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

J. Thomson 1,2, S. Hogan, 1 J. Leonardi-Bee 3, H. C. Williams 4 and F. J. Bath-Hextall 5

1Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, London, UK
2Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University London, London, UK
3Centre for Evidence Based Healthcare, Division of Epidemiology and Public Health, Clinical Sciences Building Phase 2, University of Nottingham, Nottingham, UK
4Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
5Emeritus Professor, Evidence Based Health Care, University of Nottingham, Nottingham, UK

Correspondence
Jason Thomson.
Email: jason.thomson@nhs.net

Accepted for publication
9 January 2021

Funding sources
This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Skin Group.

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.

DOI 10.1111/bjd.19809

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.

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.
Basal cell carcinoma (BCC) is the most common skin cancer and the most common cancer found in white-skinned individuals.\textsuperscript{1–3} BCCs are slow-growing, locally invasive, malignant (but not life-threatening), epidermal skin tumours.\textsuperscript{4,5} BCCs affect the head and neck region around 70% of the time, and the trunk and extremities around 30% of the time.\textsuperscript{6} A systematic review identified that the incidence of BCC is increasing in Europe by 5.5% annually.\textsuperscript{3} Between 2013 and 2015 there was a mean annual percentage increase of 5% in BCC incidence across the UK.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 time-point 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 measured 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
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 predefined 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. 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.

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. 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.
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. 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.
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 0.99, 95% CI 0.64–0.64) (moderate-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 = 61/174), 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).

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-certainty evidence)] (Table 3).
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. A second study included 57 participants (68 lesions) with nBCC in the head and neck area, with a 3-year follow-up. 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. 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.

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; I² = 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; I² = 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. Compared with MAL-PDT, imiquimod cream probably reduces...
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 investigator at 1 year on a 4-point scale (RR 0.98, 95% CI 0.84–1.16; moderate-certainty evidence).

### 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). 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)].

### Photodynamic therapy vs. cryosurgery

One study compared MAL-PDT with cryotherapy in 118 participants with 219 sBCCs with 5 years of follow-up. It showed there may have been 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. 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%...
### 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 |
|-------------------------------|--------------------------------------|--------------------------|-------------------------------|-----------------------------------|----------|
| Recurrence at 3 years         | Risk with SE: 0/1000 Risk with MAL-PDT: 364/1000 (49–13027) | RR 26.47 (1.63–429.92)   | 68 (1 RCT)                    | ⊕⊕⊝⊝⊝ LOW\(^b\)                  | –        |
| Cosmetic outcome (good/excellent) | Study population: 825/1000 Risk with MAL-PDT: 973/1000 (899–1000) | RR 1.18 (1.09–1.27)      | 309 (2 RCTs)                  | ⊕⊕⊝⊝ MODERATE\(^e\)               | Participant-rated at 1 year on 4-point scale\(^d\) |
| Cosmetic outcome (good/excellent) | Study population: 466/1000 Risk with MAL-PDT: 871/1000 (717–1000) | RR 1.87 (1.54–2.26)      | 256 (2 RCTs)                  | ⊕⊕⊝⊝ MODERATE\(^e\)               | Observer-rated at 1 year on 4-point scale\(^d\) |
| Pain                          | Study population: 61/1000 Risk with MAL-PDT: 135/1000 (37–492) | RR 2.20 (0.60–8.03)      | 101 (1 RCT)                   | ⊕⊕⊝⊝ LOW\(^a\)                   | Study reported frequency of 'pain in skin' and 'burning sensation of skin' as part of AEs |

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, Switzerland and Australia; intervention: MAL-PDT; comparison: SE. Downgraded two levels for very serious imprecision owing to very wide 95% CI (although excludes 1, there is a > 100-fold difference). Downgraded one level for serious risk of bias as unable to blind truly owing to the nature of interventions. Downgraded one level for serious risk of bias due to small sample size and wide 95% CI. Downgraded two levels for very serious imprecision owing to very wide 95% CI, indicating the possibility of important benefit or harm.

### 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 |
|-----------------------------------|--------------------------------------|--------------------------|-------------------------------|-----------------------------------|----------|
| Recurrence at 3 years             | Study population: 11/1000 Risk with ALA-PDT: 77/1000 (14–419) | RR 6.66 (1.22–36.41)     | 173 (2 RCTs)                  | ⊕⊕⊝⊝ MODERATE\(^f\)               | –        |
| Recurrence at 5 years             | Study population: 23/1000 Risk with ALA-PDT: 247/1000 (60–1000) | RR 10-87 (2.63–44.95)    | 173 (1 RCT)                   | ⊕⊕⊝⊝ MODERATE\(^b\)               | –        |
| Cosmetic outcome                  | Study population: 23/1000 Risk with ALA-PDT: 271/1000 (66–1000) | RR 11.91 (2.90–48.95)    | 173 (1 RCT)                   | ⊕⊕⊝⊝ MODERATE\(^b\)               | –        |
| Pain                              | No study addressed this outcome       | NE                       | –                             | –                                 | –        |
| Early treatment failure           | Study population: 23/1000 Risk with ALA-PDT: 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. 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. Downgraded one level for serious imprecision owing to very wide 95% CI, indicating the possibility of important benefit or harm.
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,\(^3\) 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

Table 6 Imiquimod cream vs. methyl aminolaevulinate photodynamic therapy (MAL-PDT) for low-risk basal cell carcinoma (BCC)\(^*\)

| 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      |                             |                                  |          |
|                           | Risk with PDT                         | Risk with imiquimod      |                             |                                  |          |
|                           | Study population RR 0.44 (0.32–0.62)   | Study population RR 0.42 (0.31–0.57) |                            |                                  |          |
|                           | 277 (1 RCT)                            | 228 (1 RCT)              |                             |                                  |          |
|                           | Study population RR 0.98 (0.84–1.16)   | Study population RR 0.60 (0.41–0.87) |                            |                                  |          |
|                           | 370 (1 RCT)                            | 371 (1 RCT)              |                             |                                  |          |
|                           | Study population RR 0.64 (0.37–1.09)   | Study population RR 0.37 (0.19–0.69) |                            |                                  |          |
|                           | 385 (1 RCT)                            | 395 (1 RCT)              |                             |                                  |          |
Table 7: Imiquimod cream vs. fluorouracil (5-FU) cream for low-risk basal cell carcinoma (BCC)^

| Outcomes                        | Anticipated absolute effects (95% CI) | 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 (161–339) | 233/1000 (161–339) | RR 0·68 (0·47–0·99) | 291 (1 RCT) ⊘⊕⊕⊕ ⊘ ⊘ ⊘ ⊘ | MODERATE
| Recurrence at 5 years           |                                       | Study population 460/1000 (202–400) | 285/1000 (202–400) | RR 0·62 (0·44–0·87) | 250 (1 RCT) ⊘⊕⊕⊕ ⊘ ⊘ ⊘ ⊘ | MODERATE
| Cosmetic outcome (excellent/good)|                                       | Study population 575/1000 (518–725) | 615/1000 (518–725) | RR 1·07 (0·90–1·26) | 377 (1 RCT) ⊘⊕⊕⊕ ⊘ ⊘ ⊘ ⊘ | Observer-rated at 1 year on 4-point scale
| Pain (moderate/severe)          |                                       | Study population 125/1000 (111–298) | 183/1000 (111–298) | RR 1·46 (0·89–2·38) | 365 (1 RCT) ⊘⊕⊕⊕ ⊘ ⊘ ⊘ ⊘ | 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 (57–177) | 101/1000 (57–177) | RR 0·83 (0·47–1·46) | 387 (1 RCT) ⊘⊕⊕⊕ ⊘ ⊘ ⊘ ⊘ | LOW

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, risk ratio. ^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. ◀Downgraded one level for serious imprecision as only a single study with a small sample size. ◀Four-point scale: poor; fair; good; excellent. ◀Downgraded one level for very serious imprecision as only a single study with a small sample size and a wide 95% CI. ◀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.

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. Ideally, all BCC trials should include follow-up of recurrences to 5 years.
Acknowledgments

Many thanks to the Cochrane Skin team for all their support and advice.

References

1. Verkouteren J, Ramdas K, Wakkee K et al. Epidemiology of basal cell carcinoma: scholarly review. Br J Dermatol 2017; 177:359–72.
2. Madan V, Lear JT. Basal cell carcinoma. In: Rose’s Textbook of Dermatology (Griffiths C, Barker J, Bleiker T, R Chalmers, D Creamer eds), 9th edn. Chichester: Wiley Blackwell, 2016. 411.
3. Lomas A, Leonard-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012; 166:1069–80.
4. Wong C, Strange R, Lear J. Basal cell carcinoma. BMJ 2003; 327:794.
5. Roewert-Huber J, Lange-Asschenfeldt B, Stockfleth E et al. Epidemiology and aetiology of basal cell carcinoma. Br J Dermatol 2007; 157:47–51.
6. Venables ZC, Nijsten T, Wong K-F et al. Epidemiology of basal and cutaneous squamous cell carcinoma in the UK 2013–15: a cohort study. Br J Dermatol 2019; 181:474–82.
7. Thomson J, Hogan S, Leonard-Bee J et al. Interventions for basal cell carcinoma of the skin. Cochrane Database Syst Rev 2020; 11:1465–858.
8. Bath-Hextall F, Bong J, Perkins W et al. Interventions for basal cell carcinoma of the skin. Cochrane Database Syst Rev 2003; 2:CD003412.
9. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Available at: https://handbook.5-1.cochrane.org (last accessed 29 January 2021).
10. Schinemann H, Brozek J, Guyatt G et al. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. Available at: https://gdt.gradepro.org/app/handbook/handbook.html (last accessed 29 January 2021).
11. Cornell RC, Greenway HT, Tucker SB et al. Intralesional interferon therapy for basal cell carcinoma. J Am Acad Dermatol 1990; 23:694–700.
12. Geisse JK, Rich P, Pandya A et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. J Am Acad Dermatol 2002; 47:390–8.
13. Geisse J, Caro I, Lindholm J et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol 2004; 50:722–33.
14. Marks R, Gebauer K, Shumack S et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose-response trial. J Am Acad Dermatol 2001; 44:807–13.
15. Rhodes LE, de Rie M, Enstroem Y et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol 2004; 140:17–23.
16. Schulze H, Cribier B, Requena L et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol 2005; 141:39–47.
17. Shumack S, Robinson J, Kossard S et al. Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma: comparison of dosing regimens. Arch Dermatol 2002; 138:1165–71.
18. Smets NW, Krekels GA, Ostertag JU et al. Surgical excision vs Mohs’ micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. Lancet 2004; 364:1766–72.
19. Sterry W, Ruzicka T, Herrera E et al. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomised studies comparing low-frequency dosing with and without occlusion. Br J Dermatol 2002; 147:1227–36.
20. Alpsoy E, Yilmaz E, Basaran E. Comparison of the effects of intralesional interferon alfa–2a, 2b and the combination of 2a and 2b in the treatment of basal cell carcinoma. J Dermatol 1996; 23:394–6.
21. Avril M, Auperin A, Margulis A et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. Br J Cancer 1997; 76:100.
22. Beutner KR, Geisse JK, Helman D et al. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol 1999; 41:1002–7.
23. Edwards L, Tucker SB, Perednia D et al. The effect of an intralesional sustained-release formulation of interferon alfa–2b on basal cell carcinomas. Arch Dermatol 1990; 126:1029–32.
24. Hall V, Leppard BJ, McGill J et al. Treatment of basal-cell carcinoma: comparison of radiotherapy and cryotherpay. Clin Radiol 1986; 37:33–4.
25. Romagesa R, Saap L, Givens M et al. A pilot study to evaluate the treatment of basal cell carcinoma with 5-fluourouracil using phosphatidyl choline as a transpidermal carrier. Dermatol Surg 2000; 26:338–40.
26. Rogozinski TT, Jablonska S, Brzoska JM et al. [Intralesional treatment with recombinant interferon beta is an effective alternative for the treatment of basal cell carcinoma. Double-blind, placebo-controlled study]. Przegl Dermatol 1997; 84:559–63 (in Polish).
27. Soler AM, Angell-Petersen E, Warloe T et al. Photodynamic therapy of superficial basal cell carcinoma with 5-aminolevulinic acid with dimethylsulfoxide and ethylenediaminetetraacetic acid: a comparison of two light sources. Photomol Photobiol 2000; 71:724–9.
28. Thissen M, Nieman F, Ideler A et al. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. Dermatol Surg 2000; 26:759–64.
29. Wang I, Bendsoe N, Klinteborg CAF et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. Br J Dermatol 2001; 144:832–40.
30. Miller BH, Shavin JS, Cognetta A et al. Nonsurgical treatment of basal cell carcinomas with intralesional 5-fluorouracil/epinephrine injectable gel. J Am Acad Dermatol 1997; 36:72–7.
31. Basset-Seguin N, Ibbotson SH, Emtestam L et al. Topical methyl aminolevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol 2008; 18:547–53.
32. Eigentler TK, Kamin A, Weide BM et al. A phase III, randomized, open label study to evaluate the safety and efficacy of imiquimod 5% cream applied thrice weekly for 8 and 12 weeks in the treatment of low-risk nodular basal cell carcinoma. J Am Acad Dermatol 2007; 57:616–21.
33. Kuipers DI, Thissen MR, Berretty PJ et al. Surgical excision versus curettage plus cryosurgery in the treatment of basal cell carcinoma. Dermatol Surg 2007; 33:579–87.
34. Foley P, Freeman M, Menter A et al. Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies. Int J Dermatol 2009; 48:1236–45.
35. Punjabi S, Cook L, Kersey P et al. Solasodine glycoalkaloids: a novel topical therapy for basal cell carcinoma. A double-blind, randomized, placebo-controlled, parallel group, multicenter study. Int J Dermatol 2008; 47:78–82.
46 Szeimies RM, Reinhold U, Dirschka T et al.
51 Garcia-Martin E, Gil-Arribas L, Idoipe M
49 Choi SH, Kim KH, Song KH. Er:YAG ablative fractional laser-
41 Bath-Hextall F, Ozolins M, Armstrong SJ
42 Karsai S, Friedl H, Buhck H et al.
– a randomized clinical trial.
51 – quimod 5% cream versus radiotherapy as treatment for eyelid
diclofenac 3% and calcitriol 3
2017; – month follow-up.
J Eur Acad Dermat Venereol
dynamic therapy (MAL-PDT) compared to surgical excision: a ran-
31 – :783
33 – :89.
J Am Acad Dermatol
50 – (sBCC) and nodular basal cell carcinoma (nBCC): a phase II,
methyl aminolevulinate photodynamic therapy and surgery in
595-nm pulsed dye laser for the treatment of basal cell carcinoma
54. Ingenol mebutate 0.05%
56. Wulf HC. A randomised, double-blinded parallel group study to
58. Williams HC, Bath-Hextall F, Ozolins M et al. Surgery versus 5% imiquimod and topical 5-fluorouracil in
55. Landthaler M, Braun-Falco O. [TDF factors in soft X-ray therapy].
Hautarzt 1989; 40:774–7. (in German).
54. Salmanpoor R, Motevali D, Saki N et al. Efficacy of excisional sur-
gery, curettage and combined curettage and electrodesiccation in
treatment of basal cell carcinoma. Ism J Dermatol 2012; 15:66–7.
55. Clover AJP, Salwa SP, Bourke MG et al. Electrochemotherapy for the
95. – :1393–6.
52. Haak CS, Togsvedt-Bo K, Thaysen-Petersen D et al. Fractional laser-
54. – photodynamic therapy of non-aggressive basal cell carcinoma by topical photodynamic therapy with
55. – photodynamic therapy vs. surgical excision in the
treatment of superficial basal-cell carcinoma: a single-blind, non-inferiority,
randomised controlled trial. Lancet Oncol 2013; 14:647–54.
Bath-Hextall F, Ozolins M, Armstrong SJ et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled
trial. Lancet Oncol 2014; 15:96–105.
Karsai S, Friedl H, Buick H et al. The role of the 595-nm pulsed dye laser in treating superficial basal cell carcinoma: outcome of a
double-blind randomized placebo-controlled trial. Br J Dermatol 2015; 172:677–83.
Mosterd K, Thissen M, Nelemans P et al. Fractionated 5-aminolae-
vulinic acid–photodynamic therapy vs. surgical excision in the
treatment of nodular basal cell carcinoma: results of a randomized
directed trial. Br J Dermatol 2008; 159:864–70.
Siller G, Rosen R, Freeman M et al. PEP005 (ingenol mebutate) gel for the
topical treatment of superficial basal cell carcinoma: results of a
randomized phase IIa trial. Austral J Dermatol 2010; 51:99–105.
Szmies R, Ibbotson S, Murrell D et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in
small superficial basal cell carcinoma (8–20 mm), with a 12-
month follow-up. J Eur Acad Dermat Venereol 2008; 22:1302–11.
Szmies RM, Reinhold U, Dirschka T et al. Photodynamic therapy for actinic keratosis and basal cell carcinoma using BE-200 ALA: results of pivotal phase III trials and follow-up. J Eur Acad Dermat Venereol 2017; 31:89.
Abbade L, Gige T, Amaral V et al. Higher recurrence rates of head and
neck nodular basal cell carcinoma treated with topical photody-
namic therapy (MAL-PDT) compared to surgical excision: a ran-
domized controlled study. J Am Acad Dermatol 2015; 72:AB185.
Brinkhuizen T, Frencken KJA, Nelemans PJ et al. The effect of topical diclofenac 3% and calcitriol 3µg/g on superficial basal cell carci-
noma (sBCC) and nodular basal cell carcinoma (nBCC): a phase II,
randomized controlled trial. J Am Acad Dermatol 2016; 75:126–34.
Choi SH, Kim KH, Song KH. Er:YAG ablative fractional laser-
primed photodynamic therapy with methyl aminolevulinate as an
alternative treatment option for patients with thin nodular basal
cell carcinoma: 12-month follow-up results of a randomized,
prospective, comparative trial. J Eur Acad Dermat Venereol 2016;
30:783–8.
Euzehah FL, Dawe RS, Ibbotson SH et al. A randomized parallel study to assess the safety and efficacy of two different dosing regi-
mens of 5% imiquimod in the treatment of superficial basal cell carci-
noma. J Dermal Treat 2008; 19:111–7.
Garcia-Martin E, Gil-Arribas L, Idiope M et al. Comparison of imi-
quimod 5% cream versus radiotherapy as treatment for eyelid
basal cell carcinoma. Br J Ophthmol 2011; 95:1393–6.
Haak CS, Togsvedt-Bo K, Thaysen-Petersen D et al. Fractional laser-
mediated photodynamic therapy of high-risk basal cell carcinomas – a randomized clinical trial. Br J Dermatol 2015; 172:215–22.
68 Rhodes LE, de Rie MA, Leifsdottir R et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007; 143: 1131–6.

69 Schlessinger DI, Iyengar S, Yanes AF et al. Development of a core outcome set for clinical trials in basal cell carcinoma: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. Trials 2017; 18: 490.

70 Schulz KF, Altman DG, Moher D et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Trials 2010; 11: 32.

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.