0.60 , 1.13]	

0.5 0.7 1 1.5 2
Favours two sessions Favours one session
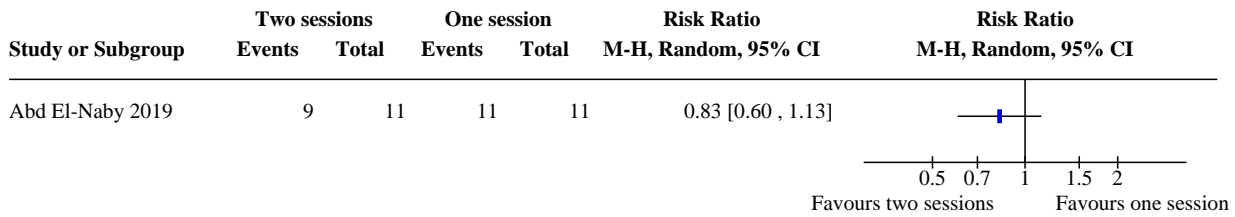
Comparison 43. PDL 7mm spot-size single pulses vs PDL 10mm spot-size stacked pulses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.1 Early treatment failure (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 43.1. Comparison 43: PDL 7mm spot-size single pulses vs PDL 10mm spot-size stacked pulses, Outcome 1: Early treatment failure (lesions)

Study or Subgroup	7mm single pulses Events	7mm single pulses Total	10mm stacked pulses Events	10mm stacked pulses Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Tran 2012	2	7	6	7	0.33 [0.10 , 1.12]	

0.01 0.1 1 10 100
Favours 10mm stacked Favours 7mm single
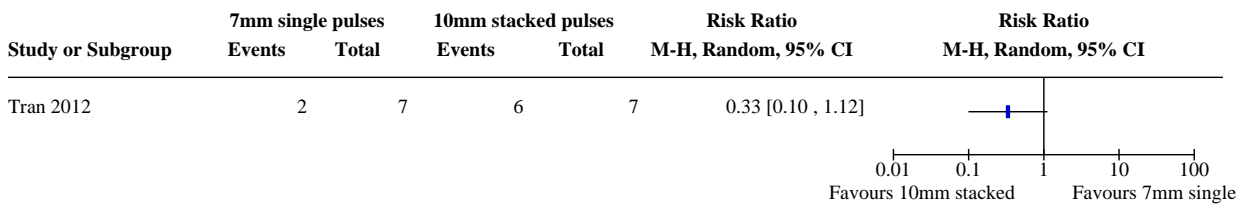
Comparison 44. PDL vs sham laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44.1 Early treatment failure (lesions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 44.1. Comparison 44: PDL vs sham laser, Outcome 1: Early treatment failure (lesions)

Study or Subgroup	PDL Events	PDL Total	sham Events	sham Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Karsai 2015	12	56	42	44	0.22 [0.14 , 0.37]	

0.1 0.2 0.5 1 2 5 10
Favours PDL Favours sham]
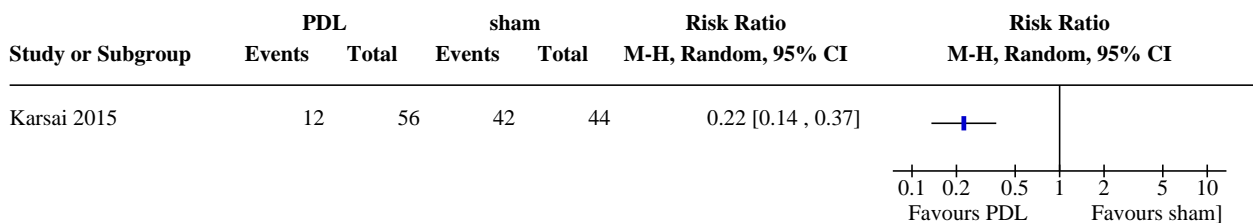
Comparison 45. PDL vs no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
45.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 45.1. Comparison 45: PDL vs no treatment, Outcome 1: Early treatment failure

	PDL		No treatment		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Eimpunth 2014	4	14	8	10	0.36 [0.15 , 0.86]	

0.01   0.1   1   10   100
Favours PDL   Favours no treatment

Comparison 46. Interferon alpha 2b vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
46.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 46.1. Comparison 46: Interferon alpha 2b vs placebo, Outcome 1: Early treatment failure

	Interferon alpha 2b		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Cornell 1990	17	120	30	42	0.20 [0.12 , 0.32]	

0.1   0.2   0.5   1   2   5   10
Favours Interferon   Favours Placebo

Comparison 47. Interferon beta vs placebo

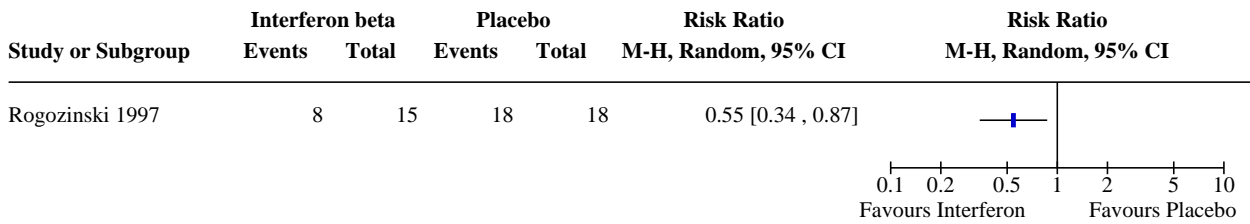| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 47.1. Comparison 47: Interferon beta vs placebo, Outcome 1: Early treatment failure

Study or Subgroup	Interferon beta		Placebo		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Rogozinski 1997	8	15	18	18	0.55 [0.34 , 0.87]	

Favours Interferon   Favours Placebo

Comparison 48. Interferon alpha 2a+2b vs interferon alpha 2a

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
48.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 48.1. Comparison 48: Interferon alpha 2a+2b vs interferon alpha 2a, Outcome 1: Early treatment failure

Study or Subgroup	IFN 2a+2b		Interferon alpha 2a		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Alpsoy 1996	4	15	5	15	0.80 [0.27 , 2.41]	

Favours IFN 2a+2b   Favours IFN 2a
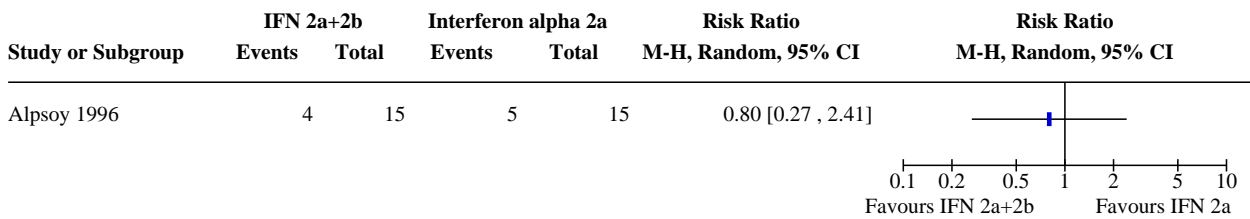
Comparison 49. Interferon alpha 2a+2b vs interferon alpha 2b

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 49.1. Comparison 49: Interferon alpha 2a+2b vs interferon alpha 2b, Outcome 1: Early treatment failure

Study or Subgroup	IFN alpha 2a+2b		IFN alpha 2b		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Alpsoy 1996	4	15	5	15	0.80 [0.27 , 2.41]	

Favours IFN 2a+2b   Favours IFN alpha2b

Comparison 50. Interferon alpha 2b vs interferon alpha 2a

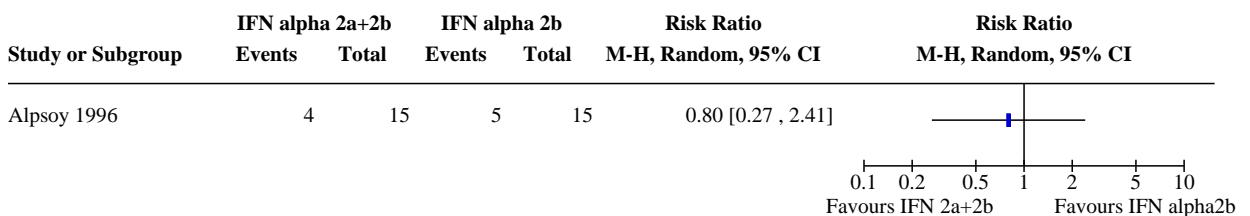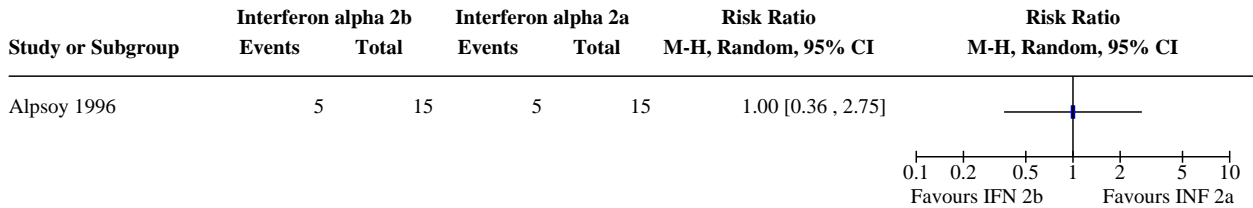| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
50.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 50.1. Comparison 50: Interferon alpha 2b vs interferon alpha 2a, Outcome 1: Early treatment failure

Study or Subgroup	Interferon alpha 2b Events	Total	Interferon alpha 2a Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Alpsoy 1996	5	15	5	15	1.00 [0.36 , 2.75]	

0.1 0.2 0.5 1 2 5 10
Favours IFN 2b   Favours INF 2a

Comparison 51. 3x a week vs single dose protamine zinc chelate IFN alpha 2b

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 51.1. Comparison 51: 3x a week vs single dose protamine zinc chelate IFN alpha 2b, Outcome 1: Early treatment failure

Study or Subgroup	Three times week Events	Total	Single dose Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Edwards 1990	6	30	16	33	0.41 [0.19 , 0.92]	

0.1 0.2 0.5 1 2 5 10
Favours 3 x week   Favours single dose
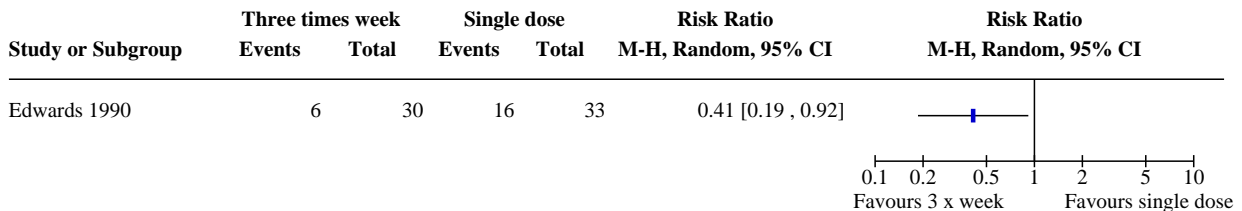
Comparison 52. Topical sinecatechin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
52.1 Early treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 52.1. Comparison 52: Topical sinecatechin vs placebo, Outcome 1: Early treatment failure

| Study or Subgroup | Sinecatechin ointment | | Placebo | | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Kessels 2017	20	21	19	21	1.05 [0.89 , 1.25]	

0.2　0.5　1　2　5
Favours sinecatechin　　Favours placebo

ADDITIONAL TABLES

Table 1. Pain table

Study (comparator)	Analgesia	Assessment	Severe pain	Other notable outcomes
Abd El-Naby 2019 (one PDL session / two PDL sessions)	Not stated.	Not stated.	Not stated.	Only 2 patients experienced pain and ulceration in the single-session group. There was no significant difference between the two groups.
Alpsoy 1996 (Interferon alpha 2a / 2b / 2a&b)	Not stated.	Not stated.	Not stated.	Transient local discomfort at injection site (requiring no treatment) experienced in all patients during injection.
Arits 2013 (MAL PDT / Imiquimod / 5-FU)	Not stated.	Weekly post-treatment patient-reported maximum score for pain and burning sensation on a visual analogue scale (0–10) for six weeks, and maximum score during the first and second photodynamic therapy sessions. Categorised as 0-3 = mild, 4-6 moderate, 7-10 = severe.	Highest overall percentage experienced pain during second PDT treatment (10%). Highest severe pain rating in imiquimod group found at week 6 (7%) and in Fluorouracil group at week 4 (4%).	Maximum duration of pain and burning sensation: Imiquimod group = 6 weeks, Fluorouracil group = 4 weeks, PDT group = 2 weeks.
Basset-Seguin 2008 (MAL-PDT / cryosurgery)	Not stated.	AEs at each follow-up visit up to three months post-treatment according to three-point severity scale (mild/moderate/severe).	1% in cryosurgery group and 5% in MAL-PDT group.	Local pain in 33% in cryosurgery group compared to 37% in MAL-PDT group.
Bath-Hextall 2014 (Imiquimod / SE)	Routine analgesia after surgery. 1 week break and restart at lower fre-	During treatment and at 16 weeks using six-point scale. Number of days of moderate to severe pain.	30% of patients in the imiquimod group and 22% patients in the SE	More patients reported pain during treatment in imiquimod group

Table 1. Pain table *(Continued)*

	quency of application if unable to tolerate Imiquimod.		group had moderate or severe pain at some time during treatment. 9% of patients treated with imiquimod had moderate or severe pain in the 16 weeks after treatment compared with 20% of patients who underwent SE.	
Brinkhuizen 2016 (diclofenac / diclofenac and calcitriol / calcitriol and no treatment)	Not stated.	Weekly patient-reported pain score on a VAS (0–10).	Not stated.	Pain at application site most likely to occur in the combination therapy group (40.6%) as compared to the diclofenac group (25.8%) and the calcitriol group (12.5%).
Choi 2016 (Er:YAG AFL-PDT / MAL-PDT)	Anaesthetic cream prior to procedure.	VAS scores (11-point scale) during illumination.	Not stated.	All patients experienced mild to moderate pain during PDT illumination. After illumination had ceased, the pain intensity immediately lessened, resolving over the next few hours. VAS scores (11-point scale) during illumination were similar with Er:YAG AFL-PDT (4.632 +/-1.257) and MAL-PDT (4.222 +/- 1.865; P = 0.437).
Ezughah 2008 (Imiquimod 8 weeks / 5 weeks)	Patients with intolerable reactions were allowed a rest period.	Weekly visual analogue scale scores (10-point scale).	One patient in 8-week arm failed to complete course due to severe pain.	Composite weekly median VAS scores for tolerability are low, suggesting little discomfort in both study arms; there was no overall difference between the two groups.
Foley 2009a/Foley 2009b (MAL-PDT / placebo)	Not stated.	Adverse effects noted at each follow-up visit and rated as mild/moderate/severe.	Not stated.	Burning more common than stinging or other skin pain. 29% in treatment arm compared to 12% in placebo group. Pain = 18% and 5%, respectively, stinging = 15% and 8%, respectively.
Garcia-Martin 2011 (Imiquimod / radiotherapy)	Tobramycin and dexamethasone drops supplied if pain reported.	Adverse effects noted at each follow-up visit.	Intense conjunctival irritation reported in 2 patents in the Imiquimod group.	50% of the patients in the radiotherapy group compared to 60% in the imiquimod group reported symptoms of discomfort with blinking during treatment. One patient complained of slight pain in the lower eyelid during radiotherapy treatment.
Geisse 2002 (Imiquimod BD / OD /	Rest period of up to	Patient-reported adverse effects at each visit.	Not stated.	Pain and tenderness at the target site were reported less frequently than itching.

Table 1. Pain table *(Continued)*

5xpw / 3xpw / vehicle)	14 days allowed.			
Geisse 2004 (Imiquimod 5xpw / 7xpw / vehicle)	Rest period allowed during which light dressing / emollient could be used.	Patient-reported adverse effects at each visit.	Patient-reported adverse effects at each visit.	Not stated.
Haak 2015 (AFXL-PDT / MAL-PDT)	Mepivacaine 10mg/mL injected prior to procedure.	Pain scores during LED illumination, scored from 0-10.	Not stated.	"AFXL pre-treatment did not influence median pain scores during LED illumination and pain intensities were similar at first and second illumination: first treatment AFXL-PDT median 3 (IQR 2–55) vs MAL-PDT 35 (25–5), second treatment AFXL-PDT 35 (3–65) vs MAL-PDT 3 (3–45), (P>0519). The presumed enhanced uptake of MAL did not affect the pain level during illumination. Pain scores were similar during AFXL-PDT and MAL-PDT and rated as mild to moderate."
Karsai 2015 (PDL / sham)	Not stated.	Pain intensity using a VAS (0 cm = 'no pain' to 10 cm = 'maximal pain') at every visit.	Not stated.	"The following median values were indicated on the pain intensity scale (ordinal scale 0–10) among patients at the four treatment sessions surveyed (minimum–maximum): Laser treatment: 2 (0–6), 3 (0–6), 3 (0–8) and 4 (0–9); Sham treatment: 0 (0–1), 0 (0–1), 0 (0–1) and 0 (0–2)."
Kessels 2017 (Sinecatechins / placebo)	Oral paracetamol for local skin reactions (if severe, treatment could be stopped for 1 week)	Subjective symptoms including pain were recorded in personal diary kept by patients once a week during treatment.	Not stated.	A burning sensation was reported in the treatment group in 5% of patients, at week four compared to 1% in the treatment group.
Kessels 2018 (MAL-PDT / two-fold fractionated ALA-PDT)	Not stated.	Pain and burning sensation were scored using a numerical rating scale (score 0–10), directly after both illuminations and 1 week later. The maximum pain scores for both illuminations were assessed.	Not stated.	"After the second illumination, mean pain scores were significantly higher in the two-fold ALA-PDT group compared with patients treated with MAL-PDT, with mean pain scores of 3.36 +- 2.57 and 2.48 +- 2.57 respectively (P=0.039). None of the patients discontinued treatment because of pain. 16.4% in the ALA-PDT group vs 5.8% in the MAL-PDT group reported the use of pain medication post-treatment."
Kuijpers 2006 (ALA-PDT / MAL-PDT)	Not stated.	Patient description of pain and rating on 10-point visual analogue scale.	None reported.	Majority of pain was reported as burning or stinging (59 and 41% respectively); also described as throbbing, lingering or tingling. Intensity and character was the same between groups. Generally pain was experienced during illumination and sporadically after, with the second cycle reported as the worst. No radiation reported.

Table 1.   Pain table *(Continued)*

Marks 2001 (Imiquimod BD / OD / BD for 3 days / OD for 2 days)	Not stated.	Three-point rating scale applied by assessor based on descriptive terms used by patient.	Not stated.	Pain more frequent in the BD group (100%) > OD group (24.2%) > BD for three days (13.3%) > OD for 2 days (3%).
Miller 1997 (Intrale-sional sus-tained-re-lease 6-fluo-rouracil / ep-inephrine in-jectable gel, variable fre-quencies)	Reduced dose if tenderness or pain at the injection site or ero-sion/ ulceration. Local anaes-thetic not permitted.	At each treatment visit, patients were asked to report injection site pain, including burning or stinging, and tender-ness.	All patients experienced transient moderate to severe sting-ing, burning or pain at the time of injec-tion lasting less than 15 to 20 minutes after drug ad-ministration.	Not stated.
Morton 2018 (BF 200 ALA-PDT / MAL-PDT)	Pain man-agement: physical cooling mea-sures, reduc-tion of light intensity at the ex-pense of longer expo-sure times, or "slight analgesia".	Local pain experienced during PDT was assessed for each PDT session (on a numerical rating pain scale). Ranking of the subjective sensations pain, burning and itching was done by the patient. Pain during PDT assessed with a nu-merical rating pain scale ranging from 0 (no pain at all) to 10 (worst possible pain).	Not stated.	Pain was one of the most frequently reported reac-tions, experienced by 100% patients undergoing MAL-PDT and 97.1% patients undergoing BF 200 ALA-PDT. Local pain experienced during each session showed little variation between both treatments and was most commonly experienced during the first two ses-sions.
Rhodes 2004 (MAL-PDT / SE)	None in MAL-PDT group, local anaes-thetic in SE group.	Local skin reactions dur-ing and after treatment at each clinic visit were documented, and rated as mild, moderate or se-vere.	One patient in MAL-PDT group discon-tinued treat-ment because of severe burning sen-sation which resolved with-out medical intervention.	14% in the MAL-PDT group experienced pain, com-pared to 6% in the SE group.
Shumack 2002a (Imiquimod, several regimes for 6 weeks)	Maximum of two 7-day periods of rest allowed if local skin	Adverse effects docu-mented at every study visit.	Not stated.	Pain was one of the three most frequent symptomatic adverse effects and two patients discontinued treat-ment due to pain.

Table 1. Pain table *(Continued)*

	reaction occurred.			
Shumack 2002b (Imiquimod, several regimes for 12 weeks)	Maximum of two 7-day periods of rest allowed if local skin reaction occurred.	Adverse effects documented at every study visit.	Two patients from the imiquimod twice daily 7-day dosing group reported severe application site reactions, one with pain at the target site and one with tenderness, stinging and pain at the target site. One patient from the once-daily, 7 day group reported severe tenderness at the target site. One patient discontinued due to pain, tenderness and drainage at the target site.	Not stated.
Siller 2010 (ingenol mebutate gel 0.0025 % / ingenol mebutate gel 0.01% / ingenol mebutate gel 0.05% / vehicle)	Treatment was withheld if there was a severe local reaction occurred after the first dose.	Adverse effects documented at every study visit.	Not stated.	Pain at the application site was most common in ingenol mebutate gel group 0.05% (n=2, treatment arm B), and 1 patient experienced pharyngolaryngeal pain in ingenol mebutate gel group 0.0025% (treatment arm A).
Soler 2000 (Laser light / broadband light)	Not stated.	Pain reported during treatment and in follow-up period (patient questionnaires).	Not stated.	83% of patients in the laser group and 76% in the broadband group reported some discomfort during and after illumination. Types of pain included stinging and burning sensation. There was no significant difference between the groups.
Sterry 2002a/Sterry 2002b (Imiquimod with / without occlusion)	Prescribed rest periods from treatment if local skin reactions or treatment	Adverse effects documented at every study visit.	Not stated.	One patient reported continuous stinging and pain at the application site; one reported irritation and another reported irritation and pruritus.

Table 1. Pain table *(Continued)*

		site adverse effects.		
Szeimies 2008 (MAL-PDT / SE)	Cooling of irradiation sites with fan-cooler during treatment.	Adverse effects documented at every study visit.	Not stated.	Post procedural pain was reported in 3 of the surgical participants and none of the MAL-PDT group. Pain was reported in 2 and 1 of the participants in the MAL-PDT and surgical groups respectively.
Wang 2001 (ALA-PDT / cryosurgery)	In the PDT group, low fluence rate to minimise thermal effects and lesions sprayed with water.	Pain recorded in first week after treatment using 115-mm visual analogue scale (VAS) for pain indication and analgesia diary.	Not stated.	Overall VAS scores low for both treatment modalities, and insignificantly higher in PDT group (43 +/- 31mm SD in PDT group, 32 +/- 27mm SD in cryosurgery group). Most pain reported during treatment.
2005-001474-27 (placebo gel + tazarotene gel / valproic acid gel + tazarotene gel)	Not stated.	Not stated.	Not stated.	8 patients in the placebo group experienced pain in comparison to 6 in the treatment group.

MAL: methyl aminolevulinate; **PDL:** pulsed dye laser; **PDT:** photodynamic therapy; **SE:** surgical excision; **VAS:** visual analogue scale; **xpw:** times per week.

Table 2. Adverse effects table

Study (comparator)	AEs associated with treatment leading to discontinuation of treatment / participation	Common AEs (number/onset/duration)	Other notable outcomes (number/onset/duration)	Comments
Abd El-Naby 2019 (one PDL session / two PDL sessions)	Not stated.	In the group who received two sessions of treatment, 4 patients experienced dyspigmentation (2 hyper- and 2 hypo-pigmentation).	Not stated.	
Arits 2013 (MAL-PDT / Imiquimod / 5-FU)	None reported.	Local skin redness reported as moderate or severe in all treatment groups.

Patients treated with imiquimod or 5-FU more often reported moderate to severe local swelling, erosion, crust formation and itching of the | Unexpected serious adverse effects in 1) Imiquimod group include wound infection (n = 1) and influenza-like symptoms (n = 8) and 2) in 5-FU group include two local wound infections, erysipelas of the lower extremity (n = 1), leg ulcer (n = 1). | Adverse reactions more common in last treatment weeks. |

Table 2. Adverse effects table (Continued)

		skin than patients treated with MAL-PDT.	The erysipelas and ulcer were treated with ambulant compression therapy and antibiotics. None of these patients needed hospitalisation.	
Avril 1997 (SE / radiotherapy)	Not stated.	Main adverse characteristics of surgical scars were "deformations" and "constrictions", affecting 25% and 5% of patients respectively by year 4. Radiodystrophy and necrosis affected 41% and 5% of the radiotherapy group at 4 years respectively.	Three ophthalmic complications were observed: 1 ectropion, 1 cataract - after surgery. One lacrimal duct stenosis after radiotherapy.	
Basset-Seguin 2008 (MAL-PDT / cryosurgery)	None reported.	Crusting: MAL PDT = 35%, cryosurgery = 47%. Erythema: MAL PDT = 30%, cryosurgery 21%.	Blisters: cryosurgery only = 21%. Suppuration: cryosurgery group only.	Most were transient, resolving in 5 days. More likely to experience severe AE in MAL-PDT group and moderate AE in cryosurgery group, although most were mild (73% and 80%, respectively).
Bath-Hextall 2014 (Imiquimod / SE)	12 (5%) participants in the imiquimod group withdrew because of adverse effects (five [42%] of these events were treatment related). Four (2%) of 229 participants withdrew because of adverse effects in the surgery group (all non-related events).	Itching: Imiquimod =211, SE = 129. Weeping: Imiquimod = 160, SE = 81.	Higher frequency adverse effects more common in imiquimod group include 1) Mild/moderate events: occurrence of new tumours, redness and swelling at tumour site, cold/influenza-like symptoms, headache, scab at tumour site, spots close to trial tumour, discomfort and bleeding, 2) Severe events: cold/flu, inflammatory reactions. Other high-frequency adverse effects, more common in SE group include 1) Mild/moderate events: Pain and swelling at tumour site and 2) Severe events: Heat attack / heart failure and pneumonia.	In the imiquimod group, 38 (15%) participants needed a dose reduction. No deaths or serious adverse effects were regarded as related to treatment.
Brinkhuizen 2016 (diclofenac / diclofenac and calcitriol / calcitriol and no treatment)	In 16 cases the severity of the application-site reactions led to discontinuation of the therapy and prescription (diclofenac = 6, calcitriol = 2, combination = 8)	Erythema: diclofenac = 21, calcitriol = 20, combined treatment = 22	Other commonly reported AEs in all groups include swelling, erosions, pruritus. Other less frequent AEs include crust formation, vesicles, scaling, and paraesthesia.	Adverse effects were mostly mild to moderate. No serious adverse effects were considered to be related to the study medication. Three patients had serious adverse effects requiring hospitalisation. No adverse effects were reported in the control group.

Table 2. Adverse effects table *(Continued)*

Choi 2016 (Er:YAG AFL MAL-PDT / MAL-PDT)	None reported.	Crusting: Er-YAG AFL-PDT = 17, MAL-PDT = 14	Erythema, burning sensation at application site, hyperpigmentation and itching more frequent in Er:YAG AFL-PDT group. Other reactions include scale, bullae, oozing and bleeding.	All patients in both groups experienced some AEs.
Eigentler 2007 (Imiquimod 8 weeks / 12 weeks)	None reported.	Erythema and oedema occurred in 92% of participants. Reporting of vesicles, erosions, ulcerations, desquamation and drainage during treatment was infrequent (12-53%). Post-treatment hypopigmentation was reported in 9% of participants. Most AEs were judged by physicians as moderate severity and by patients as moderate (17%) to severe (54%).	Authors reported "no differences between treatment arms in adverse events".	Data for AEs were not presented separately for treatment groups.
Eimpunth 2014 (Double-stacked PDL / control)	None reported.	Purpura immediately after laser treatment: 100% PDL group.	Late AEs in PDL group: blister (21.4%), dyspigmentation (21.4%) and hypertrophic scar (7.14%).	
Ezughah 2008 (Imiquimod 8 weeks / 5 weeks)	One patient in 5 week group withdrew from the study due to application site reactions.	Mild erythema (at week 1): 8-week group = 69%, 5 week group = 69%.	Other reactions include pain, swelling, weeping, broken skin and scabbing.	Erythema decreased in both groups at week 5. One patient on 8 week course developed severe erythema and soreness and was unable to apply 7th treatment. The severity of local site reactions was greatest in the first half of the treatment phase in the 8-week group.
Foley 2009a/Foley 2009b (MAL-PDT / placebo)	1 patient in MAL-PDT group received only one treatment due to local adverse event.	Burning: MAL-PDT = 19, placebo = 8. Erythema: MAL-PDT = 14, placebo = 4.	Other reactions include stinging of skin, crusting and bleeding (more frequent in treatment group). Severe events: cholangiocarcinoma, cholelithiasis, carotid stenosis, pulmonary oedema and acute MI, melanoma, femoral artery surgery.	One serious AE deemed not treatment-related. All were mild-to-moderate intensity and most lasted <1 day.
Garcia-Martin 2011 (Imiquimod / radiotherapy)	None reported.	Blink discomfort (during treatment): Imiquimod = 60%, radiotherapy = 50%.	Intense conjunctival irritation 13.3% imiquimod group, discomfort 8.3% radiotherapy group.	After treatment, radiotherapy group reported ectropion, dry eye and loss of eyelashes. imiquimod group reported no post-treatment AEs.

Table 2. Adverse effects table *(Continued)*

Geisse 2002 (Imiquimod BD / OD / 5xpw / 3xpw / vehicle)	Thirteen patients discontinued due to local skin reactions, six of which were severe and four of which were due to adverse effects (BD = 1, OD = 2, 5xpw = 1).	Itching: 5xpw = 62%, OD = 61%, 3xpw = 38%, BD = 30%, vehicle = 13%.	Other reactions include erythema, scabbing, erosion, excoriation/flaking, ulceration, vesicles, induration and oedema.	AEs occurred in all treatment groups, as did local skin reactions (all of those deemed related to study drug were in the OD group).
		Pain: BD = 30%, OD = 16%, 3xpw = 10%, 5xpw = 8%, vehicle = 0.		
		Tenderness: BD = 20%, OD = 16%, 5xpw = 8%, 3xpw = 7%, vehicle = 6%.	Severe erythema and scabbing occurred more commonly in the twice-daily treatment groups.	Six serious AEs, all unrelated to treatment, five of which resulted in hospitalisation.
	Four discontinued dosing (3 because of pain, 1 of which was severe, and one because of bleeding).			
Geisse 2004 (Imiquimod 5xpw / 7xpw / vehicle)	4% of the imiquimod 5xpw group and 2% of the 7xpw group discontinued treatment due to AE or local site reaction.	Erythema: most frequently observed and most intense LSR: 5xpw = 87, 7xpw = 92, vehicle = 48.	Other reactions include oedema, induration, vesicle, erosion, ulceration, scabbing and flaking.	Local site reactions reached maximum intensity at week 3, and most were mild.
		Itching: 5xpw = 16%, 7xpw = 26%.	The incidence of headache was statistically higher in the Imiquimod 5xpw group compared to the corresponding vehicle group (P = 0.027), although this difference was not seen in the 7xpw group.	Local site reactions were experienced in all groups but more likely in imiquimod groups, and these were statistically more likely to be severe (P = 0.001).
		Burning: 5xpw = 6%, 7xpw = 9%.		AEs occurred more frequently during treatment than after and were more likely to occur in the imiquimod 7xpw group than the 5xpw group or the vehicle groups (64% compared to 58% and 36% (combined vehicle groups).
				Local site reactions were experienced more commonly in 7xpw Imiquimod group compared to the 5xpw group (P = 0.002).
				AEs considered possibly or probably related to treatment include local site reactions and lymphadenopathy in the 7xpw Imiquimod group.
				All local site reactions were significantly more likely to be intense than 7xpw group than 5xpw group (P < 0.5).

Table 2. Adverse effects table *(Continued)*

				Overall the severe AEs experience by participants were in the 7xpw Imiquimod group. A decrease in WCC and neutrophils was noted in the treatment groups.
Haak 2015 (AFXL-PDT / MAL-PDT)	Not stated.	Immediate skin reactions (white micro-spots at the surrounding skin surface and minor pinpoint bleeding) seen in all AFXL group. Pigmentary changes and scarring similar in both groups.	Minor bleeding and bruising in debulked areas.	Scarring was the most frequently observed reaction at 3 months.
Karsai 2015 (PDL / sham)	Not stated.	Crusting (lasted an average of 10 days): intervention group only. Hyperpigmentation: intervention group only (21 of 56 cases, 37%). Hypopigmentation: intervention group only (did not manifest until after the third session; its rate increased with the number of sessions) seen in 52 of 56 cases (93%). Purpura in 100% of the laser group.	Not stated.	Purpura was considered a desired concomitant effect and was seen for an average of 6 days. Hyper- and hypopigmentation persisted until the end of the final follow-up at 6 months.
Kessels 2017 (Sinecatechins / placebo)	Not stated.	Erythema: sinecatechins 9-12%, placebo 2-6%. Oedema: sinecatechins 2-6%, placebo 0%. Erosions: sinecatechins 4-7%, placebo 1%. Crusts: sinecatechins 3-10%, placebo 2%. Itching: sinecatechins 10-13%, placebo 1-3%.	Other reactions include oedema, erosions, bullae and squamae.	Statistically significant difference for all common AEs.
Kessels 2018 (MAL-PDT / two-fold fractionated ALA-PDT)	Not stated.	Erythema: MAL-PDT = 65, ALA-PDT = 73. Wounds/erosions: MAL-PDT = 64, ALA-PDT = 72. Vesicles: MAL-PDT = 66, ALA-PDT = 72. All significantly higher after ALA-PDT compared with MAL-PDT.	Other reactions include swelling, crusts, scaling and pruritus. Four serious AEs unrelated to study treatment (three hospitalizations owing to transient ischaemic attack, chemotherapy for lung carcinoma and dizziness, and one patient died owing to cancer).	AE incidence higher during treatment period than after treatment.

Table 2.   Adverse effects table *(Continued)*

		No serious unexpected adverse reactions were reported in either group.		
Kuijpers 2007 (SE / curettage and cryosurgery)	Not stated.	Secondary wound infection requiring systemic antibiotics: curettage and cryosurgery group = 3 patients, SE group = 4 patients.		
Marks 2001 (Imiquimod BD / OD / BD for 3 days / OD for 2 days)	One patient discontinued because of a self-reported application site symptom of pruritus. No patient withdrew from the study because of signs of a local skin reaction assessed by the investigators.	Erythema: BD = 66.7%, OD = 27.3%, BDx3pw, = 13.3 %, OD x3pw = 9.1%. Itching: BD =33.3%, OD = 66.7%, BDx3pw, = 36.7%, OD x3pw = 45.5%. Weeping: decreased as the dosing frequency decreased BD = 66.7% OD = 12.1% BDx3pw, = 3.3%, OD x3pw = 0%.	Other reactions include scabbing, flaking, erosion, ulceration, oedema and induration. One patient died as the result of a coincidental cerebrovascular accident.	Local skin reactions occurred in all 4 dose regimens; dose-dependent application site reactions being reported most often. In the twice-every-day group, all the local skin reactions were assessed as severe by both the patient and the investigator in two thirds of the patients.
Miller 1997 (Intralesional sustained-release 6- fluorouracil / epinephrine injectable gel, variable frequencies)	Not stated.	Local tissue reactions were confined to the treatment site and included erythema, swelling, desquamation, erosions and eschar in most patients. Hyperpigmentation was observed in 83% of treated patients but typically cleared during the FU period. Ulcerations at the treatment site occurred in 47% of patients; only one patent had a residual scar.	Not stated.	There were no clinically significant serious or unexpected adverse effects or changes in any lab values or physical examination findings as judged by the investigator to be related to the administration of 5-FU/epi gel. The number of events per regimen ranged from 17 to 28.
Morton 2018 (BF 200 ALA-PDT / MAL-PDT)	One patient withdrew due to treatment-related AEs in the BF 200 ALA group and 2 in the MAL group. Two other patients withdrew due to related treatment emergent adverse effects	Most frequently reported reactions included pain, erythema, pruritus and oedema; most frequently at mild to moderate intensity. Frequencies were comparable between the groups and revealed no statistically significant differences.	There were ten serious AEs, none of which were related to the study medication.	

Table 2. Adverse effects table *(Continued)*

	(one in each group).			
Mosterd 2008 (ALA-PDT / SE)	None reported.	Not stated.	Secondary wound infection was observed once after ALA-PDT treatment. No serious complications such as wound dehiscence or necrosis were observed in either ALA-PDT or SE group.	
Punjabi 2008 (Solasodine glycoside cream / vehicle)	6 patients withdrew due to severity of local irritation in the treatment group.		There were four serious adverse effects in treatment group (3 unrelated, 1 unlikely to be related to treatment), and 2 in the vehicle group (one unrelated and one unlikely related to treatment).	No SAEs were considered likely or related to the treatment and there was no significant difference between the two groups.
Rhodes 2004 (MAL-PDT / SE)	One discontinuation due to adverse vent in MAL-PDT group.	Erythema: MAL-PDT = 7, SE = 1. Skin infection: MAL-PDT = 0, SE = 3.	Three patients had skin infections after SE (none in PDT group). Other local adverse effects included crusting and itching. There were three deaths, all unrelated to treatment, and one patient was diagnosed with breast cancer during treatment.	More patients with MAL-PDT than SE experienced adverse effects (52% compared to 29%).
Romagosa 2000 (5-FU in PC vehicle / 5-FU in petrolatum base)	Not stated.	Local irritation, erythema, ulceration, tenderness were common but well-tolerated.	Minimal itching in both treatment arms.	
Schulze 2005 (Imiquimod / vehicle)	Two in imiquimod group discontinued due to treatment-related AEs (one in vehicle group discontinued due to myeloma).	Erythema, oedema, induration, vesicles, erosion, ulceration, scaling/flaking and scabbing/crusting were all significantly more likely to occur in the treatment group (P < 0.001).	Imiquimod-treated patients also experienced statistically significant changes in skin quality assessment scores for hypo- or irregular pigmentation, and skin surface texture. Severe AE more common in treatment group but none due to treatment. No deaths. Central and peripheral nervous system disorders e.g. headache, gastrointestinal disorders and respiratory system disorders were also reported.	Local skin reactions were more intense in the imiquimod group (statistically significant). Local skin reactions increased at week 2 and plateaued until week 6.
Shumack 2002a (imiquimod, several regimes for 6 weeks)	One patient discontinued due to treatment related side effects (OD 7 day dosing group), one discon-	Erythema and scabbing commonly reported.	Influenza-like symptoms, probably related to drug noted in 10 patients. Fatigue in the OD 7 day group.	AEs occurred in all dosing groups (42% possibly / probably due to study treatment).

Table 2. Adverse effects table *(Continued)*

	tinued due to cerebral vascular accident.			
Shumack 2002b (imiquimod, several regimes for 12 weeks)	8 patients discontinued treatment owing to local skin reaction (2 in OD 5 day group, 4 in OD 7 day group, 2 in BD 7 day group). 2 discontinued due to AEs (1 = pain and drainage at target site and 1 = spider bite adjacent to target site).	Erythema and scabbing commonly reported.	Two patients in the BD 7 day group and one in the OD 7 day group reported severe local skin reactions. Influenza-like symptoms, probably related to drug, were noted in 5 patients.	Local skin reactions occurred in all study groups, and were the most commonly reported AE (most mild/moderate intensity).
Siller 2010 (ingenol mebutate gel 0.0025 % / ingenol mebutate gel 0.01% / ingenol mebutate gel 0.05% / vehicle)	Two discontinued due to AE (one in 0.01% group and one in 0.05% group)	The most common reactions were erythema and flaking/scaling/dryness, which occurred in a minimum of 75 and 50% respectively, of all patients in all groups (including vehicle group).	Hyper- and hypopigmentation, erosion/ulceration, oedema, scabbing/crusting, vesicles all more common in ingenol mebutate gel 0.05% group. Most were mild to moderate reactions, although 2 were severe (ingenol mebutate gel 0.01 and 0.05% respectively). Other skin reactions include itch, weeping/exudate, scarring. Other adverse effects include liver function derangement, diarrhoea, erythema, flaking, headache, oedema, pustules at application site, pustular rash, scabbing and telangiectasia.	No serious AE. Severe AE included mild/mod erythema extending beyond treatment site and headache. 10 severe local skin reactions seen in Arm A in ingenol mebutate gel 0.01% / ingenol mebutate gel 0.05% groups.
Smeets 2004 (MMS / SE)	Not stated.	AEs in SE group include wound infection, necrosis of grafts or flaps or post-operative bleeding.	33 patients died due to conditions not related to the treatment.	12% complications in MMS group and 14% in SE group (P = 0.981).
Soler 2000 (laser light / broadband light)	Not stated.	During the 1st week after treatment, 68% patients in the laser group and 74% of those in the broadband group also reported some degree of discomfort (stinging, itching, pain, suppuration headache, sensation of warmth or blushing).	Not stated.	No serious AEs reported in the 6-month follow-up period. There was no statistically significant difference between the groups.
Spelman 2014 (Ingenol mebutate	81.5% tolerated only one treatment in full-ODr group,	Not stated.	Local skin reactions in 11.3 full ODr group, 7,5 in semi-ODr group and 8.9 in no-ODr group.	The majority of AEs were not considered treatment related. The percentage of AEs was similar across all treat-

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Table 2. Adverse effects table *(Continued)*

under different occlusion types: full ODr, Semi-ODr or no-ODr)	compared to 20.8% in semi-ODr group and 4.2% in non-ODr group.		ment groups, the most common being application site pain. The majority of treatment-related AEs were in the ALU group, and in this group the majority only tolerated one treatment due to the severity of the local skin reaction.
Sterry 2002a, sBCC study (Imiquimod with / without occlusion, both 2 or 3 days per week)	Two patients discontinued from the study, one due to an adverse event (neurological dysregulation; not treatment-related) and one due to a local skin reaction. One patient in without-occlusion group required interrupted dosing and two required rest periods (3xpw with occlusion and 2xpw without occlusion).	Itching, burning and hypopigmentation most frequently reported AEs.	Two severe application site reactions were considered due to the medication (in 2xpw without occlusion group and in 3xpw with occlusion group). Fever and influenza-like symptoms were infrequently reported. Four patients experienced serious adverse effects unrelated to the medication.	AEs occurred in all treatment groups with 59% reporting at least one. 32% reported application site reactions, which occurred more often in groups treated three times per week.
Sterry 2002b, nBCC study (Imiquimod with / without occlusion, both 2 or 3 days per week)	Two discontinued due to local skin reactions (severe erythema, oedema and crust) and three discontinued due to application site reactions. Rest periods were taken by three patients.	Bleeding, itching and irritation most frequently reported AEs. Erythema was the most frequently reported local skin reaction and was most common in the 3xpw group.	Five experienced severe application site reactions considered probably related to the study drug. In groups receiving 3xpw treatment, severe local skin reactions were most common. Four experienced severe AEs unrelated to study drug.	70% reported adverse effects. 42% reported application site reactions; local skin reactions occurred in all treatment groups, most frequently in the 3xpw occlusion group.
Szeimies 2008 (MAL-PDT / SE)	2 patients in MAL-PDT group and one in SE group (none treatment related).	Photosensitivity reactions: MAL-PDT = 37%, SE = 0%. Wound infection: MAL-PDT = 0%, SE = 5.2%.	Other reported AEs included erythema, post-procedural pain, milia and wound dehiscence. 21 serious AEs were reported; none were considered related and any permanent discontinuations were unrelated to treatment.	Treatment-related AEs were higher in MAL-PDT group than in SE group (37% versus 14.6%). All AEs were mild to moderate severity except one severe wound infection in SE group.
Tran 2012 (PDL 7mm spot sin-	Not stated.	Both treatment group participants developed eschars at 2 weeks, followed by mild	Not stated.	

Table 2. Adverse effects table *(Continued)*

gle puls-es / PDL 10mm stacked pulses)		erythema at 1 month and hy-popigmentation at 5 months.		
Kuijpers 2007 (cryosurgery / SE)	Not stated.	Infections: SE = 2, cryosurgery = 3. In the cryosurgery group, 90% complained about moderate to severe swelling of the treatment area, followed by leaking from the defect.	One death (unrelated to study tumour).	
Wang 2001 (ALA-PDT / cryosurgery)	Not stated.	Not stated.	There were two patient deaths, and both were unrelated to the BCC or the treatment. One patient reported pain radiating from treatment site (PDT group) and one developed bacterial infection cryosurgery group).	
2005-001474-17 (placebo gel + Tazarotene gel / Baceca® + Tazarotene gel)	Not stated.	Erythema (17/25 and 20/25 in the two treatment groups).	Itch (18 versus 15 patients), ulceration (11 versus 16 patients) and local pain (8 versus 6 patients).	No significant differences between the two groups. Extension phase outcomes not reported.

MAL: methyl aminolevulinate; **PDL:** pulsed dye laser; **PDT:** photodynamic therapy; **SE:** surgical excision; **xpw:** times per week.

Table 3. Curettage and cryosurgery compared to surgical excision for basal cell carcinoma of the skin

Curettage & cryosurgery compared to surgical excision for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from a single-centre in The Netherlands
Intervention: curettage & cryosurgery
Comparison: surgical excision

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgical excision	**Risk with Curettage & cryosurgery**				
Recurrence at 3 years	Study population		RR 3.36 (0.73 to 15.40)	100 (1 RCT)	⊕⊕⊝⊝ LOW [1]	-
	41 per 1000	137 per 1000 (30 to 629)				
Recurrence at 5 years	Study population		RR 2.78 (0.93 to 8.34)	85 (1 RCT)	⊕⊕⊕⊝ MODERATE [2]	-
	85 per 1000	237 per 1000				

Table 3.   Curettage and cryosurgery compared to surgical excision for basal cell carcinoma of the skin *(Continued)*

		(79 to 710)				
Cosmetic outcome (good/excellent)	Study population		RR 0.88 (0.78 to 0.98)	96 (1 RCT)	⊕⊕⊝⊝ LOW [3]	Participant-rated at 1 year on a 3-point scale.[4]
	1000 per 1000	880 per 1000 (780 to 980)				
Cosmetic outcome (good/excellent)	Study population		RR 0.28 (0.16 to 0.47)	96 (1 RCT)	⊕⊕⊝⊝ LOW [3]	Observer-rated at 1 year on a 3-point scale.[4]
	833 per 1000	233 per 1000 (133 to 392)				
Early treatment failure	No study addressed this outcome		not estimable	-	-	-
Pain	No study addressed this outcome		not estimable	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for very serious imprecision as very wide 95% CI indicating the possibility of important benefit or harm.
[2] Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI and downgraded one level for serious risk of bias as unable to truly blind due to the nature of interventions.
[3] Downgraded one level for serious imprecision as only a single study with a small sample size.
[4] 3-point scale: bad, fair, good.

Table 4.   ALA-PDT compared to surgical excision for basal cell carcinoma of the skin

ALA-PDT compared to surgical excision for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from a single-centre in the Netherlands
Intervention: ALA-PDT
Comparison: surgical excision

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgical excision	Risk with ALA-PDT				
Recurrence at 3 years	Study population		RR 10.87 (2.63 to 44.95)	173 (1 RCT)	⊕⊕⊕⊝ MODERATE [1]	-
	23 per 1000	247 per 1000 (60 to 1000)				

Table 4. ALA-PDT compared to surgical excision for basal cell carcinoma of the skin *(Continued)*

Recurrence at 5 years	Study population		RR 11.91 (2.90 to 48.95)	173 (1 RCT)	⊕⊕⊕⊝ MODERATE [1]	-
	23 per 1000	271 per 1000 (66 to 1000)				
Cosmetic outcome	No study addressed this outcome.		not estimable	-	-	-
Pain	No study addressed this outcome.		not estimable	-	-	-
Early treatment failure	Study population		RR 3.18 (0.66 to 15.32)	171 (1 RCT)	⊕⊕⊝⊝ LOW [2]	-
	23 per 1000	72 per 1000 (15 to 348)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI.
[2] Downgraded two levels for very serious imprecision as very wide 95% CI indicating the possibility of important benefit or harm.

Table 5. MAL-PDT compared to cryosurgery for basal cell carcinoma of the skin

PDT compared to cryosurgery for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from France, UK, Sweden, Italy, Belgium and Austria
Intervention: MAL-PDT
Comparison: cryosurgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cryosurgery	**Risk with MAL-PDT**				
Recurrence at 3 years	Study population		RR 1.14 (0.65 to 1.98)	193 (lesions)[4] (1 RCT)	⊕⊕⊝⊝ LOW [1]	-
	194 per 1000	221 per 1000 (126 to 383)				
Recurrence at 5 years	Study population		RR 1.08 (0.62 to 1.86)	193 (lesions)[4] (1 RCT)	⊕⊕⊝⊝ LOW [1]	-
	220 per 1000	205 per 1000 (119 to 352)				

Table 5. MAL-PDT compared to cryosurgery for basal cell carcinoma of the skin *(Continued)*

Cosmetic outcome (good/ excellent)	Study population		RR 1.23 (1.07 to 1.41)	99 (1 RCT)	⊕⊕⊕⊖ MODER- ATE [2]	Participant-rated at 1 year on a 4- point scale.[2]
	813 per 1000	999 per 1000 (869 to 1000)				
Cosmetic outcome (good/ excellent)	Study population		RR 1.46 (1.14 to 1.88)	99 (1 RCT)	⊕⊕⊕⊖ MODER- ATE [2]	Observer-rated at 1 year on a 4- point scale.[2]
	604 per 1000	882 per 1000 (689 to 1000)				
Early treatment failure	Study population		RR 0.57 (0.14 to 2.33)	201 (lesions)[4] (1 RCT)	⊕⊕⊖⊖ LOW [1]	-
	51 per 1000	29 per 1000 (7 to 119)				
Pain	Study population		RR 1.12 (0.68 to 1.84)	118 (1 RCT)	⊕⊕⊖⊖ LOW [1]	Frequency reported as AE during the follow-up period.
	328 per 1000	367 per 1000 (223 to 603)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: adverse event; **CI:** Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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[1] Downgraded two levels for very serious imprecision as very wide 95% CI indicating the possibility of important benefit or harm.
[2] Downgraded one level for serious risk of bias as unable to truly blind due to the nature of interventions.
[3] 4-point scale: poor (extensive occurrence of scarring, atrophy, or induration), fair (slight to moderate occurrence of scarring, atrophy or induration), good (no scarring, atrophy or induration and moderate redness or increase in pigmentation compared with adjacent skin), excellent (no scarring, atrophy, or induration and slight or no redness or change in pigmentation compared with adjacent skin).
[4] Includes participants with multiple lesions which means differences between groups could be over-estimated.

Table 6. 5-FU cream compared to MAL-PDT for basal cell carcinoma of the skin

5-FU cream compared to MAL-PDT for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from seven hospitals in the Netherlands
Intervention: 5-FU cream
Comparison: MAL-PDT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PDT	Risk with 5-FU cream				

Table 6. 5-FU cream compared to MAL-PDT for basal cell carcinoma of the skin *(Continued)*

Recurrence at 3 years	Study population		RR 0.65 (0.49 to 0.86)	272 (1 RCT)	⊕⊕⊕⊖ MODER-ATE [1]	-
	524 per 1000	340 per 1000 (257 to 450)				
Recurrence at 5 years	Study population		RR 0.67 (0.53 to 0.84)	226 (1 RCT)	⊕⊕⊕⊖ MODER-ATE [1]	-
	686 per 1000	460 per 1000 (364 to 576)				
Cosmetic outcome (excellent/good)	Study population		RR 0.92 (0.78 to 1.09)	379 (1 RCT)	⊕⊕⊕⊖ MODER-ATE [1]	Blinded observer-rated at 1 year on 4-point scale.[3]
	624 per 1000	574 per 1000 (486 to 680)				
Pain (moderate/severe)	Study population		RR 0.41 (0.26 to 0.63)	374 (1 RCT)	⊕⊕⊕⊖ MODER-ATE [1]	During treatment: comparing the week of treatment with highest frequency of reported moderate/severe pain (treatment cycle 2 for PDT, week 4 for 5-FU cream).
	305 per 1000	125 per 1000 (79 to 192)				
Early treatment failure	Study population		RR 0.77 (0.47 to 1.26)	394 (1 RCT)	⊕⊕⊖⊖ LOW [2]	-
	158 per 1000	122 per 1000 (74 to 199)				

*The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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[1] Downgraded one level for serious imprecision as only a single study with a small sample size.
[2] Downgraded two levels for very serious imprecision as very wide 95% CI indicating the possibility of important benefit or harm.
[3] 4-point scale: poor, fair, good, excellent.

Table 7. Imiquimod cream compared to 5-FU cream for basal cell carcinoma of the skin

Imiquimod cream compared to 5-FU cream for low-risk BCC

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from seven hospitals in the Netherlands
Intervention: imiquimod cream
Comparison: 5-FU cream

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Table 7.   Imiquimod cream compared to 5-FU cream for basal cell carcinoma of the skin *(Continued)*

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 5-FU cream	Risk with Imiquimod cream				
Recurrence at 3 years	Study population		RR 0.68 (0.47 to 0.99)	291 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	-
	342 per 1000	233 per 1000 (161 to 339)				
Recurrence at 5 years	Study population		RR 0.62 (0.44 to 0.87)	250 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	-
	460 per 1000	285 per 1000 (202 to 400)				
Cosmetic outcome (excellent/good)	Study population		RR 1.07 (0.90 to 1.26)	377 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	Observer-rated at 1 year on 4-point scale.[4]
	575 per 1000	615 per 1000 (518 to 725)				
Pain (moderate/severe)	Study population		RR 1.46 (0.89 to 2.38)	365 (1 RCT)	⊕⊕⊕⊖ MODERATE[2]	During treatment: comparing the week of treatment with highest frequency of reported moderate/severe pain (week 6 for imiquimod, week 4 for 5-FU cream).
	125 per 1000	183 per 1000 (111 to 298)				
Early treatment failure	Study population		RR 0.83 (0.47 to 1.46)	387 (1 RCT)	⊕⊕⊖⊖ LOW [3]	-
	121 per 1000	101 per 1000 (57 to 177)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio.

__GRADE Working Group grades of evidence__
__High certainty:__ we are very confident that the true effect lies close to that of the estimate of the effect.
__Moderate certainty:__ we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
__Low certainty:__ our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
__Very low certainty:__ we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for serious imprecision as only a single study with a small sample size.
[2] Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI.
[3] Downgraded two levels for very serious imprecision as very wide 95% CI indicating the possibility of important benefit or harm.
[4] 4-point scale: poor, fair, good, excellent.

Table 8.   ALA-PDT compared to cryosurgery for basal cell carcinoma of the skin

PDT compared to cryosurgery for low-risk BCC

Table 8. ALA-PDT compared to cryosurgery for basal cell carcinoma of the skin *(Continued)*

Patient or population: adults with basal cell carcinoma of the skin
Setting: secondary care with outpatients from a single hospital in Sweden

Intervention: ALA-PDT
Comparison: cryosurgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cryosurgery	**Risk with ALA-PDT**				
Recurrence at 3 years	No study addressed this outcome.		not estimable	-	-	No study addressed this outcome.
Recurrence at 5 years	No study addressed this outcome.		not estimable	-	-	No study addressed this outcome.
Cosmetic outcome (good/excellent)	Study population		RR 1.72 (1.26 to 2.34)	79 (1 RCT)	⊕⊕⊕⊝ MODERATE 1	Observer-rated at 1 year on a 4-point scale.3
	541 per 1000	930 per 1000 (681 to 1000)				
Early treatment failure	No study addressed this outcome.		not estimable	-	-	-
Pain	Study population		not estimable	88 (1 RCT)	⊕⊕⊕⊝ MODERATE 2	Pain during treatment assessed by VAS (115mm, where 115mm corresponds to 'unbearable pain' and 0mm corresponds to 'no pain'.
	The mean pain was 32 mm	MD 11mm higher (1.12 lower to 23.12 higher)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; V**AS:** visual analogue scale.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

1 Downgraded one level for serious risk of bias as unable to truly blind due to the nature of interventions.
2 Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI.
3 4-point scale: blemished, acceptable, good, excellent.

A P P E N D I C E S

Appendix 1. Skin Group Specialised Register (CRS) search strategy

(basal cell* and (cancer* or epithelioma* or carcinoma* or naev* or nev* or tumor* or tumour* or neoplasm*)) or bcc or "gorlin syndrome" or ((rodent or Jacob*) and ulcer*) or basalioma or nmsc or (keratinocyte* and (cancer* or carcinoma*)) or nonmelanoma or "non melanoma" or "basal keratinocyte*"

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Carcinoma, Basal Cell] explode all trees
#2 MeSH descriptor: [Neoplasms, Basal Cell] explode all trees
#3 MeSH descriptor: [Basal Cell Nevus Syndrome] explode all trees
#4 (basal cell* next (cancer* or epithelioma* or carcinoma* or naev* or nev* or tumor* or tumour* or neoplasm*)):ti,ab,kw
#5 bcc:ti,ab,kw
#6 gorlin syndrome:ti,ab,kw
#7 (rodent next ulcer*):ti,ab,kw
#8 (jacob* next ulcer*):ti,ab,kw
#9 basalioma*:ti,ab,kw
#10 nmsc:ti,ab,kw
#11 (keratinocyte* and (cancer* or carcinoma*)):ti,ab,kw
#12 nonmelanoma skin cancer*:ti,ab,kw
#13 non melanoma skin cancer*:ti,ab,kw
#14 basal keratinocyte*:ti,ab,kw
#15 {or #1-#14}

Appendix 3. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Carcinoma, Basal Cell/
12. (basal cell$ and (cancer$ or epithelioma$ or carcinoma$ or naev$ or nev$ or tumor$ or tumour$ or neoplasm$)).mp.
13. exp Neoplasms, Basal Cell/
14. bcc.ti,ab.
15. gorlin syndrome.mp.
16. Basal Cell Nevus Syndrome/
17. rodent ulcer$.mp.
18. jacob$ ulcer$.mp.
19. basalioma$.mp.
20. nmsc.ti,ab.
21. (keratinocyte$ and (cancer$ or carcinoma$)).mp.
22. nonmelanoma skin cancer$.mp.
23. non melanoma skin cancer$.mp.
24. basal keratinocyte$.mp.
25. or/11-24
26. 10 and 25

[Lines 1-10: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format, from section 3.6.1 in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 4. Embase (Ovid) search strategy

1. exp Basal Cell Carcinoma/

2. (basal cell$ and (cancer$ or epithelioma$ or carcinoma$ or naev$ or nev$ or tumor$ or tumour$ or neoplasm$)).mp.
3. bcc.ti,ab.
4. gorlin syndrome.mp.
5. exp Basal Cell Nevus Syndrome/
6. rodent ulcer$.mp.
7. jacob$ ulcer$.mp.
8. basalioma$.mp.
9. (keratinocyte$ and (cancer$ or carcinoma$)).mp.
10. nonmelanoma skin cancer$.mp.
11. non melanoma skin cancer$.mp.
12. basal keratinocyte$.mp.
13. nmsc.ti,ab.
14. or/1-13
15. crossover procedure.sh.
16. double-blind procedure.sh.
17. single-blind procedure.sh.
18. (crossover$ or cross over$).tw.
19. placebo$.tw.
20. (doubl$ adj blind$).tw.
21. allocat$.tw.
22. trial.ti.
23. randomized controlled trial.sh.
24. random$.tw.
25. or/15-24
26. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
27. human/ or normal human/
28. 26 and 27
29. 26 not 28
30. 25 not 29
31. 14 and 30

[Lines 15-25: Based on terms suggested for identifying RCTs in Embase (section 3.6.2) in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 5. CINAHL (EBSCO) search strategy

S1 TI basal cell and (cancer* or epithelioma* or carcinoma* or naev* or nev* or tumor* or tumour* or neoplasm*)) or AB basal cell and (cancer* or epithelioma* or carcinoma* or naev* or nev* or tumor* or tumour* or neoplasm*))
S2 (MH "Carcinoma, Basal Cell") OR (MH "Neoplasms, Basal Cell+")
S3 TI ((non melanoma or nonmelanoma) and skin cancer*) or AB ((non melanoma or nonmelanoma) and skin cancer*)
S4 "gorlin syndrome"
S5 Jacob* nr1 ulcer*
S6 (rodent next ulcer*)
S7 TI bcc or AB bcc
S8 TX basalioma*
S9 TI nmsc or AB nmsc
S10 TX (keratinocyte* nr2 (cancer* or carcinoma*))
S11 TI basal keratinocyte* or AB basal keratinocyte*
S12 TX random*
S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S14 S12 AND S13

Appendix 6. LILACS search strategy

Searched on the advanced search page with ti and ab fields only, and using the Controlled clinical trials topic-specific query filter.
("basal cell" or "basal cells" or "rodent ulcer" or "rodent ulcers" or "jacobs ulcer" or "jacobs ulcers" or basalioma or nmsc or "non melanoma skin cancer" or "non melanoma skin cancers"):ti,ab

WHAT'S NEW

Date	Event	Description
9 September 2020	New citation required and conclusions have changed	This update included studies of many more interventions, with several new studies of non-surgical interventions compared to surgical interventions and other non-surgical interventions. It also includes long-term follow-up data from previously included studies. These new data have led to new and updated conclusions.
19 February 2020	New search has been performed	Since the 2007 review, we have identified 26 new randomised controlled trials. This updated review now has a total of 52 studies that randomised 6690 participants.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 2, 2003

Date	Event	Description
22 May 2008	Amended	Converted to new review format.
9 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JT was the contact person with the editorial base, JT co-ordinated contributions from the co-authors, and wrote the final draft of the review.
JT, FB-H, and SH screened papers against eligibility criteria.
JT, FB-H, and SH obtained data on ongoing and unpublished studies.
JT, FB-H, and SH appraised the quality of papers.
JT, FB-H, and SH extracted data for the review and sought additional information about papers.
JT, FB-H, and SH entered data into RevMan.
FB-H, JT, SH and JL-B analysed and interpreted data.
FB-H and JT worked on the methods sections.
JT and HW drafted the clinical sections of the background and responded to the clinical comments of the referees.
JL-B responded to the methodology and statistics comments of the referees.
JT is the guarantor of the update.

Disclaimer

DECLARATIONS OF INTEREST

Jason Thomson: none known
Sarah Hogan: none known
Jo Leonardi-Bee: none known
Hywel C Williams and Fiona J Bath-Hextall were involved in the SINS trial that compared topical imiquimod versus surgery and is a trial that is included in this review (Bath-Hextall 2014). The trial was funded by Cancer Research UK, a UK cancer charity. They were not involved in extracting data from the trial nor commenting on the evidence from this trial. Neither the charity, Fiona J Bath-Hextall or Hywel Williams have any links with industry.

SOURCES OF SUPPORT

Internal sources

- Cochrane Skin, UK

External sources

- The National Institute for Health Research (NIHR), UK

  The NIHR, UK, is the largest single funder of Cochrane Skin.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have amended the primary and secondary outcomes of this updated review to reflect the outcomes that are important for both clinicians and patients as well as to conform to the recommendations from Cochrane. Specifically, we have separated "recurrence at 3 to 5 years" to "recurrence at 3 years" and "recurrence at 5 years". The reason for this was because "3 to 5 years" is a wide time range and we did not feel it would be appropriate to compare three-year outcomes with five-year outcomes. This was not such a concern for the 2007 review as very few studies had long term follow-up data, but for this review we were aware that many more studies would have follow-up data up to five years.

We have also amended the cosmetic outcome. In the 2007 review this outcome was "Aesthetic appearance to participants/observer: atrophy, scarring, changes in pigmentation" and was categorised as an "adverse effect". We did not feel this was appropriate and have changed this to "cosmetic outcome (participant- and observer-rated)", and after discussion with HW, who had not seen the results, if multiple time points were reported, we included the time point closest to one year (but not less than one year) following treatment, as this is the minimum time taken for a scar to mature. Additionally, on Cochrane Skin's advice we have made the cosmetic outcome a primary outcome so as to include both a benefit and harm as primary outcomes.

We have renamed the secondary outcome "discomfort to participants in terms of pain during treatment and thereafter" to "pain during treatment and thereafter" to make it clearer and more specific. All adverse effects data were recorded but due to the heterogeneous nature of these data and the way they were presented, we did not perform analyses or present them in the 'Summary of findings' tables. Instead we collated all these into a separate adverse effects table.

In methods, a section has been added detailing the addition of GRADE assessments of the certainty of evidence as well as 'Summary of findings' tables and how they were produced.

Due to the large number of studies and to improve readability of the review, we excluded studies that did not measure any of our outcomes of interest in accordance with MECIR C40.

We decided to include studies that compared an active treatment against a no treatment arm. The reason we departed from the protocol on this was because we did not have a strong justification for excluding such studies and we were challenged on this by two of our peer-reviewers.

JT, SH and J-LB are new authors since the last review. JB and WB are not authors on this update.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [therapeutic use]; Carcinoma, Basal Cell [surgery] [*therapy]; Cryotherapy; Photochemotherapy; Radiotherapy; Randomized Controlled Trials as Topic; Skin Neoplasms [surgery] [*therapy]; Treatment Outcome

MeSH check words

Adult; Humans