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SYSTEMATIC REVIEW

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Interventions for basal cell carcinoma: abridged Cochrane systematic review and GRADE assessments

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Summary

Background Basal cell carcinoma (BCC) is the most common cancer affecting white-skinned individuals, and the worldwide incidence is increasing. Although rarely fatal, BCC is associated with significant morbidity and costs.

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

Methods We updated our searches of the following databases to November 2019: Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL and LILACS. Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation method. We used standard methodological procedures expected by Cochrane.

Results We included 52 randomized controlled trials with 6990 participants (median age 65 years; range 20–95). Mean study duration was 13 months (range 6 weeks–10 years). Ninety-two per cent (n = 48/52) of studies exclusively included histologically low-risk BCC (nodular and superficial subtypes). The certainty of evidence was predominantly low or moderate for the outcomes of interest. Overall, surgical interventions have the lowest recurrence rates, and there may be slightly fewer recurrences with Mohs micrographic surgery over surgical excision for primary, facial BCC (high-risk histological subtype or located in the 'H-zone' or both) (low-certainty evidence). Nonsurgical treatments, when used for low-risk BCC, are less effective than surgical treatments, but recurrence rates are acceptable and cosmetic outcomes are probably superior.

Conclusions Surgical interventions have lower recurrence rates and remain the gold standard for high-risk BCC. Of the nonsurgical treatments, topical imiquimod has the best evidence to support its efficacy for low-risk BCC. Priorities for future research include agreement on core outcome measures and studies with longer follow-up.

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Conflicts of interest
H.C.W. and F.J.B.-H. were co-investigators in the SINS trial that compared topical imiquimod vs. surgery, and is a trial that is included in this review. They were not involved in extracting data from the trial or commenting on the evidence from this trial.

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What is already known about this topic?

- Basal cell carcinoma (BCC) is the most common cancer to affect white-skinned individuals, and worldwide incidence is increasing.
- A 2007 Cochrane review concluded that there was very little good-quality research on treatments for BCC and that surgical interventions and radiotherapy had the lowest recurrence rates.

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What does this study add?

- The body of evidence has now doubled to 52 trials, but most deal with low-risk lesions.
- The quality of evidence remains generally low to moderate.
- Surgical interventions still have the lowest recurrence rates, and there may be slightly fewer recurrences with Mohs micrographic surgery over surgical excision for high-risk facial primary BCC.
- Nonsurgical treatments are less effective than surgery, but recurrence rates are acceptable for low-risk lesions and cosmetic outcomes are probably superior.

Basal cell carcinoma (BCC) is the most common skin cancer and the most common cancer found in white-skinned individuals.[1–3] BCCs are slow-growing, locally invasive, malignant (but not life-threatening), epidermal skin tumours.[4,5] BCCs affect the head and neck region around 70% of the time, and the trunk and extremities around 30% of the time.[6] A systematic review identified that the incidence of BCC is increasing in Europe by 5·5% annually.[3] Between 2013 and 2015 there was a mean annual percentage increase of 5% in BCC incidence across the UK.[6]

Clinicopathological features are used to differentiate BCCs into high- and low-risk subtypes, which has implications on management. High-risk BCCs include morphoeic, infiltrative and micronodular histological subtypes; the presence of perineural or perivascular invasion; size > 5 cm; a recurrent lesion; a centrofacial location, including periocular areas and the ears; and host immunosuppression.[2] Low-risk BCCs include superficial and nodular histological subtypes when they are located at a low-risk site (e.g. not centrofacial location).

Numerous interventions are available for treating BCC, with the primary aim of treatment being to remove or destroy the lesion completely, resulting in cure with minimal risk of recurrence. Tumour removal should also be balanced against the patient's requirement for a good/acceptable cosmetic result. The first-line treatment of BCC is often surgical excision (SE) with Mohs micrographic surgery (MMS) reserved for high-risk sites. Numerous alternatives are available and include surgery under frozen section margin control; radiotherapy; photodynamic therapy (PDT); curettage and cautery ('electrodesiccation'); cryosurgery ('cryotherapy'); laser; electrochemotherapy; immunomodulators; topical chemotherapy; intralesional chemotherapy; systemic chemotherapy; and targeted molecular therapy (hedgehog pathway inhibitors).

This article is a summary of a Cochrane review that evaluated the effects of interventions for BCC,[7] providing the best available evidence to healthcare providers and patients so that they can weigh up the risks and benefits of treatments, and to allow and promote shared decision-making.

Materials and methods

We followed the protocol from an earlier version of this review, which was published in 2003.[8] One important deviation from the original protocol is that we assessed recurrence rates at 3 and 5 years separately, whereas previously we considered all recurrences between 3 and 5 years. The reason for this change was to ensure that we could detect any important differences in recurrences at 3 and 5 years, given that several studies have reported on longer follow-up data.

Selection criteria

Inclusion criteria were randomized controlled trials (RCTs) of interventions for BCC in immunocompetent adults with histologically proven primary BCC. Studies that included participants with Gorlin (basal cell naevus) syndrome, organoid naevi or other genetic syndromes were excluded. Persistent or recurrent tumours were excluded. We aimed to identify all relevant RCTs, regardless of language or publication status.

Outcome measures

Primary outcome measures were recurrence at 3 years and 5 years (measured clinically), and cosmetic outcome (participant- and observer-rated using any validated method for assessing cosmetic outcome). We did not prespecify a timepoint for our cosmetic outcome, but aimed to include outcomes measured after at least 1 year (minimum time taken for a scar to mature). If multiple timepoints were reported, we reported the closest timepoint to 1 year (but not less than 1 year). Secondary outcomes measures were pain during treatment and thereafter, early treatment failure (within 6 months, measured histologically) and adverse effects.

Search strategy

We searched MEDLINE, Embase, the Cochrane Skin Specialised Register, CENTRAL, CINAHL and LILACS from inception until 19 November 2019. The trial registries ISRCTN, ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry, International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register were searched on 3 March 2019 using the term 'basal cell carcinoma'. We checked references from included studies to identify further trials. Details of the databases and search strategy are available in Table S1 and Appendices S1–S6 (see Supporting Information). Three

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authors (J.T., S.H., F.J.B.-H.) independently carried out study selection, and disagreements were resolved by discussion.

Data extraction and risk of bias assessment

Three authors (J.T., S.H., F.J.B.-H.) independently extracted the data, using a prederived data extraction form. Missing data were obtained from the trial authors where possible. Any disagreements in study selection or data extraction were resolved by discussion and/or by involving a fourth author (H.C.W.). The Cochrane risk-of-bias assessment framework was used to evaluate the internal validity of studies.[9] Two authors (J.T., S.H.) independently assessed the risk of bias in included studies. Any disagreements were resolved through discussion between the authors, including a third author (H.C.W.).

Data synthesis and statistical analysis

We expressed the results as a risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous outcomes, and difference in means with 95% CIs for continuous outcomes. For studies with a similar type of active intervention, we performed a meta-analysis, to calculate a weighted treatment effect across trials, using a random-effects (DerSimonian and Laird) model. Where it was not possible to perform a meta-analysis, we summarized 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.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess quality of the body of evidence separately for each outcome.[10]

Results

Description of included studies

A total of 52 RCTs (6690 participants) met our inclusion criteria, with 26 studies from the previous review and 26 new studies (Figure 1).[11–67] Table S2 (see Supporting Information) summarizes the characteristics of all included studies. The median age of participants was 65 years (range 20–95). There were more male than female participants (male-to-female ratio 1·48 : 1). Studies all recruited from secondary care clinics and the average study duration was 13 months (range 6 weeks–10 years). The number of participants randomized in each study ranged from 13 to 724 (median 89 participants). The majority of studies (n = 48/52) exclusively included BCC of low-risk histological subtypes [nodular (nBCC), superficial (sBCC)]. Only four studies included high-risk histological subtypes.[18,20,21,55] Overall, 22 studies were industry funded, with studies of imiquimod and PDT being over-represented in this group.

Studies evaluated 15 categories of surgical and nonsurgical interventions. The most common comparators were nonsurgical treatments, with 20 RCTs comparing a nonsurgical treatment to another nonsurgical treatment. Fourteen RCTs compared a nonsurgical treatment with placebo. Eighteen RCTs had a surgical treatment comparator, with 10 RCTs comparing a surgical treatment to a nonsurgical treatment, five RCTs comparing a surgical treatment to a surgical treatment and three RCTs comparing a surgical treatment to placebo.

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).

Risk of bias within studies

Figure 2 and Figure S1 (see Supporting Information) summarize the risk of bias per domain and per study, respectively. Only one study was identified as having a high risk of selection bias.[51] Only 37% of studies (n = 19) were assessed as being at low risk of bias for blinding of the outcome assessor. We rated 62% of studies (n = 32) as having an unclear risk of incomplete outcome data. Only 12% of studies (n = 6) were deemed at low risk of selective outcome reporting bias, and only 21% of studies (n = 11) prospectively registered their RCT.

Effects of interventions

We have presented our primary outcomes for the seven most important comparisons in this article. This was based on the study authors' experiences 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. Tables 1–7 summarize the results of all outcomes (apart from adverse effects) and the GRADE assessments for these seven comparisons. Table S3 (see Supporting Information) provides an explanation of the GRADE Working Group grades.

Mohs micrographic surgery vs. surgical excision

One study compared SE against MMS in 374 participants (408 lesions) with high-risk facial primary BCCs (high-risk histological subtype and/or located in the 'H-zone' of the face).[18,36] The study used 3-mm margins for both treatments to standardize the two modalities (smaller margins are usually used for MMS). Our analyses found that there may be slightly fewer recurrences with MMS vs. SE at 3 years [1·9% (n = 3/160) vs. 2·9% (n = 5/171); RR 0·64, 95% CI 0·16–2·64 (low-certainty evidence)] and at 5 years [3·2% (n = 4/125) vs. 5·2% (n = 7/134); RR 0·61, 95% CI 0·18–2·04 (low-certainty evidence)] (Table 1).

No significant differences in cosmetic outcomes between MMS and SE were reported; however, the data were not presented. The study reported that there was 'no difference in post-operative complications between SE and MMS'; however, raw data were not presented for this outcome to verify this. See Table 1.

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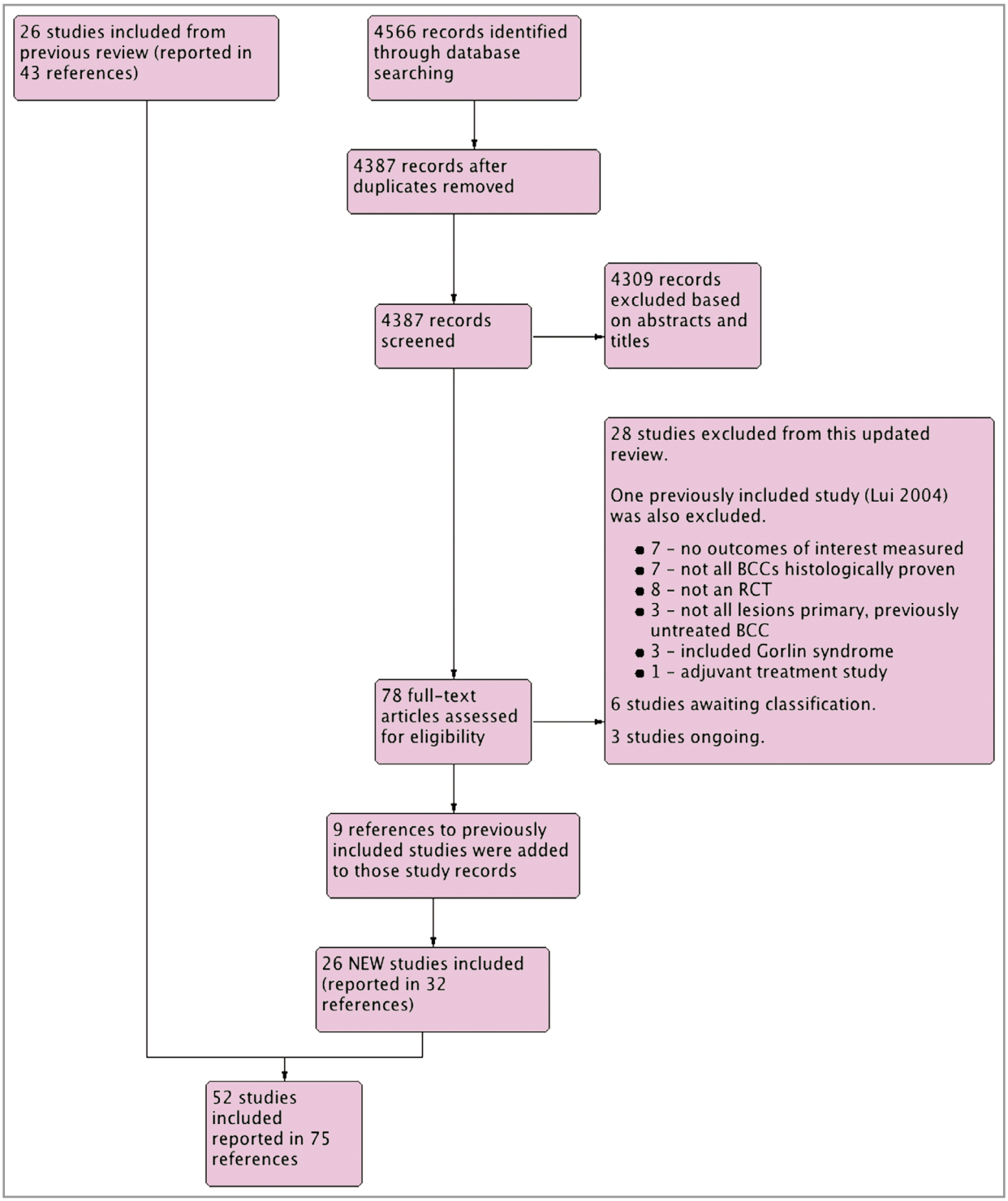

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram. BCC, basal cell carcinoma; RCT, randomized controlled trial.

Imiquimod vs. surgical excision

One study compared imiquimod with SE in 501 participants with nBCC or sBCC at low-risk sites in a noninferiority trial design with 5 years of follow-up.[41] Imiquimod probably results in more recurrences (16·4%, n = 35/213) than SE (1·6%, n = 3/188) at 3 years corresponding to a 10-fold increased risk of recurrence with imiquimod [RR 10·30, 95% CI 3·22–32·94 (moderate-certainty evidence)]. By 5 years, imiquimod may result in more recurrences (17·5%, n = 36/206) than SE (2·3%, n = 4/177) with a nearly eightfold increased risk of recurrence [RR

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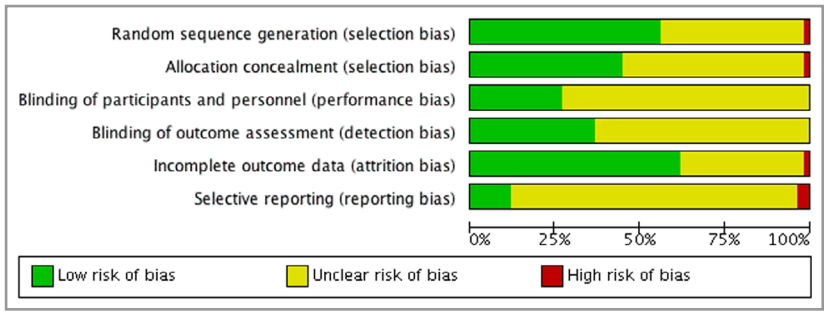

Figure 2 Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies.

Table 1 Mohs micrographic surgery (MMS) vs. surgical excision (SE) for high-risk basal cell carcinoma[a]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SE	Risk with MMS				
Recurrence at 3 years	Study population 29/1000	19/1000 (5–77)	RR 0·64 (0·16–2·64)	331 (1 RCT)	⊕⊕⊖⊖ LOW[b]	Study measured outcome at 30 months
Recurrence at 5 years	Study population 52/1000	32/1000 (9–107)	RR 0·61 (0·18–2·04)	259 (1 RCT)	⊕⊕⊖⊖ LOW[b]	–
Cosmetic outcome	Although a reported outcome, raw data were not available. The authors of the study state that, overall, cosmetic outcomes did not significantly differ between groups.[18,36] The cosmetic outcomes were judged by participants 18 months postoperatively, and photographs of a selected group of tumours (first 139 primary) were judged retrospectively by a panel of six individuals		NE	(1 RCT)	⊕⊕⊖⊖ LOW[c]	–
Pain	No study addressed this outcome		NE	–	–	–
Early treatment failure	No study addressed this outcome		NE	–	–	–

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NE, not estimable; RR, risk ratio; RCT, randomized controlled trial. [a]Patient or population: adults with high-risk BCC; setting: secondary care with outpatients from hospitals in the Netherlands; intervention: MMS; comparison: SE. [b]Downgraded two levels for very serious imprecision due to very wide 95% CI, indicating the possibility of important benefit or harm. [c]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.

7·73, 95% CI 2·81–21·30 (moderate-certainty evidence)] (Table 2).

When participant-rated, there may be little-to-no difference between imiquimod (91·9%, n = 147/160) and SE (92·2%, n = 153/166) on the rate of good/excellent cosmetic outcomes [RR 1·00, 95% CI 0·94–1·06 (low-certainty evidence)]. When rated by a dermatologist, imiquimod may improve the rate of good/excellent cosmetic outcomes [60·6% (n = 103/170) vs. SE 35·6% (n = 62/174), corresponding to a 70% increased rate for imiquimod (RR 1·70, 95% CI 1·35–2·15; low-certainty evidence)].

Radiotherapy vs. surgical excision

One study compared SE (with the option for frozen section margin control) with radiotherapy in 374 participants with BCCs < 4 cm diameter on the face (high- and low-risk histological subtypes).[21]

At 3 years radiotherapy may lead to increased risk of recurrence vs. SE, with recurrence rates of 5·2% (n = 9/173) and 0% (n = 0/174), respectively [RR 19·11, 95% CI 1·12–325·78 (low-certainty evidence)] (Table 3).

By 4 years, radiotherapy may result in a higher risk of recurrence than SE, with recurrence rates of 6·4% (n = 11/173) and 0·6% (n = 1/174), respectively [RR 11·06, 95% CI 1·44–84·77 (low-certainty evidence)].

Dyspigmentation and telangiectasia occurred in the majority of patients treated with radiotherapy, and by comparing the rate of participant-reported good cosmetic outcomes (3-point scale: bad, fair or good) at 4 years between the groups, radiotherapy probably worsens the rate of good cosmetic outcome, compared with SE [RR 0·76, 95% CI 0·63–0·91 (moderate-

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Table 2 Imiquimod vs. surgical excision (SE) for low-risk basal cell carcinoma (BCC)[a]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participant (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SE	Risk with imiquimod				
Recurrence at 3 years	Study population 16/1000	164/1000 (51–526)	RR 10·30 (3·22–32·94)	401 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Recurrence at 5 years	Study population 23/1000	175/1000 (64–481)	RR 7·73 (2·81–21·30)	383 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Cosmetic outcome (good/excellent)	Study population 922/1000	922/1000 (866–977)	RR 1·00 (0·94–1·06)	326 (1 RCT)	⊕⊕⊖⊖ LOW[c]	Participant-rated at 3 years on 6-point scale[d]
Cosmetic outcome (good/excellent)	Study population 356/1000	606/1000 (481–766)	RR 1·70 (1·35–2·15)	344 (1 RCT)	⊕⊕⊖⊖ LOW[c]	Observer-rated at 3 years on 6-point scale[d]
Pain (moderate/severe)	Study population 219/1000	298/1000 (215–412)	RR 1·36 (0·98–1·88)	443 (1 RCT)	⊕⊕⊖⊖ LOW[e]	Pain measured during treatment[f]
Pain (moderate/severe)	Study population 199/1000	94/1000 (58–153)	RR 0·47 (0·29–0·77)	439 (1 RCT)	⊕⊕⊖⊖ LOW[e]	Pain measured during follow-up[f]
Early treatment failure	No study addressed this outcome		NE	–	–	–

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NE, not estimable; RR, risk ratio; RCT, randomized controlled trial. [a]Patient or population: adults with low-risk BCC; setting: secondary care with outpatients from hospitals in the UK; intervention: 5% imiquimod cream; comparison: SE. [b]Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI. [c]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 blind truly owing to the nature of interventions (i.e. presence or absence of scar will unblind to treatment allocation). [d]Six-point scale: unable to see lesion; very poor; poor; fair; good; excellent. [e]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 SE group. [f]Measured on following scale: no pain; mild pain; mild-to-moderate pain; moderate pain; moderate-to-severe pain; and severe pain.

certainty evidence)]. At 4 years, radiotherapy probably worsens the rate of dermatologist-assessed cosmesis based on the scar (bad, clearly marked or slightly visible), compared with SE [RR 0·48, 95% CI 0·37–0·62 (moderate-certainty evidence)].

Photodynamic therapy vs. surgical excision

Three studies compared PDT with the photosensitizer methyl aminolaevulinate (MAL) against SE. One study included nBCC of the face (103 participants; 118 lesions) with a 5-year follow-up.[15,68] Another study included 57 participants (68 lesions) with nBCC in the head and neck area, with a 3 year follow-up.[47] A noninferiority study included 196 participants with 246 sBCCs (between 8 mm and 20 mm in diameter located anywhere except mid-face) with a 1-year follow-up.[45] Only one study compared fractionated PDT using the photosensitizer aminolaevulinic acid (ALA) to SE in 171 primary nBCCs (149 participants) with 5 year follow-up.[43]

At 3 years, MAL-PDT may increase the risk of recurrence vs. SE [36·4% (n = 12/33) vs. 0% (n = 0/35); RR 26·47, 95% CI 1·63–429·92 [low-certainty evidence]) (Table 4). Compared with SE, ALA-PDT probably increases the risk of recurrence at 3 years [24·7% (n = 21/85) vs. 2·3% (n = 2/88); RR 10·87, 95% CI 2·63–44·95 (moderate-certainty evidence)] (Table 5). By 5 years, ALA-PDT probably increases the risk of recurrence, compared with SE [27·1% (n = 23/85) vs. 2·3% (n = 2/88); RR 11·91, 95% CI 2·90–48·95 (moderate-certainty evidence)].

In pooling cosmetic results, we found that, when measured at 1 year, MAL-PDT probably slightly reduces the rate of participant-rated good/excellent cosmetic outcomes, compared with SE [RR 1·18, 95% CI 1·09–1·27; I^2 = 0% (moderate-certainty evidence)]. When investigator-rated at 1 year, MAL-PDT probably increases the rate of good/excellent cosmetic outcomes vs. SE [RR 1·87. 95% CI 1·54–2·26; I^2 = 0% (moderate-certainty evidence)].

Imiquimod vs. photodynamic therapy

One study assessed whether fluorouracil (5-FU) cream and imiquimod cream were noninferior to MAL-PDT in 601 participants with a single sBCC (anywhere except high-risk face/scalp) in a three-arm RCT with 5 years of follow-up.[40,59] Compared with MAL-PDT, imiquimod cream probably reduces

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Table 3 Radiotherapy vs. surgical excision (SE) for high- and low-risk basal cell carcinoma (BCC)[a]

Outcomes	Anticipated absolute effects (95% CI) Risk with SE	Risk with radiotherapy	Relative effect (95% CI)	No. of participant (studies)	Certainty of the evidence (GRADE)	Comments
Recurrence at 3 years	Study population 0/1000	52/1000 (6–1883)	RR 19·11 (1·12–325·78)	347 (1 RCT)	⨁⨁◯◯ LOW[b]	–
Recurrence at 4 years	Study population 6/1000	64/1000 (8–487)	RR 11·06 (1·44–84·77)	347 (1 RCT)	⨁⨁◯◯ LOW[c]	–
Cosmetic outcome (good/excellent)	Study population 661/1000	502/1000 (416–601)	RR 0·76 (0·63–0·91)	347 (1 RCT)	⨁⨁⨁◯ MODERATE[d]	Participant-rated at 4 years on 3-point scale.[e] ITT analysis performed
Cosmetic outcome	Study population 603/1000	290/1000 (223–374)	RR 0·48 (0·37–0·62)	347 (1 RCT)	⨁⨁⨁◯ MODERATE[d]	Observer-rated ("slightly visible") at 4 years on 3-point scale.[e] [f]ITT analysis performed
Pain	No study addressed this outcome		NE	–	–	–
Early treatment failure	No study addressed this outcome		NE	–	–	–

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ITT, intention to treat; NE, not estimable; RCT, randomized controlled trial; RR, risk ratio. [a]Patient or population: adults with high- and low-risk BCC; setting: secondary care with outpatients from a single hospital in France; intervention: radiotherapy; comparison: SE (with or without frozen section margin control). [b]Downgraded two levels for very serious imprecision due to very wide 95% CI (although excludes 1, there is a > 100-fold difference). [c]Downgraded one level for serious indirectness (outcome outside our prespecified timepoints) and downgraded one level for serious imprecision as only a single study with a small sample size. [d]Downgraded one level for serious risk of bias as unable to blind truly owing to the nature of interventions. [e]Three-point scale: bad; fair; good. [f]Three-point scale of scar appearance: bad, clearly marked, slightly visible.

the risk of recurrence at 3 years [22·8% (n = 34/149) vs. 51·6% (n = 66/128), respectively; RR 0·44, 95% CI 0·32–0·62 (moderate-certainty evidence)] (Table 6). At 5 years, imiquimod cream probably reduces the risk of recurrence, compared with MAL-PDT [28·6% (n = 36/126) vs. 68·6% (n = 70/102), respectively; RR 0·42, 95% CI 0·31–0·57; moderate-certainty evidence)].

There is probably little-to-no difference between imiquimod and MAL-PDT with regard to the rate of good/excellent cosmetic outcomes when rated by a blinded observer at 1 year on a 4-point scale (RR 0·98, 95% CI 0·84–1·16; moderate-certainty evidence).[40,59]

Imiquimod cream vs. 5-fluorouracil cream

Compared with 5-FU cream, imiquimod probably reduces the risk of recurrence at 3 years [34·2% (n = 34/145) vs. 23·4% (n = 50/146), respectively; RR 0·68, 95% CI 0·47–0·99 (moderate-certainty evidence)] (Table 7).[40,59] Compared with 5-FU cream, imiquimod probably reduces the risk of recurrence at 5 years [46·0% (n = 36/126) vs. 28·6% (n = 57/124), respectively; RR 0·62, 95% CI 0·44–0·87 (moderate-certainty evidence)].

When blinded observer-rated at 1 year, there is probably little-to-no difference between imiquimod and 5-FU cream in the rate of good/excellent cosmetic outcomes [61·4% (n = 113/184) vs. 57·5% (n = 111/193); RR 1·07, 95% CI 0·90–1·26 (moderate-certainty evidence)].[40,59]

Photodynamic therapy vs. cryosurgery

One study compared MAL-PDT with cryotherapy in 118 participants with 219 sBCCs with 5 years of follow-up.[31] It showed there may be little-to-no difference between MAL-PDT and cryosurgery on the risk of recurrence at 3 years [22% (n = 22/100) vs. 19·4% (n = 18/93), respectively; RR 1·14, 95% CI 0·65–1·98 (low-certainty evidence)].

When participant-rated at 1 year on a 4-point scale, MAL-PDT probably increases the rate of good/excellent cosmetic outcomes vs. cryosurgery [100% (n = 51/51) vs. 81·3% (n = 39/48), respectively; RR 1·23, 95% CI 1·07–1·41 (moderate-certainty evidence)]. When rated by an investigator on a 4-point scale, MAL-PDT probably increases the rate of good/excellent cosmetic outcomes vs. cryosurgery [89% (n = 45/51) vs. 61% (n = 29/48); RR 1·46, 95% CI 1·14–1·88 (moderate-certainty evidence)].

Another study compared ALA-PDT with cryotherapy in 88 participants with nBCC and sBCC with only 1 year of follow-up and we are therefore unable to comment on recurrence rate.[29] The study showed that, compared with cryosurgery, ALA-PDT probably increases the rate of good/excellent cosmetic outcomes at 1 year [92.8% (n = 39/42) vs. 54%

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Table 4 Methyl aminolaevulinate photodynamic therapy (MAL-PDT) vs. surgical excision (SE) for low-risk basal cell carcinoma (BCC)[a]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SE	Risk with MAL-PDT				
Recurrence at 3 years	Study population 0/1000	364/1000 (49–13027)	RR 26·47 (1·63–429·92)	68 (1 RCT)	⊕⊕⊖⊖ LOW[b]	–
Cosmetic outcome (good/excellent)	Study population 825/1000	973/1000 (899–1000)	RR 1·18 (1·09–1·27)	309 (2 RCTs)	⊕⊕⊕⊖ MODERATE[c]	Participant-rated at 1 year on 4-point scale[d]
Cosmetic outcome (good/excellent)	Study population 466/1000	871/1000 (717–1000)	RR 1·87 (1·54–2·26)	256 (2 RCTs)	⊕⊕⊕⊖ MODERATE[c]	Observer-rated at 1 year on a 4-point scale[d]
Pain	Study population 61/1000	135/1000 (37–492)	RR 2·20 (0·60–8·03)	101 (1 RCT)	⊕⊕⊖⊖ LOW[e]	Study reported frequency of 'pain in skin' and 'burning sensation of skin' as part of AEs
Early treatment failure	Study population 11/1000	77/1000 (14–419)	RR 6·66 (1·22–36·41)	173 (2 RCTs)	⊕⊕⊕⊖ MODERATE[f]	

AE, adverse event; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, risk ratio. [a]Patient or population: adults with low-risk BCC; setting: secondary care with outpatients from hospitals in Brazil, the UK, Germany, Switzerland and Australia; intervention: MAL-PDT; comparison: SE. [b]Downgraded two levels for very serious imprecision owing to very wide 95% CI (although excludes 1, there is a > 100-fold difference). [c]Downgraded one level for serious risk of bias as unable to blind truly owing to the nature of interventions. [d]Four-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 vs. adjacent skin); excellent (no scarring, atrophy or induration, and slight or no redness or change in pigmentation vs. adjacent skin). [e]Downgraded two levels for very serious imprecision as very wide 95% CI, indicating the possibility of important benefit or harm. [f]Downgraded one level for serious imprecision due to small sample size and wide 95% CI.

Table 5 Aminolaevulinic acid photodynamic therapy (ALA-PDT) vs. surgical excision (SE) for low-risk basal cell carcinoma (BCC)[a]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SE	Risk with ALA-PDT				
Recurrence at 3 years	Study population 23/1000	247/1000 (60–1000)	RR 10·87 (2·63–44·95)	173 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Recurrence at 5 years	Study population 23/1000	271/1000 (66–1000)	RR 11·91 (2·90–48·95)	173 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Cosmetic outcome	No study addressed this outcome		NE	–	–	–
Pain	No study addressed this outcome		NE	–	–	–
Early treatment failure	Study population 23/1000	72/1000 (15–348)	RR 3·18 (0·66–15·32)	171 (1 RCT)	⊕⊕⊖⊖ LOW[c]	–

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NE, not estimable; RCT, randomized controlled trial; RR, risk ratio. [a]Patient or population: adults with low-risk BCC; setting: secondary care with outpatients from a single-centre in the Netherlands; intervention: ALA-PDT; comparison: SE. [b]Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI. [c]Downgraded two levels for very serious imprecision as very wide 95% CI, indicating the possibility of important benefit or harm.

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Table 6 Imiquimod cream vs. methyl aminolaevulinate photodynamic therapy (MAL-PDT) for low-risk basal cell carcinoma (BCC)[a]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participant (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PDT	Risk with imiquimod cream				
Recurrence at 3 years	Study population 516/1000	227/1000 (165–320)	RR 0·44 (0·32–0·62)	277 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Recurrence at 5 years	Study population 686/1000	288/1000 (213–391)	RR 0·42 (0·31–0·57)	228 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Cosmetic outcome (excellent/good)	Study population 624/1000	611/1000 (524–723)	RR 0·98 (0·84–1·16)	370 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Blinded observer-rated at 1 year on 4-point scale[c]
Pain (moderate/severe)	Study population 305/1000	183/1000 (125–266)	RR 0·60 (0·41–0·87)	371 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	During treatment: week of treatment with highest frequency of reported moderate/severe pain (week 6 for imiquimod, treatment cycle 2 for PDT)
Early treatment failure	Study population 158/1000	101/1000 (59–172)	RR 0·64 (0·37–1·09)	385 (1 RCT)	⊕⊕⊕⊖ MODERATE[d]	–

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, risk ratio. [a]Patient or population: adults with low-risk BCC; setting: secondary care with outpatients from seven hospitals in the Netherlands; intervention: 5% imiquimod cream; comparison: MAL-PDT. [b]Downgraded one level for serious imprecision as only a single study with a small sample size. [c]Four-point scale (poor, fair, good, excellent). [d]Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI.

(n = 20/37); RR 1·72, 95% CI 1·26–2·34 (moderate-certainty evidence)].

Discussion

This systematic review included the full spectrum of interventions for primary BCC by including 52 RCTs (52 comparisons) of varying methodological quality. Overall, the quantity of research on interventions for BCC has doubled and quality has improved since our 2007 update,[37] with several RCTs now publishing appropriate long-term follow-up data. Many included studies still yield low- or moderate-certainty evidence that should be interpreted with caution.

Surgery remains the most effective treatment modality for BCC in terms of reducing recurrences, and there may be a slightly reduced recurrence rate with MMS than with 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 trial 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). Radiotherapy may also lead to increased recurrence vs. SE (low-certainty evidence) and is therefore best reserved for tumours not amenable to surgery. Three other RCTs assessed radiotherapy against other interventions (see full review).[7] These were all conducted over 20 years ago and, as techniques and protocols have developed over time, the outcomes may not be reflective of current-day radiotherapy outcomes. Therefore, new studies comparing radiotherapy against other interventions are needed.

Nonsurgical treatments are less effective than surgical treatments, 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, compared with SE, imiquimod may increase

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Table 7 Imiquimod cream vs. fluorouracil (5-FU) cream for low-risk basal cell carcinoma (BCC)[a]

	Anticipated absolute effects (95% CI)					
Outcomes	Risk with 5-FU cream	Risk with imiquimod cream	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Recurrence at 3 years	Study population 342/1000	233/1000 (161–339)	RR 0·68 (0·47–0·99)	291 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Recurrence at 5 years	Study population 460/1000	285/1000 (202–400)	RR 0·62 (0·44–0·87)	250 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	–
Cosmetic outcome (excellent/good)	Study population 575/1000	615/1000 (518–725)	RR 1·07 (0·90–1·26)	377 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Observer-rated at 1 year on 4-point scale[c]
Pain (moderate/severe)	Study population 125/1000	183/1000 (111–298)	RR 1·46 (0·89–2·38)	365 (1 RCT)	⊕⊕⊕⊖ MODERATE[d]	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)
Early treatment failure	Study population 121/1000	101/1000 (57–177)	RR 0·83 (0·47–1·46)	387 (1 RCT)	⊕⊕⊖⊖ LOW[e]	–

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, risk ratio. [a]Patient or population: adults with low-risk BCC; setting: secondary care with outpatients from seven hospitals in the Netherlands; intervention: imiquimod cream; comparison: 5-FU cream. [b]Downgraded one level for serious imprecision as only a single study with a small sample size. [c]Four-point scale: poor; fair; good; excellent. [d]Downgraded one level for serious imprecision as only a single study with a small sample size and a wide 95% CI. [e]Downgraded two levels for very serious imprecision as very wide 95% CI, indicating the possibility of important benefit or harm.

the number of observer-rated good/excellent cosmetic outcomes (low-certainty evidence).

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 3 years than SE (low-certainty evidence; no useable data for measurement at 5 years) but probably increases the number of good/excellent cosmetic results (moderate-certainty evidence).

The majority of studies were 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 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.

The strengths of this review include our comprehensive, systematic search strategy that aimed to include all relevant studies, irrespective of language or publication status. Additionally, we conducted this review according to the rigorous standards of the Cochrane Collaboration, including assessing the risk of bias using the Cochrane risk-of-bias framework and assessing the quality of evidence using the GRADE approach. 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 majority of these single studies were multicentre, but many were limited by small sample sizes, and consequently, many of the outcomes reported in this review have wide CIs. This means that there is a large amount of imprecision in the results, and therefore several of our results are of low-certainty evidence, which threatens their external validity and reproducibility. A further limitation of our review is that currently there are no formally agreed core outcome sets for BCC clinical trials – a task that is currently in progress.[69] Consensus on how to measure outcomes such as recurrence (e.g. clinically or histopathologically) and cosmetic outcomes, as well as the optimal timepoint, will improve our ability to assess the relative benefits and harms of interventions for BCC. Future trials of BCC should register their trial prospectively and report randomization, blinding and all outcomes according to CONSORT criteria.[70] Ideally, all BCC trials should include follow-up of recurrences to 5 years.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Appendix S1 Skin Group Specialised Register (CRS) search strategy.

Appendix S2 CENTRAL (Cochrane Library) search strategy.

Appendix S3 MEDLINE (Ovid) search strategy.

Appendix S4 Embase (Ovid) search strategy.

Appendix S5 CINAHL (EBSCO) search strategy.

Appendix S6 LILACS search strategy.

Table S1 Electronic databases and trial registers searched.

Table S2 Characteristics of included studies.

Table S3 GRADE Working Groups grades of evidence.

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