Comparative Effectiveness Review
Number 199

Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin

AHRQ
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(with addendum)

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Key Messages

Purpose of Review

Assess comparative effectiveness and safety of treatments for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Key Messages

- Comparative evidence on treatment of BCC and SCC is limited. Many comparisons were evaluated in one or two randomized controlled trials only.
- Surgery and radiotherapy have lower recurrence rates for BCC than interventions that destroy lesions with heat or cold, photodynamic therapy (PDT), or curettage.
- There is moderate confidence that PDT for BCC is associated with better cosmetic outcomes than surgery.
- Serious adverse events, events leading to treatment discontinuation, and treatment site infections were uncommon with all treatments for BCC.
- Recurrence rates for SCC in situ were lower with PDT and cryotherapy than with drugs. Evidence was insufficient to draw conclusions for other treatments.

This report is based on research conducted by the Brown Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00002-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

 This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin

Structured Abstract

Introduction. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are among the most common malignancies in the United States. There are many potential management strategies for BCCs and SCCs, and the choice of management strategy for an individual patient is not straightforward. We aimed to comprehensively collect information on the comparative effectiveness and safety of each currently used therapeutic strategy for both BCC and SCC.

Data sources. We conducted literature searches in MEDLINE®, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, and Embase® up to March 2017. We also perused the reference lists of published relevant clinical practice guidelines and systematic reviews. We recorded information on recurrence, histologic clearance, clinical clearance, patient- or observer-rated cosmetic outcomes, adverse effects, quality of life, costs and resources, mental health, patient satisfaction, and mortality. We estimated intervention effects (differences in outcomes between treatments) and the mean frequency of the outcome with each treatment using network meta-analyses.

Results We identified 58 randomized controlled trials and 51 nonrandomized comparative studies comparing 21 interventions in 9 categories. Nearly all reported results for recurrence or cure rate outcomes and adverse events, and many reported results for cosmetic outcomes. Few studies reported results using validated instruments for quality of life, mental health, or patient satisfaction with treatment. Data were sparse, especially for analyses at the individual-intervention level. For BCCs, surgical interventions and radiation were associated with lower recurrence rates than interventions that destroy lesions with heat or cold and photodynamic therapy (PDT), and may have lower recurrence rates than curettage. Recurrence rates did not differ significantly between imiquimod and excision. The data were not sufficient to draw conclusions about the comparison of curettage with interventions that destroy lesions with heat or cold, or PDT versus other intervention categories. For SCC in situ, interventions that destroy the lesions with heat or cold and PDT were associated with lower recurrence rates than 5-fluorouracil. Data on the relative effect of thermal interventions versus PDT were not precise enough to draw conclusions.

Conclusions. Based on sparse evidence, surgical and radiation treatments have lower recurrence rates than other modalities for the treatment of low-risk BCC, and PDT appears to have superior cosmetic outcomes. Large gaps remain in the literature regarding the comparison of individual interventions and SCC in situ, with very little or no information on immunocompromised patients, patients with limited life expectancy, and patients with specific lesion categories, including high-risk BCCs and invasive SCCs.

May 2019 update: an addendum is located at the end of the main report, before the appendixes.

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Evidence Summary

Introduction

Skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies in the United States.[1] BCC and SCC, the 2 most common skin cancers, are collectively referred to as keratinocyte carcinomas. Over 5.4 million of these lesions are diagnosed in 3.3 million people in the United States annually,[2, 3] and the global burden of disease from keratinocyte carcinomas is estimated at 12.9 disability-adjusted life years per 100,000 persons.[4] Generally keratinocyte carcinomas are not aggressive and do not metastasize or kill as often as melanoma, which is the third most common skin cancer.[5] However, SCC can metastasize and is estimated to kill between 3900 and 8800 people in the United States each year.[6] A more common problem is that BCC and SCC and their treatment may result in disfigurement or disability, which can adversely impact quality of life.[3] The recent Surgeon General's call to action to prevent skin cancer at the population level emphasizes the public health importance of dealing with these cancers.[7]

There are many potential management strategies for BCC and SCC, including surgical excision without intraoperative evaluation of the margins, surgical excision with intraoperative evaluation of the margins, destruction via temperature gradients, ionizing radiation, photodynamic interventions, medical therapies, various combinations of the aforementioned therapies, and watchful waiting.

The choice of management strategy for an individual patient with a specific keratinocyte carcinoma is complex, and it is not clear how various therapeutic options perform relative to each other. In addition, interventions for treating skin cancers differ substantially in cost.[3, 8-10]

The objective of this systematic review is to comprehensively synthesize information on the comparative effectiveness and safety of each of the above-mentioned therapeutic strategies for both BCC and SCC.

Key Questions

The review addresses two Key Questions for adult patients with BCC or SCC of the skin. Each Key Question will be answered separately for BCC and SCC:

Key Question 1: What is the comparative effectiveness of various interventions, overall and in subgroups of interest?

Key Question 2: How do the adverse events associated with the various interventions compare overall and in subgroups of interest?

Methods

The Brown Evidence-based Practice Center (EPC) conducted this review based on a systematic review of the published scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[11] The Prospero registration number is CRD42016043353. Below is a summary of the methods; details are provided in the methods section of the full report.

Eligibility Criteria

We use the population, intervention, comparator, outcomes, timing, and setting (PICOTS formalism to define the characteristics of the eligible studies for this review. Details are in Table A.

Table A. Population, interventions, outcomes, timing, and setting

PICOTS and Description
Population
Primary basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)
Subpopulations of interest
People who are immunocompromised
People with a limited life expectancy
We excluded subpopulations based on rare genetic factors
Subgroups as defined by location or grade of lesion
Interventions (organized into categories A through J)
A. Surgical excision without intraoperative evaluation of the margins
B. Surgical excision with intraoperative evaluation of the margins Mohs micrographically controlled surgery Surgery with examination of frozen sections
C. Interventions that destroy the lesion via temperature gradients (C1) Cryotherapy (C2) Diathermy/electrodesiccation (C3) Curettage of the lesion plus diathermy (cauterization) of margins (C4) Curettage of the lesion plus cryotherapy (C5) CO_2 laser therapy
D. Interventions that destroy the lesion with ionizing radiation (D1) External beam radiation with photons (X or gamma rays), electrons (beta rays), or positively charged particles (e.g., protons, helium nuclei/alpha rays), at orthovoltage or megavoltage energies, or using in-office radiation machines (D2) Brachytherapy with superficial application or interstitial application (pleisiotherapy) of radiation sources (usually emitting beta or alpha rays)
E. Photodynamic interventions (E1) 5-aminolevulinic acid (ALA) + blue light (E2) Methyl aminolevulinate (MAL) + red light (E3) Other forms of PDT
F. Medical interventions (F1) 5-fluorouracil (5-FU) (F2) Imiquimod (F3) Interferon (IFN alpha-2a/2b or INF beta) (F4) Ingenol mebutate (F5) Other medical interventions, including BEC-5 cream, Bleomycin, Methotrexate, Diclofenac, and Hedgehog inhibitors (Vismodegib, Sonidegib)
G. Shave excision
H. Curettage without diathermy
I. Placebo

PICOTS and Description
J. No treatment
Outcomes
Recurrence
Histological clearance
Clinical clearance
Cosmetic outcomes
Quality of life
Mental health
Patient satisfaction with treatment
Mortality
Adverse events
Timing: any
Setting: any

Design

We evaluated all randomized controlled trials (RCTs) and all comparative nonrandomized controlled studies (NRCSs) that took steps to control for patient- or lesion-level confounders such as medical history, age, education, lesion type, size, location and stage. NRCSs that reported only crude results were identified and tabulated but were excluded from the report. Those results are in Appendix G.

Evidence Identification, Data Extraction, and Assessment of Methodological Risk of Bias of Individual Studies

We conducted literature searches of studies in PubMed, the Cochrane Central Trials Registry, the Cochrane Database of Systematic Reviews, and EMBASE up to March 8, 2017 to identify primary research studies meeting our criteria. All citations found through literature searches and other sources were independently screened by two researchers.

Each study was extracted by one member of the review team and reviewed and confirmed by at least one other experienced methodologist. Disagreements were resolved by discussion among the team. Data was extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov).

We assessed elements of the design of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[12] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used relevant questions from the Newcastle Ottawa Scale.[13] We obtained a minimum bound for the number of unpublished studies through a clinicaltrials.gov search.

Data Synthesis and Grading the Strength of Evidence (SOE)

All included studies were summarized in narrative form and in summary tables that include the important features of the study populations. Lesions were divided by subtype (superficial, nodular, or high-risk BCC, SCC, or mixed populations) for analysis to ensure that the treatments would be most comparable. Where possible, lesions were also evaluated by size and location. Trial arms with fewer than five lesions were not included in the analysis, because they contribute

minimal information, and in some instances, necessitated adding model parameters that were difficult to estimate.

We conducted pairwise and network meta-analyses with mixed effects (random intercepts and fixed intervention slopes) or full-random effects (random intercepts and random slopes) multilevel models within the generalized linear and latent mixed models. To aid the interpretation of these analyses we also present model-based estimates for the mean frequency of an outcome in the examined interventions, as well as forecasts of the frequency of the outcome in a new setting (e.g., a new study, or in a new population) that is similar to the studies in the meta-analysis.

For each major conclusion, we graded the strength of the body of evidence as per the AHRQ Methods Guide on assessing the strength of evidence.[11] We judged the applicability within and across studies with reference to demographics of enrolled participants, the location and severity of the lesions, and the availability of treatments.

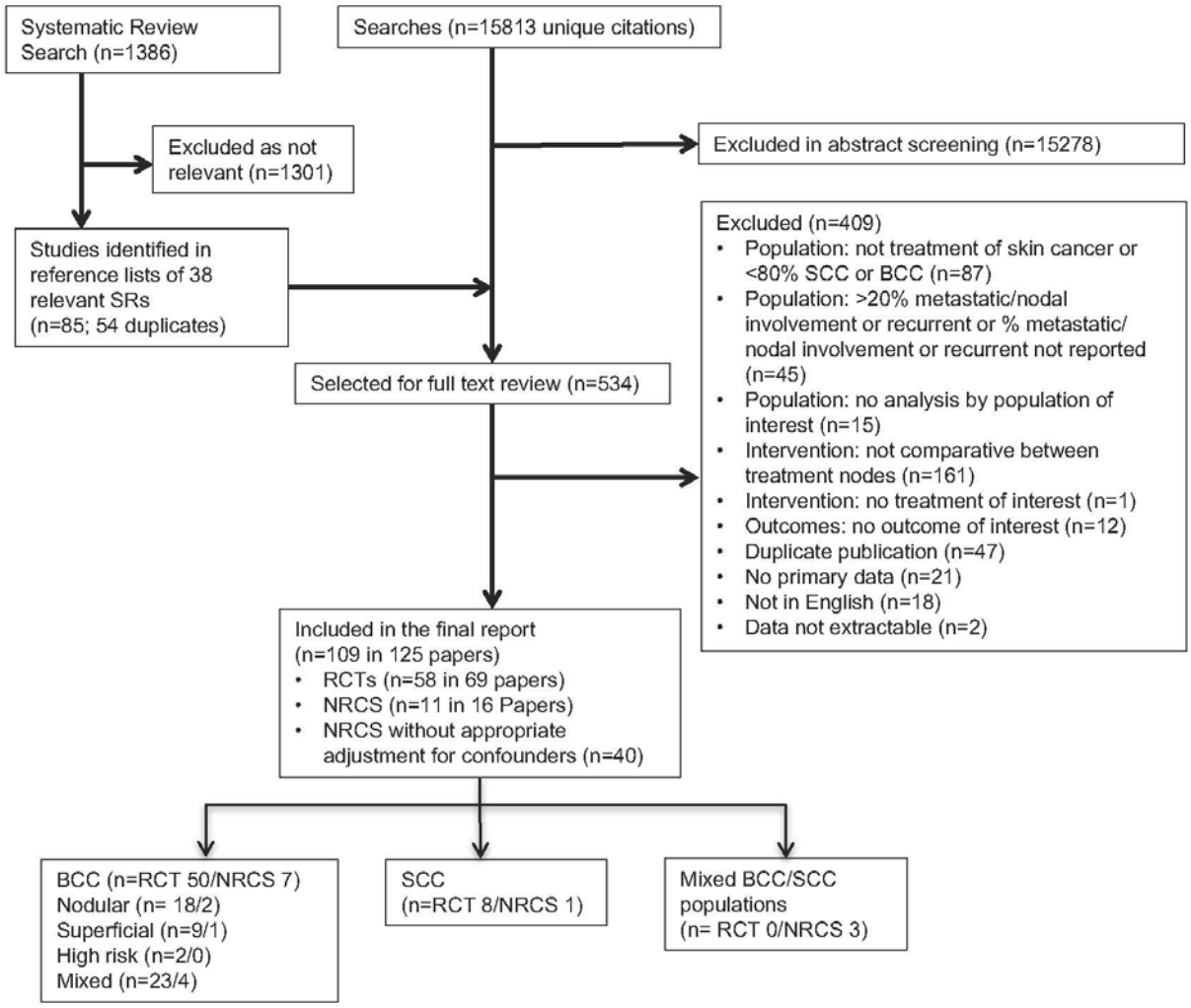
Peer Review

A draft version of this report was reviewed by invited and public reviewers. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports have also been reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

The literature searches yielded 15813 citations (Figure A), of which 15278 were excluded in abstract screening. A search of the reference lists of relevant systematic reviews yielded another 85 studies, which brought the total number screened in full text to 534. The 109 included studies (described in 125 papers) report 58 RCTs and 51 NRCSs.

Figure A. Literature flow diagram



SR = systematic review; SCC = squamous cell carcinoma; BCC = basal cell carcinoma; RCT = randomized controlled trial; NRCS = nonrandomized comparative study

The studies primarily reported on BCC, with a minority reporting results for SCC. Nearly all reported results for recurrence or cure rate outcomes and adverse events, and many reported results for cosmetic outcomes. Few studies reported results using validated instruments for quality of life, mental health, or patient satisfaction with treatment. Because there was insufficient evidence for these outcomes, these results are presented in the full report only, as are results for specific types of BCC and other subgroups.

Details on how to read the graphs and tables are provided in the methods section of the full report. Analyses by specific intervention and results of studies that could not be included in the meta-analysis are given in the results section of the full report.

Basal Cell Carcinoma

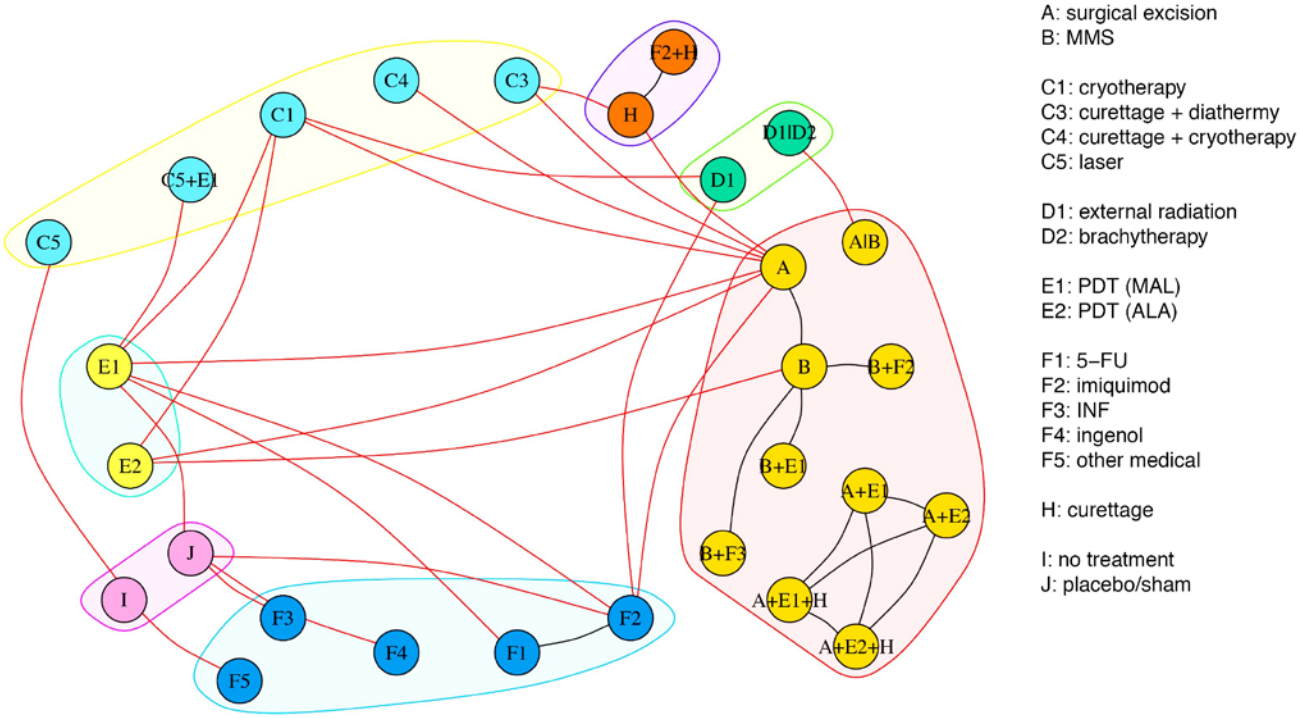
The evidence graph in Figure B suggests that limited conclusions can be drawn about which individual intervention is best (with respect to each outcome) for two reasons: (1) some

interventions have never been compared with other interventions, directly or indirectly, and (2) There are few studies for any given comparison.

The evidence is even more sparse when one considers the information that is actually available for specific outcomes. Figure C shows the evidence graphs for the outcomes for which we have the most data, namely recurrence, lack of histologic clearance, and lack of clinical clearance. Results are given in Table B.

The RCTs included patients and lesions that are typically encountered in clinical practice, but the lack of information on treatment effect heterogeneity with respect to patient-level factors limits extrapolation to individual patients. No RCT focused on patients who were immunocompromised or had substantially limited life expectancy.

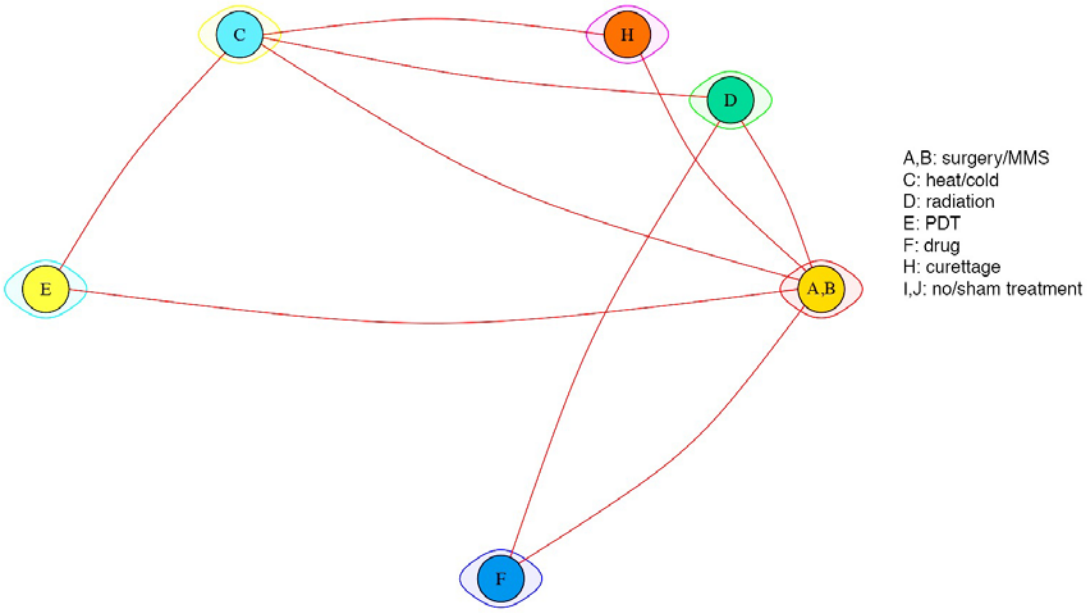
Figure B. Evidence graph depicting compared treatments in RCTs of BCC lesions



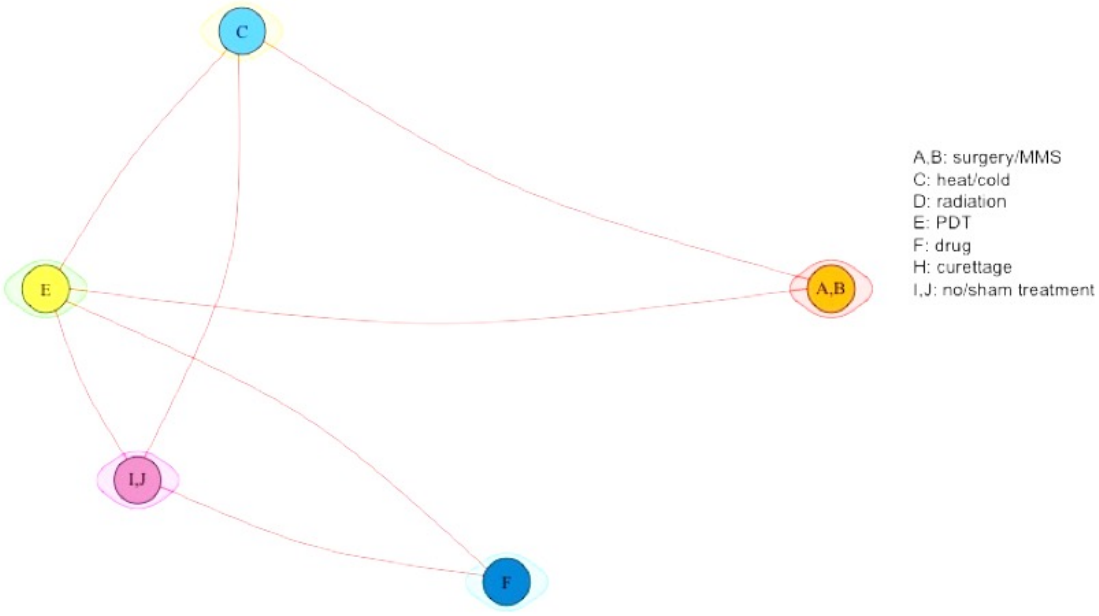
MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil, INF = interferon

Figure C. Evidence graphs for recurrence, histologic clearance, and clinical clearance from RCTs of BCC lesions

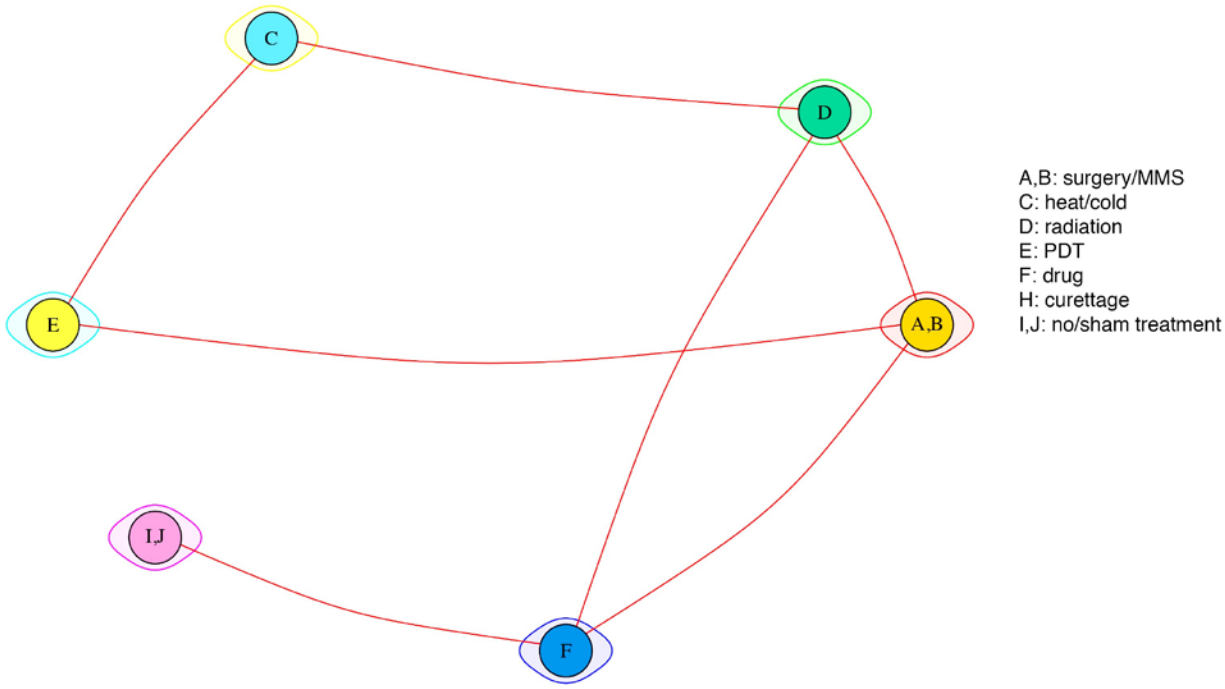
(A) Recurrence



(B) Lack of histologic clearance



(C) Lack of clinical clearance



MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Table B. Mean frequency (percent) of outcomes per intervention category based on direct and indirect data (all BCCs)

Intervention Type	Recurrence (95% CI)	Lack of Histologic Clearance (95% CI)	Lack of Clinical Clearance (95% CI)	Cosmetic Outcomes: Patient Reported (95% CI)	Cosmetic Outcomes: Observer Reported (95% CI)	AEs Leading to Discontinuation (95% CI)	Serious AEs (95% CI)	AEs: Pain (95% CI)	AEs: Infection (95% CI)
Surgery/ MMS (A,B)	3.4 (1.5, 7.6)	1.2 (0.1, 15.9)	3.0 (0.8, 10.7)	88.8 (73.7, 95.7)	55.0 (34.7, 73.8)	Not defined*	0.6 (0.2, 2.4)	21.5 (8.1, 46.2)	5.5 (2.8, 10.7)
Heat/cold (C)	21.2 (14.0, 30.7)	24.9 (8.2, 55.0)	11.9 (4.2, 29.1)	60.5 (32.4, 83.0)	74.3 (51.5, 88.8)	0.9 (0.0, 20.1)	2.6 (0.2, 31.0)	12.9 (0.8, 73.1)	NA
Radiation (D)	4.4 (1.7, 10.5)		4.7 (0.8, 23.4)	79.1 (55.2, 92.1)	25.5 (7.1, 60.7)				
PDT (E)	21.1 (14.0, 31.3)	19.5 (6.4, 46.4)	14.7 (6.1, 31.3)	97.9 (93.1, 99.4)	88.7 (78.9, 94.2)	Not defined*	0.7 (0.2, 2.7)	20.7 (8.2, 43.3)	0.5 (0.1, 2.4)
Drugs (F)	3.1 (0.2, 39.0)	35.6 (16.5, 60.8)	16.6 (5.3, 41.6)	94.2 (37.5, 99.8)	76.3 (52.8, 90.2)	4.9 (2.0, 11.6)	3.6 (2.0, 6.5)	9.9 (4.4, 20.9)	0.5 (0.1, 3.7)
Curettage (H)	20.0 (5.4, 51.9)								
No/sham treatment (I,J)		83.5 (65.5, 93.1)	84.2 (50.6, 96.5)		89.8 (40.1, 99.1)	1.0 (0.2, 4.4)	2.4 (0.3, 15.2)	2.9 (0.9, 9.4)	NA

Note: Black cells indicate interventions that have no data for that outcome.

AE = adverse event; MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma; NA = not applicable; CI = confidence interval

* Surgical interventions and PDT are one-time therapies that cannot be "discontinued". For parsimony of exposition, however, in the descriptive analyses in the Table we assigned 0 discontinuation to these interventions.

Recurrence

In total, 13 RCTs (1664 lesions) were included in this analysis, and cumulative sample sizes per comparison ranged from 27 to 355.

For parsimony of exposition, we only list predicted mean frequencies of events with each intervention category across the included RCTs, based on their estimated relative effects in network meta-analysis (Table B). (For more results, including by specific intervention and for subgroups, refer to the full report.)

Lack of Histological Clearance

In total, 15 RCTs (1940 lesions) were included in this analysis, and cumulative sample sizes per comparison ranged from 44 to 1196. Table B shows the mean fraction of lesions without histologic clearance across the included RCTs. (For more results, refer to the full report.)

Lack of Clinical Clearance

In total, 14 RCTs (1734 lesions) were included in this analysis, and cumulative sample sizes per comparison ranged from 27 to 420. For each intervention category, Table B shows the mean fraction of lesions without clinical clearance across the included RCTs. (For more results, refer to the full report.) In general, the mean fractions for lack of histologic clearance for individual

interventions are in congruence with the corresponding fractions estimated for intervention categories.

Patient-Reported Cosmetic Outcomes, All BCC Lesions

In total, seven RCTs (752 lesions) were included in this analysis. In Table B drugs and photodynamic therapy (PDT) are associated with highest percentages of good cosmetic outcomes, followed by surgical treatments, radiation, and interventions that use heat or cold to destroy the lesion. (For detailed results, refer to the full report.)

Observer-Reported Cosmetic Outcomes, All BCC Lesions

In total, 10 RCTs (1460 lesions) were included in this analysis. Table B shows that the percentage of lesions with good or better cosmetic outcomes ranged between 74.3 and 89.8 percent for interventions that destroy the lesion with heat or cold (C), drugs (F), PDT (E) and no or sham treatment (I,J), and was 55.0 percent for surgical treatments (A,B). Radiation (D) had the smallest percentage of good or better cosmetic outcome. However, the confidence intervals for these proportions are wide, so we could not draw any strong conclusions.

Adverse Events, All BCC Lesions

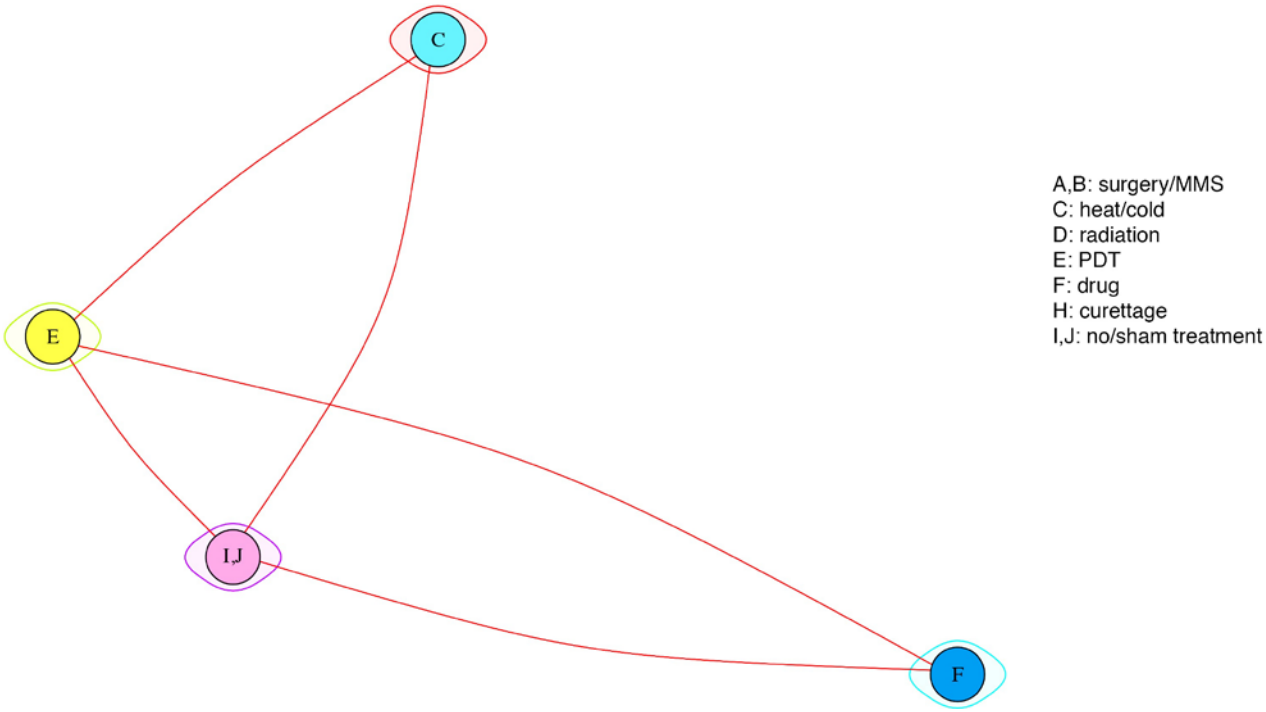
In Table B drugs were most likely to have adverse events leading to discontinuation (4.9%; 95% CI, 2.0 to 20.1); other interventions types had a much smaller percentage (1.2%). The number of adverse events characterized as “serious” by the investigators was smaller than 3.6 percent for all intervention categories. Pain after treatment was most commonly encountered for surgical interventions (21.5%) and for PDT (20.7%). Infections at the treatment site were described in 5.5 percent of lesions with surgical treatments (95% CI 28 to 10.7) and were reported in less than 1 percent for PDT and drugs. No information on infections was available for treatments that destroy lesions with heat or cold or for no (or sham) treatment.

Squamous Cell Carcinoma

The evidence graphs in Figures D and E depict eight comparisons between 10 interventions organized in four intervention categories, none of which are in the surgical or radiation category. Most RCTs included only participants with SCC in situ (SCCIS); one included participants with microinvasive SCC. It is not included in this analysis, but is summarized in the full report. Information on each comparison is provided by at most three RCTs, and for most comparisons, by a single RCT.

Figure E shows the corresponding evidence graphs for the outcomes for which we have the most data, namely recurrence and lack of clinical clearance. Evidence on other outcomes (quality of life, cosmetic outcomes, costs or resource use) is even sparser and is given in the full report. Results are given in Table C.

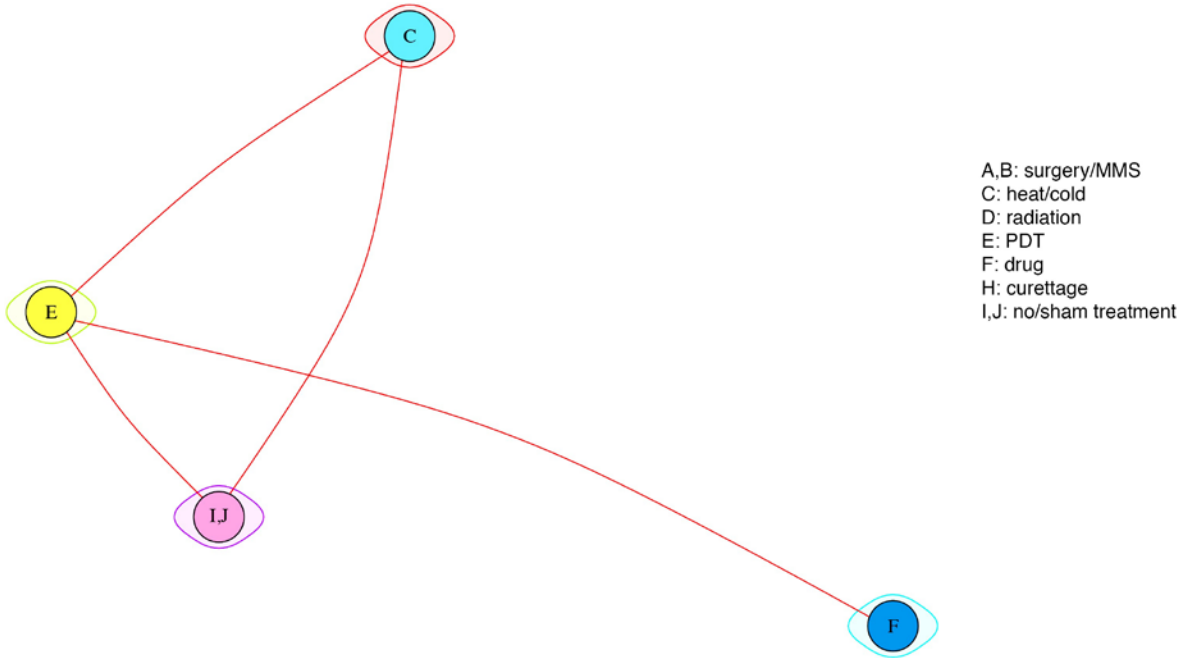
Figure D. Evidence graph depicting compared interventions in RCTs of SCC lesions



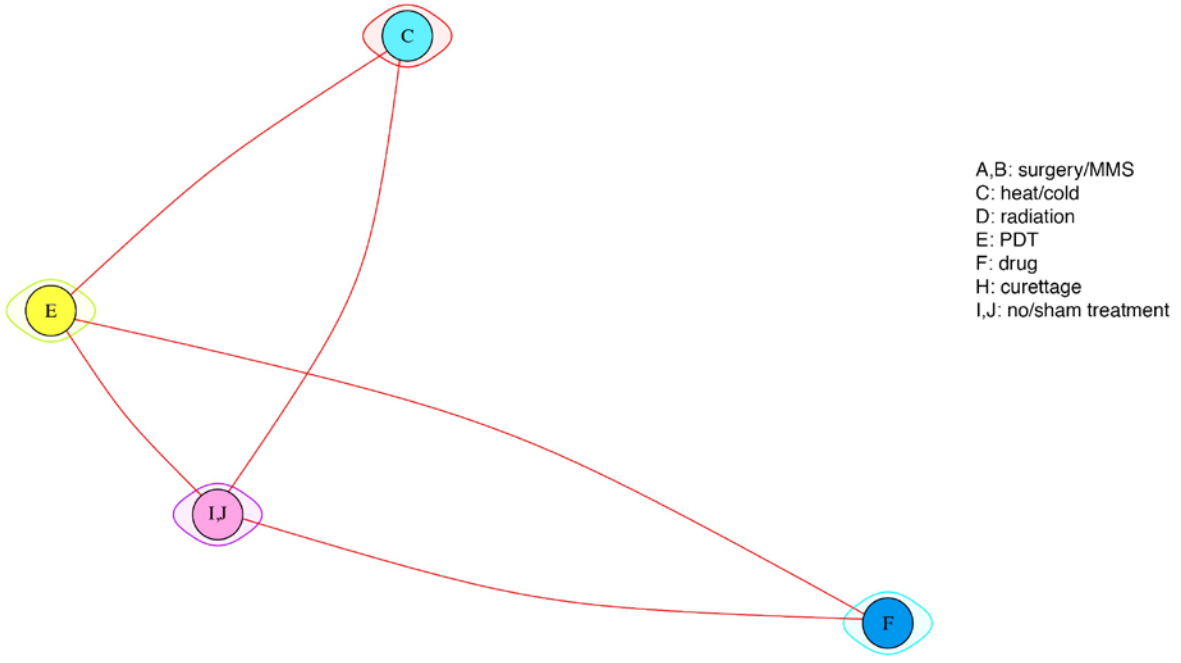
MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Figure E. Evidence graphs for recurrence, histologic clearance, and clinical clearance for RCTs of SCC lesions

(A) Recurrence



(B) Lack of clinical clearance



MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Table C. Mean frequency of outcomes per intervention category based on direct and indirect data (SCCIS)

Treatment type	Recurrence Rates (95% CI)	Lack of Clinical Clearance (95% CI)	Adverse Events Leading to Discontinuation (95% CI)	Serious Adverse Events (95% CI)	Adverse Events: Pain After Treatment (95% CI)	Adverse Events: Infection (95% CI)
Heat/ cold (C)	15.1 (8.1, 26.5)	10.8 (3.1, 31.3)	1.9 (0.6, 6.4)	0.9 (0.1, 6.1)	34.1 (20.0, 51.6)	0 (0, 31)
PDT (E)	17.7 (10.8, 27.8)	14.9 (5.4, 34.9)	Not defined*	0.5 (0.0, 7.7)	23.4 (12.4, 39.5)	0 (0, 31)
Drugs (F)	51.5 (28.9, 73.5)	29.2 (8.4, 65.1)	13.3 (3.4, 40.5)	NA	NA	NA
No/ sham treatment (I,J)	50.0 (11.2, 88.8)	88.0 (54.2, 97.8)	4.7 (0.9, 20.1)	0 (0, 32.2)	28.4 (9.7, 59.3)	NA

AE= adverse event; PDT=photodynamic therapy; SCCIS=squamous cell carcinoma in situ; NA=not applicable. CI=confidence interval.

*PDT is a one time interventions that cannot be "discontinued"; for parsimony of exposition, however, in the descriptive analyses in the Table we assigned 0 discontinuation events to PDT.

Recurrence

In Table C interventions that destroy the lesion with heat or cold (C) and PDT (E) had on average lower recurrence rates (15.1 and 17.7 percent, respectively) compared to drugs or no/sham treatment. Of note, the average recurrence rate with drugs is 51.5 percent (95% CI 28.9 to 73.5), reflecting the high recurrence rates observed in the single RCT comparing 5-FU with PDT (ALA).

Lack of Histological Clearance

Data were very sparse (2 RCTs, 50 lesions), and results are not summarized here. Refer to the full report.

Lack of Clinical Clearance

In Table C the fraction of lesions without clinical clearance was between 10.8 and 29.2 percent in the active treatments and 88 percent with placebo, which is similar to the results by individual comparisons. However, the confidence intervals for each estimate are wide.

Patient-Reported Cosmetic Outcomes, All SCC Lesions

We did not identify any studies with results for this outcome in this population.

Observer-Reported Cosmetic Outcomes, All SCC Lesions

Data were very sparse (2 RCTs, 204 lesions), and results are not summarized here. Refer to the full report.

Adverse Events, All SCCIS Lesions

In Table C the highest mean frequency of adverse events leading to treatment discontinuation (3 RCTs; 292 participants) was 13.3 percent (95% CI, 3.4 to 40.5) for drugs (F); it was less than 1.2 percent for other intervention categories. The frequency of adverse events characterized as "serious" by the investigators (1 RCT; 225 participants) was smaller than 1 percent for all intervention categories. In the two RCTs that reported pain after treatment, between 23.4 and

34.1 percent reported pain regardless of treatment (including sham treatments). The outcome of infection at the treatment site was reported in a single RCT (36 participants) at 0 percent.

Discussion

Within the existing evidence, with respect to BCC recurrence, surgical treatments and radiation therapy appear to be (statistically significantly) better than interventions that destroy lesions with heat or cold, PDT, or curettage. However, PDT was associated with improved cosmetic outcomes. With regards to drugs for the treatment of BCC, recurrence rates with imiquimod were not significantly different than with surgical excision in a single large RCT. Given that lack of recurrence is, essentially, cure from disease, these results support the effectiveness of surgical and radiation treatment for low-risk BCC. Full details in Tables D and E.

We acknowledge that the clinical applicability of some of these results is limited. The comparisons between intervention categories are not as informative as comparisons between individual interventions. We have provided analyses at the individual intervention level, but opt not to draw conclusions based on them, because most are based on indirect data and small numbers. In addition, the analyses cannot adequately account for heterogeneity of the populations in included studies, particularly for low-risk BCCs, because, although the RCTs had comparable populations (see Tables 3-6 of the full report), many did not stratify their results by histologic subtype (superficial or nodular) or location. Thus, we were unable to incorporate these important factors into the analyses. For example, radiation (because of its expense and poor cosmetic outcomes) is rarely used in routine clinical practice to treat low-risk BCC; its use is generally limited to patients with high risk or recurrent disease or for patients with contraindications to surgery. However, the four RCTs that included radiation arms did not differ significantly in population from the other studies included in the low-risk BCC network, with the exception that they included a larger percentage of lesions in high-risk (face, eyelids) areas. Conversely, use of topical drugs is generally limited to primary, superficial tumors. Therefore, comparisons of the efficacy of radiation and drugs for the low-risk BCCs included in our study may not be relevant in the clinical decision making for most patients and clinicians. That said, the analysis contains an RCT that looks at the direct comparison of radiation and imiquimod in a high-risk location (eyelids), so it might be that they are more relevant for low-risk lesions in high-risk locations.[14]

For SCCIS, the use of cryotherapy and PDT is supported over topical 5-fluorouracil with regards to recurrence. However, how these treatments perform for SCCIS compared with surgical treatments, which are commonly used in clinical practice, is not ascertainable based on the currently available evidence.

For patients and clinicians, though, cure is not the only important endpoint. All of the treatments under study are associated with benefits and drawbacks that patients and clinicians consider routinely. For example, while external beam radiation therapy is effective, its remote sequelae, such as skin atrophy and the development of secondary tumors, make it less advisable for younger patients. For patients for whom cosmesis is a primary concern, treatment with PDT may be preferable despite its higher recurrence rates. Despite sparse evidence on their ability to cure BCC and SCCIS, some patients may prefer the convenience provided by topical medical treatments such as 5-fluorouracil and imiquimod, which can be applied by the patient at home; this contrasts with the multiple visits to hospitals or specialty clinics required for radiation therapy which are not be practical for some patients. Access to treatments will also impact

clinical decisionmaking. Specialty care is not available in all communities; while primary care physicians can perform basic surgical procedures and prescribe topical medications, they do not have access to specialized treatments, such as Mohs micrographic surgery (MMS), radiotherapy, and PDT.

Perhaps the most striking observation is the dearth of information that is available comparing interventions for these very common cancers. For example, only 13 RCTs (1664 lesions) examining BCC recurrence were included, of which 20 lesions were treated with curettage. Further, the amount of evidence in the 10 comparisons with head to head data was limited: the number of RCTs per comparison ranged between 1 and 3, and the cumulative number of lesions ranged between 27 and 347. The small sample sizes of these RCTs adds to concerns about the generalizability of our results to the treatment of all cutaneous BCC and SCC.

For SCC, data on recurrence are even sparser. For SCCIS, only 4 RCTs (348 lesions) compared 4 types of interventions, namely a drug (imiquimod), interventions that destroy lesions with heat or cold, PDT, and sham treatments. Surgical interventions and curettage, therapies commonly used for SCCIS in clinical practice, were not examined.

Only one RCT evaluated treatments for invasive SCC, the subgroup of SCC that are most likely to recur or metastasize, and thus most important to evaluate.[15] In clinical practice, these lesions are routinely treated with surgical excision with or without intraoperative margin evaluation, and in most cases are considered appropriate for Mohs surgery in the American Academy of Dermatology appropriate use criteria.[16] Radiation is also used for invasive SCC. The lack of evidence comparing efficacy among these commonly used treatments is striking.

Adjuvant radiotherapy and new drugs (including epidermal growth factor receptor inhibitors, such as cetuximab and erlotinib) that may be used as adjuvant treatment in the case of positive margins postexcision or in the case of advanced disease were not within the scope of this review but also have utility in treating BCC and SCC lesions.

With few exceptions and for most outcomes, individual studies were deemed to have at most moderate risk of confounding, selection, or measurement biases. The risk of bias of individual studies was not a major determinant for the conclusions in the tables. By far the major concern is that the evidence is sparse when one considers the richness of the clinical questions that can be posed, including questions that may have important health and cost implications for insurers and patients. For example, there are no studies on the effectiveness of external radiation therapy delivered with portable machines in the office setting versus radiation therapy delivered in specialized facilities or other interventions. Empirical data on this radiation therapy modality would be useful because there are only limited data on radiation therapy to extrapolate from.

Other large gaps remain in the knowledge base: There is no information on subgroups of patients who have limited life expectancy, are frail, or who are immunocompromised (e.g., have chronic lymphocytic leukemia and other malignancies, immunodeficiency disorders, or who receive immunomodulating or immunosuppressive treatments). There is limited or no information on high risk BCC lesions, and on invasive SCCs. There is limited data on patient- and lesion-specific modifiers of intervention effects.

Finally, outcomes such as histological clearance and clinical clearance are surrogates for lesion recurrence. In particular, clinical clearance may help physicians choose among PDT, medical, and radiation-based therapies, but is not an informative outcome for surgical interventions: any surgical treatment, regardless of margin control, removes all clinically visible tumor. Therefore, our conclusion in Table D that surgical interventions are better than all other interventions with respect to clinical clearance, while very likely to be true, is almost

meaningless. Adverse events were inconsistently reported. For analysis, they were grouped based on study author's definitions, which may have led to some misclassification.

Evidence Gaps

We have identified a number of important gaps in the medical literature on the topic of treating BCC and SCC. First, more trials are needed comparing commonly used treatment modalities such as simple excision, Mohs surgery, PDT and topical medical therapy. Further, in order to justify routine use of various forms of radiotherapy for these patients, more trials comparing radiotherapy with other modalities are needed in select populations for whom radiotherapy may be appropriate.

Second, all trials for BCC and SCC should, where possible, use recurrent disease as a primary or secondary outcome, as in our opinion it is the most clinically important outcome. Trials should also attempt to incorporate measures of health care resource utilization, which were lacking in our review of the existing evidence save for one RCT and one NRCS.[17, 18] Future trials would also benefit from standardization and consistent definition of all outcomes, particularly adverse events and patient-reported outcomes such as cosmesis. To this end, we encourage the development of a core outcome set as is being done for other skin diseases such as psoriasis (The International Dermatology Outcome Measures)[19] and atopic dermatitis (Harmonizing Outcome Measures for Eczema).[20]

Third, while more evidence is needed overall, future research should also focus on specific subgroups that have minimal evidence to date. Aggressive histologic subtypes of BCC, including infiltrative and sclerosing patterns, account for very little of the evidence found in our review. No comparative evidence was found on keratinocyte carcinomas in high-risk groups such as organ transplant recipients and patients with other altered immune states. Patients with limited life-expectancy are another subgroup of interest.

Fourth, better monitoring of population trends in BCCs and SCCs can help focus research on the most consequential subtypes. Such monitoring can be performed by the Surveillance, Epidemiology, and End Results (SEER) Program (which currently ignores these cancers), the Centers for Disease Control and Prevention (CDC), or large health organizations. While the volume of these tumors makes surveillance logistically difficult and costly, advances in health information technology and big data analytic techniques should make it more feasible.[21]

Given how common these tumors are and their burden on the health care system, research funding directed to determine the most effective and cost-effective measures for these tumors is needed. It is incumbent on funding agencies and health care payers to fund research examining important questions in this field. Patients, clinicians, payers, and research funders would benefit from a decision analysis of the management of BCC and SCC lesions.

Conclusions

Based on sparse evidence, surgical, radiation and topical drug treatments have lower recurrence rates than other modalities for the treatment of low-risk BCC, and PDT appears to have superior cosmetic outcomes. Large gaps remain in the literature regarding the comparison of individual interventions, and very little or no information on immunocompromised patients, patients with limited life expectancy, and on patients with specific lesion categories, including high risk BCCs and invasive SCCs. In order for clinicians, patients and payers to make informed decisions regarding the treatment of these lesions, new RCT or high-quality NRCS evidence is needed.

Table D. Summary conclusions for BCC lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, all BCC						
(1) Surgical interventions (A,B) and radiation (D) were associated with lower recurrence rates than interventions that destroy lesions with heat or cold (C), and PDT (E) (moderate to high strength of evidence) (2) Curettage (H) may have higher recurrence rates than surgical interventions (A,B) or radiation (D) (3) Imiquimod (F) was associated with recurrence rates that were not significantly different than that of surgical interventions (A,B) (4) [Imprecise data on the comparison on curettage and interventions that destroy lesions with heat or cold (C) or PDT (E)]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) Moderate to High (2) Low (3) Low (4) [Insufficient]	• Surgery/MMS (A,B) had significantly fewer recurrences than heat/cold, PDT, and curettage; not significantly fewer than radiation; and not significantly more than drugs (7 RCTs; 2 NRCSs) • Heat/cold (C) interventions had significantly more recurrences than surgery and radiation; not significantly more than drugs and curettage, and not significantly fewer than PDT (7 RCTs) • Radiation (D) had significantly fewer recurrences than thermal interventions and PDT, not significantly fewer than curettage, and not significantly more than surgery and drugs (3 RCTs) • PDT (E) had significantly more recurrences than radiation and surgery, and not significantly more than heat/cold, drugs, and curettage (6 RCTs, 1 NRCS) • Imiquimod (F) had more recurrences than surgery, but not significantly so (1 RCT) • Curettage (H) had significantly more recurrences than surgery, not significantly more recurrences than drugs and radiation, and not significantly fewer recurrences than PDT and heat/cold (2 RCTs)
Histologic clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better histological clearance outcomes and were statistically significantly better than interventions that destroy lesions with heat or cold (C), PDT (E), drugs (F), and placebo (I,J). (2) Interventions that destroy lesions with heat or cold (C), PDT (E), and drugs (F) have better histological outcomes than placebo (I,J) (3) [imprecise data on the relative comparisons of nonsurgical active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed significantly better than heat/cold, drugs, and placebo, and nonsignificantly better than PDT (2 RCTs) • Thermal interventions (C) performed significantly better than placebo, nonsignificantly better than drugs, nonsignificantly worse than PDT, and significantly worse than surgery (2 RCTs) • PDT (E) performed significantly better than placebo, nonsignificantly better than drugs and heat/cold, and nonsignificantly worse than surgery (7 RCTs, 1 NRCS) • Drugs (F) performed significantly better than placebo, nonsignificantly worse than PDT and heat/cold, and significantly worse than surgery (8 RCTs, 2 (NRCSs)
Clinical clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better clinical clearance outcomes than PDT (E), drugs (F) and placebo (I,J) (2) All active treatments were associated with better clinical clearance outcomes than placebo (3) [Imprecise data on relative comparisons between nonsurgical active treatments]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed statistically significantly better than drugs and placebo, and nonsignificantly better than heat/cold and PDT (4 RCTs); this comparison is less relevant as surgery ought to achieve 100% clinical clearance • Thermal interventions (C)performed statistically significantly better than plecebo, nonsignificantly better than drugs and PDT, and nonsignificantly worse than surgery (3 RCTs) • PDT (E) performed statistically significantly better than placebo, nonsignificantly better than drugs, and nonsignificantly worse than surgery and heat/cold (7 RCTs) • Drugs (F) performed statistically significantly better than placebo,

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
						nonsignificantly worse than PDT and heat/cold, and significantly worse than surgery (5 RCTs)
Patient-reported cosmetic outcomes, all BCC						
(1) PDT is associated with better cosmetic outcomes than other intervention categories (2) [Imprecise data on relative comparisons between nonsurgical active intervention categories]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Low (2) Insufficient	• (A,B) Surgery had significantly better outcomes than heat/cold and radiation, significantly worse outcomes than PDT, and nonsignificantly worse outcomes than drugs (4 RCTs) • Thermal interventions (C)had significantly worse outcomes than surgery and PDT and nonsignificantly worse than radiation and drugs (2 RCTs) • Radiation (D) had nonsignificantly better outcomes than heat/cold, nonsignificantly worse outcomes than drugs, and significantly worse outcomes than PDT and surgery (2 RCTs) • PDT (E) had significantly better outcomes than surgery, heat/cold, and radiation and nonsignificantly better outcomes than drugs (4 RCTs) • Drugs (F) had better outcomes than surgery, heat/cold, and radiation, and nonsignificantly worse outcomes than PDT, but not statistically significantly so (1 RCT)
Observer-reported cosmetic outcomes, all BCC						
(1) PDT is associated with significantly better cosmetic outcomes than surgery (A,B) (2) [PDT may be associated with better cosmetic outcomes compared to nonsurgical active intervention categories] (3) [Imprecise data on relative comparisons between heat/cold (C), radiation, and drugs (D)]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) [Insufficient] (3) [Insufficient]	• (A,B) Surgery had nonsignificantly better outcomes than radiation, significantly worse outcomes than PDT, and nonsignificantly worse outcomes than drugs, heat/cold, and placebo (4 RCTs, 1 NRCS) • (C) Heat/cold interventions had significantly better outcomes than radiation, nonsignificantly better outcomes than surgery, and nonsignificantly worse outcomes than PDT, drugs, and placebo (1 RCT) • Radiation (D) had significantly worse outcomes than heat/cold, PDT, drugs, and placebo, and nonsignificantly worse outcomes than surgery (1 RCT, 2 NRCS) • PDT (E) had significantly better outcomes than surgery and radiation, nonsignificantly better outcomes than drugs and heat/cold, and nonsignificantly worse outcomes than placebo (7 RCTs, 1 NRCS) • Drugs (F) had significantly better outcomes than radiation, nonsignificantly better outcomes than surgery and heat/cold, and nonsignificantly worse outcomes than PDT and placebo (1 RCT)
Adverse effects, all BCC						
(1) Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with surgical interventions (A,B), heat or cold (C), PDT (E) and drugs (F) (2) For the interventions above, on average, 1 in 10 to 1 in 5 patients report experiencing pain after treatment	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events have wide 95%	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) Low	• For active interventions, the percentage of discontinuation of treatment, serious adverse events, and infection of the treatment site ranged from 0/not defined to 5.5%. Forecast CIs are wide (as high as 29%) • For active interventions, the percentage of pain after treatment ranged between 9.9 and 21.6%. Forecast CIs are wide (as high as 88%)

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
			CIs			
Other outcomes, all BCC						
[Evidence on quality of life, mental health, patient satisfaction, mortality, cost and resource use is reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

Note: When a summary conclusion cannot be made, the description is given in square brackets.

RoB = risk of bias; BCC = basal cell carcinoma; SCC = squamous cell carcinoma; MMS = Mohs micrographic surgery; PDT = photodynamic therapy; RCT = randomized controlled trial; NRCS = nonrandomized comparative study; CI = confidence interval

Table E. Summary conclusions for SCCIS lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, SCCIS						
(1) Interventions that destroy the lesions with heat or cold (C) and PDT (E) were associated with lower recurrence rates than 5 FU (F) (2) [Imprecise data on the relative effect of thermal interventions versus PDT]	Moderate	Possibly consistent (No robust indications of inconsistency)	Moderately precise. Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) Low (2) [Insufficient]	• Thermal interventions (C)had statistically significantly fewer recurrences than drugs, and not significantly fewer than PDT or placebo (2 RCTs) • PDT (E) had statistically significantly fewer recurrences than drugs, but not statistically significantly fewer than placebo or more than heat/cold (4 RCTs) • Drugs (F) had statistically significantly more recurrences than heat/cold and PDT, and not significantly more than placebo (1 RCT)
Histologic clearance, SCCIS						
(1) [Laser (C5) + PDT with ALA (E2) results in better histologic clearance over laser alone] (2) 5-FU (F) results in better histologic clearance than placebo (I,J)	(1) Low (2) High	[Not rated]	(1) Imprecise (2) Precise	(1) Direct (2) Direct	(1) [Insufficient] (2) Low	[2 RCTs, 50 patients.]
Clinical clearance, SCCIS						
(1) Examined types of active interventions (heat/cold [C], PDT (E), and drugs [5-FU, imiquimod; F]) were associated with better clinical outcomes than placebo (2) [Imprecise data on relative comparisons between types of active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) High (2) [Insufficient]	• Thermal interventions (C)performed significantly better than placebo, and nonsignificantly better than drugs and PDT (4 RCTs) • PDT (E) performed significantly better than placebo, nonsignificantly better than drugs, and nonsignificantly worse than heat/cold (5 RCT) • Drugs (F) (5-FU, imiquimod) performed significantly better than placebo, and nonsignificantly worse than PDT and heat/cold (2 RCT)
Observer-reported cosmetic outcomes, SCCIS						
(1) Cryotherapy plus 5-FU (C1+F1) is associated with better outcomes than PDT (MAL) (E1) (2) [No difference between laser pretreatment of the lesion before PDT versus PDT alone]	Low	Unclear (Consistency cannot be rated)	(1) Precise (2) Imprecise	Mix of direct and indirect data	(1) Moderate (2) [Insufficient]	[2 RCTs, 204 patients.]
Adverse effects, SSCIS						
(1) [Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with heat or cold (C), PDT (E) and drugs (F)] (2) [On average, 1 in 4 and 1 in 3 patients report experiencing pain after treatment with PDT (E) and heat or cold (C),	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events	Mix of direct and indirect data (most comparisons based on indirect data)	(1) [Insufficient] (2) [Insufficient]	[3 RCTs 292 patients.]

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
respectively]			have wide 95% CIs			
Other outcomes, SCCIS						
[Evidence on patient-reported cosmetic outcomes, quality of life, mental health, patient satisfaction, mortality, cost and resource use id reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

Note: When a summary conclusion cannot be made, the description is given in square brackets.

RoB = risk of bias; BCC = basal cell carcinoma; SCCIS = squamous cell carcinoma in situ; MMS = Mohs micrographic surgery; PDT = photodynamic therapy; RCT = randomized controlled trial; NRCS = nonrandomized comparative study; CI = confidence interval

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Introduction

Background

Skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies in the United States.[1] BCC and SCC, the 2 most common skin cancers, are collectively referred to as keratinocyte carcinomas. Over 5.4 million of these cancers are diagnosed in 3.3 million people in the United States annually,[2, 3] and the global burden of disease from keratinocyte carcinomas is estimated at 12.9 disability-adjusted life years per 100,000 persons.[4] Generally keratinocyte carcinomas are not aggressive and do not metastasize or kill as often as melanoma, which is the third most common skin cancer.[5] However, SCC can metastasize and is estimated to kill between 3900 and 8800 people in the United States each year.[6] Aggressive behavior is of particular concern in people who are immunosuppressed, including organ transplant recipients whose mortality is increased after being diagnosed with SCC.[7] A more common problem is that basal and squamous cell carcinomas and their treatment may result in disfigurement or disability, which can adversely impact quality of life.[3] The recent Surgeon General's call to action to prevent skin cancer at the population level emphasizes the public health importance of dealing with keratinocyte carcinomas.[8] Because of their frequency, BCC and SCC are the fifth most expensive cancer at the population level, and, being more common in older adults, their management is of great importance to Medicare.[2, 3, 9] It is estimated that in 2012 over 2 million Medicare beneficiaries underwent intervention for BCC or SCC.[2]

There are many potential management strategies for keratinocyte carcinoma, and they can be broadly grouped into eight main categories: (1) surgical excision without intraoperative evaluation of the margins, (2) surgical excision with intraoperative evaluation of the margins, (3) destruction via temperature gradients, (4) ionizing radiation, (5) photodynamic interventions, (6) medical therapies, along with (7) combinations of these therapies, and (8) watchful waiting. Surgical management is used most commonly, followed by radiation.[10-12] In individuals over 65, surgery is used to treat 61 percent of keratinocyte carcinomas (excision 42% and Mohs micrographic surgery 19%) followed by electrodessication and curettage (39%).[13] Specific surgical techniques include simple surgical excision with prespecified margins, surgery with intra-operative margin control (e.g. Mohs micrographic surgery or excision with examination of frozen sections), and curettage, which is usually combined with secondary destruction using electrodessication.[14] Cryotherapy with liquid nitrogen is another destructive method. Ionizing radiation modalities include traditional external beam radiation as well as brachytherapy, in which radioactive implants are placed directly in the tumor. Topical medical treatments include topical chemotherapy (such as 5-fluorouracil) and topical immunomodulatory medications (such as imiquimod). Photodynamic therapy involves application of a topical photosensitizer (such as 5-aminoleveulinic acid (ALA) and methyl-ALA) followed by exposure to specific wavelengths of light to destroy tumor cells. New targeted systemic agents, such as vismodegib, for BCC[15] are also available, but are reserved for advanced or metastatic cases and are used much less commonly than the modalities listed above. Additionally, active nonintervention (watchful waiting) has recently been advanced as a therapeutic strategy, particularly for patients with decreased life expectancy.[16, 17]

The choice of management strategy for an individual patient with a specific keratinocyte carcinoma is complex. Factors that are important include patient factors (e.g. age, frailty,

immunosuppression, and personal preference) and tumor factors (e.g. histologic subtype, size, and location). A lack of clarity regarding the comparative efficacy and safety of the available options overall and in specific circumstances further complicates the choice of treatment for both physicians and patients.

There is general agreement that surgical removal is the gold standard. However, despite several dozen randomized controlled trials (RCTs) and nonrandomized comparative studies (NRCS), it is not clear how various surgical techniques and other therapeutic options perform relative to each other (e.g., see references[18-23]). None of the over 30 systematic reviews and meta-analyses (e.g., see references[24-31]) on this topic to date includes all treatment modalities for both BCC and SCC. The Australian and Finnish clinical practice guidelines for keratinocyte carcinoma management allude to the difficulty in interpreting the existing evidence-base, which comprises comparisons among pairs of several available treatments.[32, 33] Furthermore, existing guidance is not based on systematic assessments of the evidence. It is hoped that the information in this review will be useful in the development of future guidelines, such as the guidelines on keratinocyte carcinomas from the American Academy of Dermatology, anticipated later in 2016.

Interventions for treating skin cancers differ substantially in cost and have a huge economic impact.[3, 9, 34, 35] Payers are faced with increased utilization of costly therapies, such as brachytherapy, without clear evidence for relative benefits to justify increased costs.[36]

Estimates of keratinocyte carcinoma treatments' comparative effectiveness and safety with respect to patient-relevant outcomes are needed to inform clinical decisionmaking and payer coverage decisions. The objective of this systematic review is to comprehensively collect and synthesize information on the comparative effectiveness and safety of each of the above-mentioned therapeutic strategies for both BCC and SCC.

Key Questions

The review addresses two Key Questions for adult patients with basal cell or squamous cell carcinoma of the skin. Each Key Question will be answered separately for SCC and BCC:

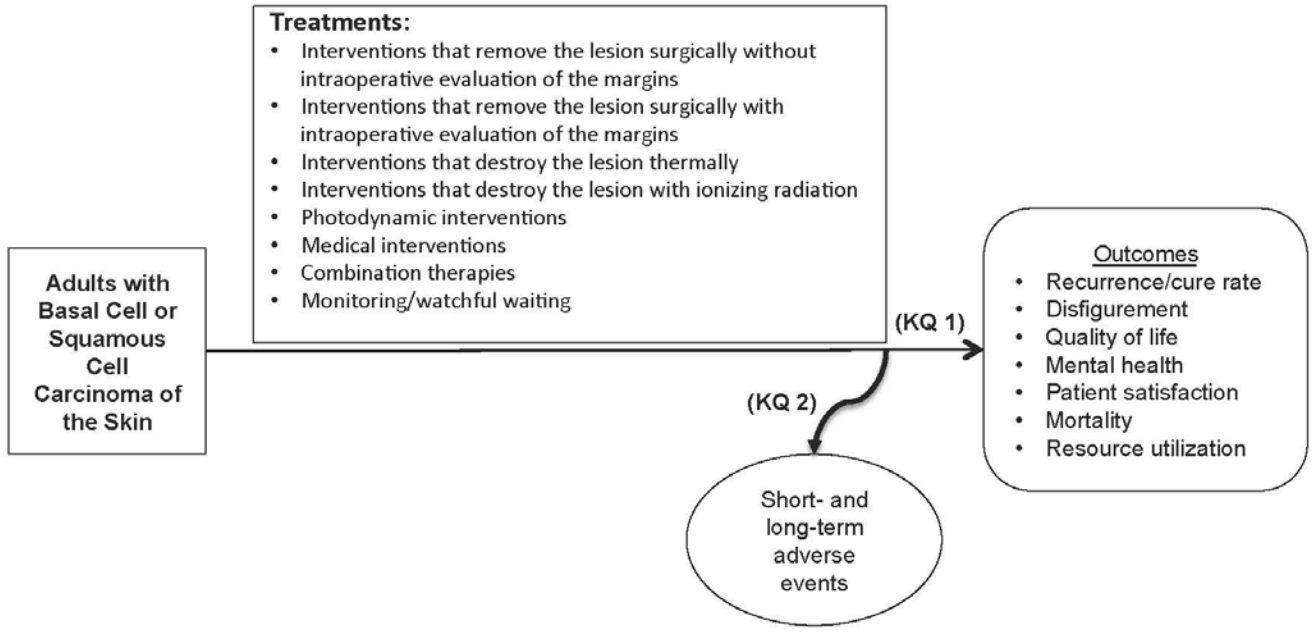
Key Question 1: What is the comparative effectiveness of various interventions, overall and in subgroups of interest?

Key Question 2: How do the adverse events associated with the various interventions compare overall and in subgroups of interest?

Analytic Framework

The analytic framework in Figure 1 depicts the chain of logic that evidence must support to link the studied interventions.

Figure 1. Analytic framework for treatments for basal cell and squamous cell carcinoma of the skin



Methods

The Brown Evidence-based Practice Center (EPC) conducted this review based on a systematic review of the published scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[37] The Prospero registration number is CRD42016043353.

Eligibility Criteria

We use the population, intervention, comparator, outcomes, and designs (PICOTS) formalism to define the characteristics of the eligible studies for this review.

Population

The population of interest is people with primary squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). This specifically excludes recurrent or metastatic disease. If populations were mixed, we included studies with at least 80 percent primary, nonmetastatic BCC or SCC. We excluded studies of recurrent or metastatic cancers in which it was not clear whether the advanced lesions were less than 20 percent of the total lesions studied.

We were also interested in the following specific subpopulations: (1) people who are immunocompromised, including those who have had a solid organ or bone marrow transplant, human immunodeficiency virus (HIV), chemotherapy, Chronic Lymphocytic Leukemia (CLL) or other leukemias and lymphomas, or other iatrogenic; (2) people with a limited life expectancy (e.g., the very elderly, those with terminal cancer, those with end stage renal disease). We have excluded subpopulations based on rare genetic factors (e.g., basal-cell nevus syndrome and xeroderma pigmentosa).

In addition, we were interested in the effects of treatments in subgroups as defined by location (e.g. face, hands, trunk, or extremities) and grade of lesion (e.g. superficial or nodular BCC or SCC in situ [Bowen's Disease] in SCC).

Interventions

The interventions of interest are organized into intervention categories (A through J):

A. Surgical excision without intraoperative evaluation of the margins
B. Surgical excision with intraoperative evaluation of the margins
    Mohs micrographically controlled surgery
    Surgery with examination of frozen sections
C. Interventions that destroy the lesion via temperature gradients
    (C1) Cryotherapy
    (C2) Diathermy/electrodesiccation
    (C3) Curettage of the lesion plus diathermy (cauterization) of margins
    (C4) Curettage of the lesion plus cryotherapy
    (C5) CO_2 laser therapy
D. Interventions that destroy the lesion with ionizing radiation

(D1) External beam radiation with photons (X or gamma rays), electrons (beta rays), or positively charged particles (e.g., protons, helium nuclei/alpha rays), at orthovoltage or megavoltage energies, or using in-office radiation machines
(D2) Brachytherapy with superficial application or interstitial application (pleisiotherapy) of radiation sources (usually emitting beta or alpha rays)

E. Photodynamic interventions
(E1) 5-aminolevulinic acid (ALA) + blue light
(E2) Methyl aminolevulinate (MAL) + red light
(E3) Other forms of PDT

F. Medical interventions
(F1) 5-fluorouracil (5-FU)
(F2) Imiquimod
(F3) Interferon (IFN alpha-2a/2b or INF beta)
(F4) Ingenol mebutate
(F5) Other medical interventions, including BEC-5 cream, Bleomycin, Methotrexate, Diclofenac, and Hedgehog inhibitors (Vismodegib, Sonidegib)

G. Shave excision
H. Curettage without diathermy
I. Placebo
J. No treatment

Outcomes

We evaluated the outcomes in the following list. We did not use strict *a priori* definitions of the outcomes, but included all reported outcomes as defined by study researchers. We evaluated outcomes at any and all time points given in a specific study. We used our best judgment to categorize outcomes when studies failed to clearly define their reported outcomes.

- Recurrence/cure rate (as defined in studies)
- Disfigurement/cosmetic outcome
- Quality of Life (only if they use validated instruments to measure – e.g. Short Form Health Survey-36, Skindex, Skin Cancer Index, Skin Cancer Quality of Life Impact Tool)
- Mental health, anxiety, depression, intrusive thoughts (only if they use validated instruments to measure – e.g. State-Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, Impact of Event Scale)
- Patient satisfaction with treatment (only if they use validated instruments to measure – e.g. Patient Satisfaction Questionnaire-18, Skin Cancer Index patient satisfaction subscale)
- Mortality
- Adverse events, including those that are reported by patients and clinically, as well as actively and passively. Both short-term (e.g. pain, skin irritation) and long-term (e.g. radiation exposure, scarring) adverse events were recorded. We systematically reviewed the following endpoints: “any serious adverse event” (leading to treatment discontinuation, or as defined by each study), “pain” and “infection”. We enumerated the set of other reported events.

Design

We evaluated all randomized controlled studies and all comparative nonrandomized controlled studies. We excluded studies enrolling fewer than 10 people total because they were unlikely to yield precise or broadly applicable conclusions. We excluded non-English studies, as there were very few of them and there is empirical evidence that excluding them typically has minimal impact on conclusions.[38] Studies in any setting were acceptable.

As described by Linos et al.,[17] patient treatment is often determined by factors, such as disease stage, medical history, age and education, that could confound assessment of the outcomes of interest. Thus for the nonrandomized comparative studies (NRCSs), we required that studies included an analysis that accounted for confounders, such as inclusion in a multivariate model, balancing or quasi-randomization, or clearly matched groups. NRCSs that report only crude results were identified and tabulated but were excluded from the analysis in the full report.

Evidence Identification

We conducted literature searches of studies in PubMed, the Cochrane Central Trials Registry, the Cochrane Database of Systematic Reviews, and Embase to identify primary research studies meeting our criteria through March 8, 2017. These databases should adequately cover the published literature on this topic. The full search strategy for all databases is in Appendix A. We screened all references in published clinical practice guidelines, relevant narrative and systematic reviews, and Scientific Information Packages from manufacturers or other stakeholders. We searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) for ongoing studies and studies that are not published in the medical literature. In addition, we searched the Food and Drug Administration drugs and devices portals for unpublished data. We did not find any studies with results that were not included in the published literature. Our requests to manufacturers for scientific information packets also did not yield any new data. We have extracted and incorporated all studies de novo and have not summarized or incorporated existing systematic reviews, per se. All articles identified through these sources have been screened for eligibility, using the same criteria as was used for articles identified through literature searches. The search will be updated upon submission of the draft report for peer and public review.

All citations found by literature searches and other sources were independently screened by two researchers. At the start of abstract screening, we implemented a training session, in which all researchers screened the same articles and conflicts were discussed. During title and abstract double-screening, we resolved conflicts as a group. All title and abstract screening was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/).[39] All potentially relevant studies were rescreened in full text with double-screening to ensure eligibility.

Data Extraction and Data Management

Each study has been extracted by one member of the review team, which includes clinicians and methodologists. The extraction was reviewed and confirmed by at least one other experienced methodologist. Any disagreements were resolved by discussion among the team. Data was extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the Key

Questions. Upon completion of the review, the SRDR database will be made accessible to the general public (with capacity to read, download, and comment on data). The basic elements and design of the extraction form are the similar to those used for other AHRQ comparative effectiveness reviews and include elements that address population characteristics, including method of diagnosis; descriptions of the interventions, exposures, and comparators analyzed; outcome definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias questions. If information was stratified by carcinoma subtype for BCC (e.g. superficial or nodular) and SCC (e.g. SCC in situ, well-differentiated, or poorly differentiated), we recorded that information as well.

Assessment of Methodological Risk of Bias of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[40] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used relevant questions from the Newcastle Ottawa Scale.[41] For RCTs, the review team discussed each article, based on methodological (design and analysis) items that are related to the aforementioned biases for each outcome of each trial. To obtain information on (a lower bound of) the number of yet unpublished trials, we searched clinicaltrials.gov for completed trials, and examined the publication status of thus identified studies.

Data Synthesis

All included studies were summarized in narrative form and in summary tables that include the important features of the study populations, design, intervention, outcomes, and results. Lesions were divided by subtype (superficial, nodular, or high-risk BCC, SCC, or mixed populations) for analysis to ensure that the treatments would be most comparable. Where possible, lesions were also evaluated by size and location. Trial arms with fewer than 5 lesions were not included in the analysis, because they contribute minimal information, and in some instances, necessitated adding model parameters that were difficult to estimate.

We conducted pairwise and network meta-analyses with mixed effects (random intercepts and fixed intervention slopes) or full-random effects (random intercepts and random slopes) multilevel models within the generalized linear and latent mixed models. We used the normal approximation to discrete likelihoods with a canonical (logit) link function. Treatment effect estimates from such models are odds ratios. We fit models by maximizing the restricted likelihood. We explored clinical and methodological heterogeneity in subgroup analyses. We did not conduct dose-response meta-analyses because there was substantial heterogeneity in the definitions of intervention intensity (dose) across studies; instead, we summarized dose-response results qualitatively. To aid the interpretation of these analyses we also present model-based estimates for the mean frequency of an outcome in the examined interventions, as well as forecasts of the frequency of the outcome in a new setting (e.g., a new study, or in a population) that is similar to the studies in the meta-analysis. The forecasts' point estimate about the frequency of the outcome is very close to the point estimate of the mean frequency of the outcome over the meta-analyzed studies. However, the 95% confidence interval (CI) for a forecast of the frequency of an outcome in a new setting accounts for between-study

heterogeneity, and will, thus, be broader than the corresponding 95% CI for the mean frequency of the outcome across the analyzed studies. See the next paragraph about the presentation of results. Inconsistency was assessed by comparing the fit of models that do not assume consistent intervention effects versus typical network meta-analysis models, that assume consistent treatment effects. Analyses did not identify statistical evidence of inconsistency. Because such analyses are known to be underpowered, we also compared qualitatively the agreement of estimates based only on direct data versus of estimates based on both direct and indirect data. Such estimates were deemed to be congruent.

Presentation of Results

We present results with plots and tables. We briefly describe three expository formats that are not commonly used in EPC reports, namely, evidence graphs, league tables, and relative effects tables.

Evidence Graphs

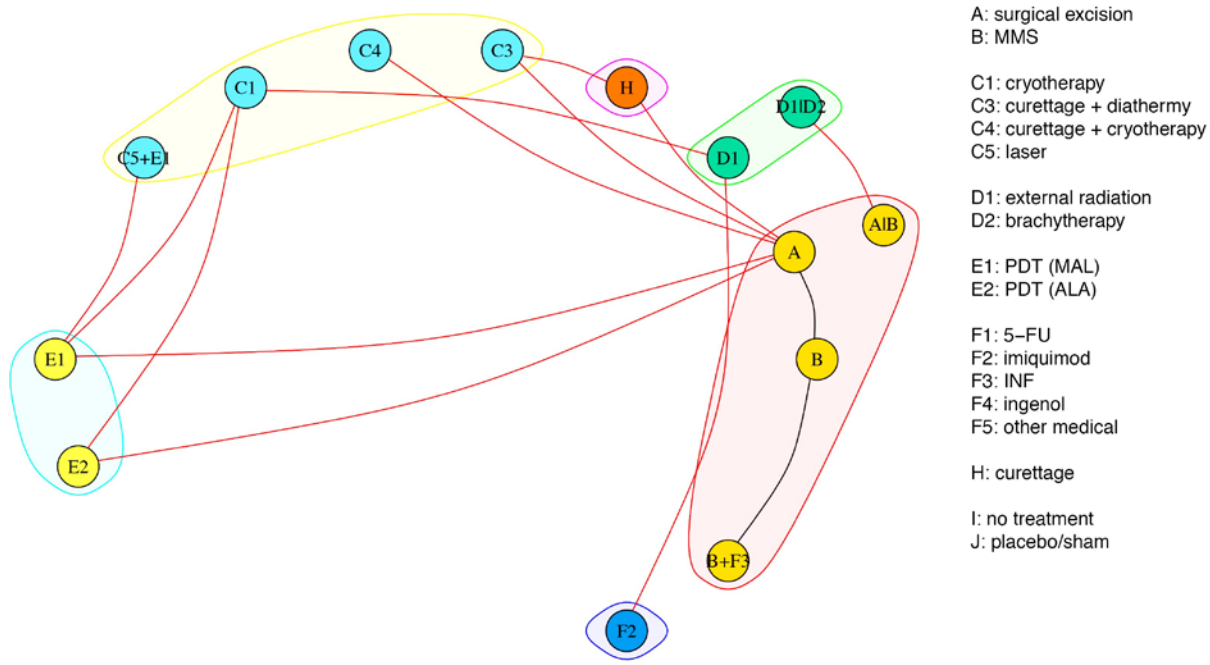
We use evidence graphs such as the one in Figure 2 to describe which interventions have been compared with others. An evidence graph comprises nodes, which represent interventions, and edges (depicted by a line linking nodes). Edges connect a pair of nodes only if the corresponding interventions have been compared in at least one head-to-head study. In Figure 2, nodes for interventions from the same intervention category are in a shaded area. For example, nodes E1 (corresponding to PDT with MAL) and E2 (corresponding to PDT with ALA) are within the same shaded area which represents PDT as the type of intervention), and analogously for other nodes and interventions in the figure. The organization of interventions in intervention categories has been described in the Interventions paragraph. We use the term *connected subgraph* to describe a set of nodes that are connected through one or more edges. For example, Figure 2 has 2 connected subgraphs, which include the following nodes:

1. A|B, D1|D2, and
2. all remaining nodes in the evidence graph, namely A, B, A|B, B+F3, D1, F2, H, C3, C4, C1, C5+E1, E1, and E2.

If all the nodes in the graph were connected, then there would be a single connected subgraph—which would be the whole graph. Identifying connected subgraphs is important, because we do not statistically compare interventions that belong to different connected subgraphs.

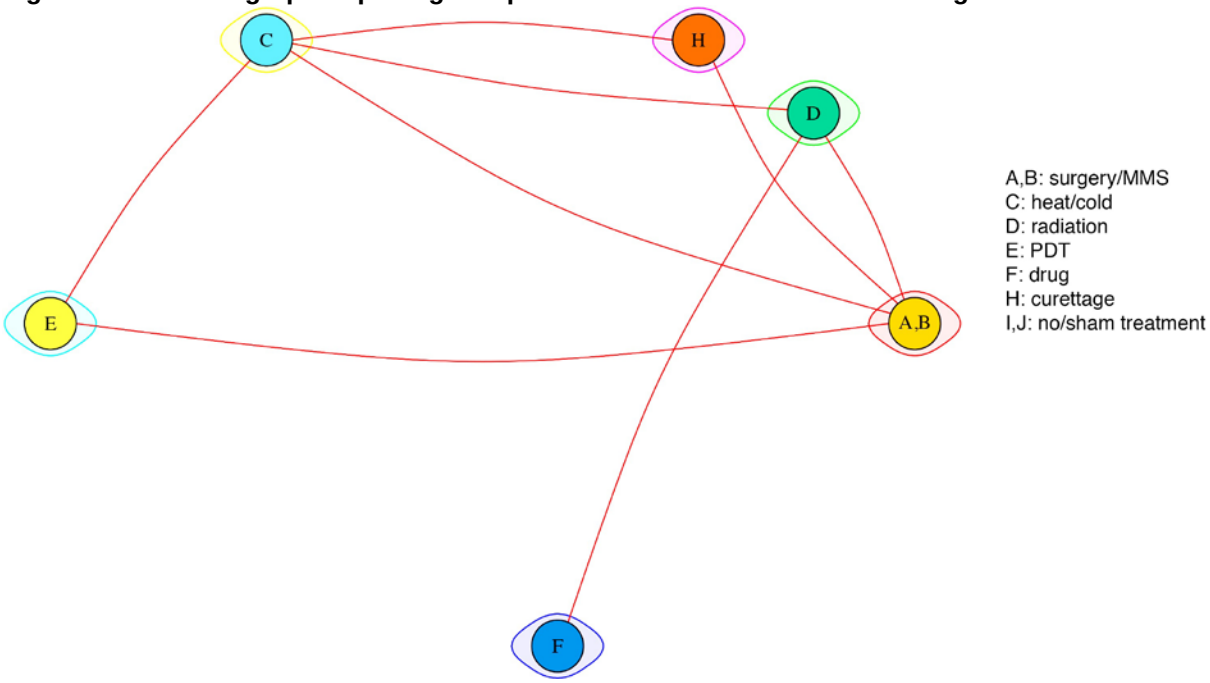
Figure 3 is an analogous representation of the comparisons between intervention categories for the same network of interventions depicted in Figure 2. When one considers intervention categories, comparisons between interventions that belong to the same type are not pertinent. Such comparisons are represented by edges enclosed in the shaded areas in the evidence graph in Figure 2. Observe also that comparing between intervention categories happened to result in a single connected subgraph in Figure 3.

Figure 2. Example evidence graph depicting comparisons between individual interventions



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

Figure 3. Evidence graph depicting comparisons between intervention categories



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL= methyl aminolevulinate; FU = fluorouracil; INF = interferon

Relative Effects Tables

Relative effects tables describe odds ratio estimates and 95% CIs for all pairwise comparisons in a connected subgraph. Table 1 is an example; it is the analysis that corresponds to the evidence graph in Figure 3. Each cell has a (row, column) address, and reports the estimated odds ratio between the intervention in the row versus the intervention in the column. Consider the cell in the second row, fourth column: The odds ratio comparing interventions that destroy lesions with heat or cold (with code letter C; the intervention in the row) versus PDT (E; the intervention in the column) was 0.91 (95% CI, 0.43 to 1.95). The cell in the *fourth* row, *second* column is the odds ratio for a comparison between the same interventions but in the other direction: 1.10 (95% CI, 0.51, 2.34) is the odds ratio of PDT (E) versus interventions that destroy the lesion with heat or cold (C). The unshaded cells correspond to comparisons for which there is head-to-head information, i.e., there is an edge between these corresponding nodes in the evidence graph. The estimated treatment effects in these cells are informed by direct and indirect evidence. The shaded cells correspond to comparisons that have not been empirically observed (there is no edge between these corresponding nodes in the evidence graph), and are based only on indirect comparisons.

Table 1. Relative odds ratios for an outcome between intervention categories (Figure 3)

Surgery/MMS (A,B)	*0.13 (0.05, 0.35)*	0.77 (0.22, 2.73)	*0.12 (0.04, 0.32)*	1.09 (0.05, 24.23)	*0.14 (0.03, 0.77)*
7.71 (2.83, 20.98)	Heat/cold (C)	*5.95 (2.03, 17.4)*	0.91 (0.43, 1.95)	8.44 (0.41, 173.75)	1.09 (0.23, 5.16)
1.3 (0.37, 4.59)	*0.17 (0.06, 0.49)*	Radiation (D)	*0.15 (0.05, 0.45)*	1.42 (0.06, 32.2)	0.18 (0.03, 1.04)
8.45 (3.08, 23.16)	1.10 (0.51, 2.34)	*6.52 (2.21, 19.21)*	PDT (E)	9.25 (0.45, 190.91)	1.19 (0.25, 5.68)
0.91 (0.04, 20.24)	0.12 (0.01, 2.44)	0.7 (0.03, 15.99)	0.11 (0.01, 2.23)	Drugs (F)	0.13 (<0.005, 3.56)
7.08 (1.3, 38.49)	0.92 (0.19, 4.35)	5.46 (0.96, 31.02)	0.84 (0.18, 3.99)	7.75 (0.28, 214.11)	Curettage (H)

Note: This example is for analyses of recurrence among patients with BCC lesions. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy

League Tables

League tables such as Table 2, describe the mean fraction of lesions with the outcome of interest for each intervention (or intervention category) over the populations included in the meta-analysis, and the corresponding forecasted fraction in a new setting that is analogous to the settings of the analyzed studies. The results in the league table and the results in the relative effects table are from the same analysis. The league table explains what the relative effects imply about the probability of the outcome under each treatment. In the example, over the meta-analyzed studies the probability of the event with PDT (E) was 23.0 percent (95% CI 14.8 to 33.9) and with interventions that destroy the lesion with heat or cold (C) it was 21.4 percent (95% CI 13.8 to 31.6). The expected frequency of the event in a setting that is analogous to the settings in which the meta-analyzed studies where conducted is shown in the forecast column.

Note that the confidence intervals for the forecast are always larger than the confidence intervals for the mean.

Imagine that you are hiking along a trail from east to west, through six camp sites. The camp sites serve as the analogue for the interventions. A table showing the signed distances[a] between pairs of campsites would be the analogue of the relative effects table. A table showing how far each campsite is from the easternmost end of the trail would be the analogue of the league table.

Table 2. Mean and forecasted event fractions by intervention category

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Surgery/MMS (A,B)	3.4 (1.5, 7.6)	3.4 (1.0, 11.4)
Heat/cold (C)	21.4 (13.8, 31.6)	21.4 (8.3, 45.1)
Radiation (D)	4.4 (1.8, 10.4)	4.4 (1.2, 15.0)
PDT (E)	23.0 (14.8, 33.9)	23.0 (8.9, 47.5)
Drugs (F)	3.1 (0.2, 38.8)	3.1 (0.1, 42.5)
Curettage (H)	20.0 (5.5, 51.9)	20.0 (4.1, 59.1)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; CI = confidence interval

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We graded the strength of the body of evidence as per the AHRQ Methods Guide on assessing the strength of evidence.[37] We assed the strength of evidence for each outcome. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we have assigned a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating are summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating.

We assessed the applicability within and across studies with reference to demographics of enrolled participants (e.g. age and sex distributions), the location and severity of the lesions, and the availability of treatments (e.g. with respect to radiation treatments).

Peer Review

A draft version of this report was reviewed by invited and public reviewers. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports have also been reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

[a]A signed distance encodes the direction of movement and the distance traveled.

Results

Summary of Studies

The literature searches yielded 15813 citations (Figure 4), of which 15278 were excluded in abstract screening. A search of the reference lists of relevant systematic reviews yielded another 85 studies, which brought the total number screened in full text to 534. Appendix A presents the literature search strategies (for each database searched). Appendix B lists the articles that were reviewed in full text that were excluded, with their rejection reasons.

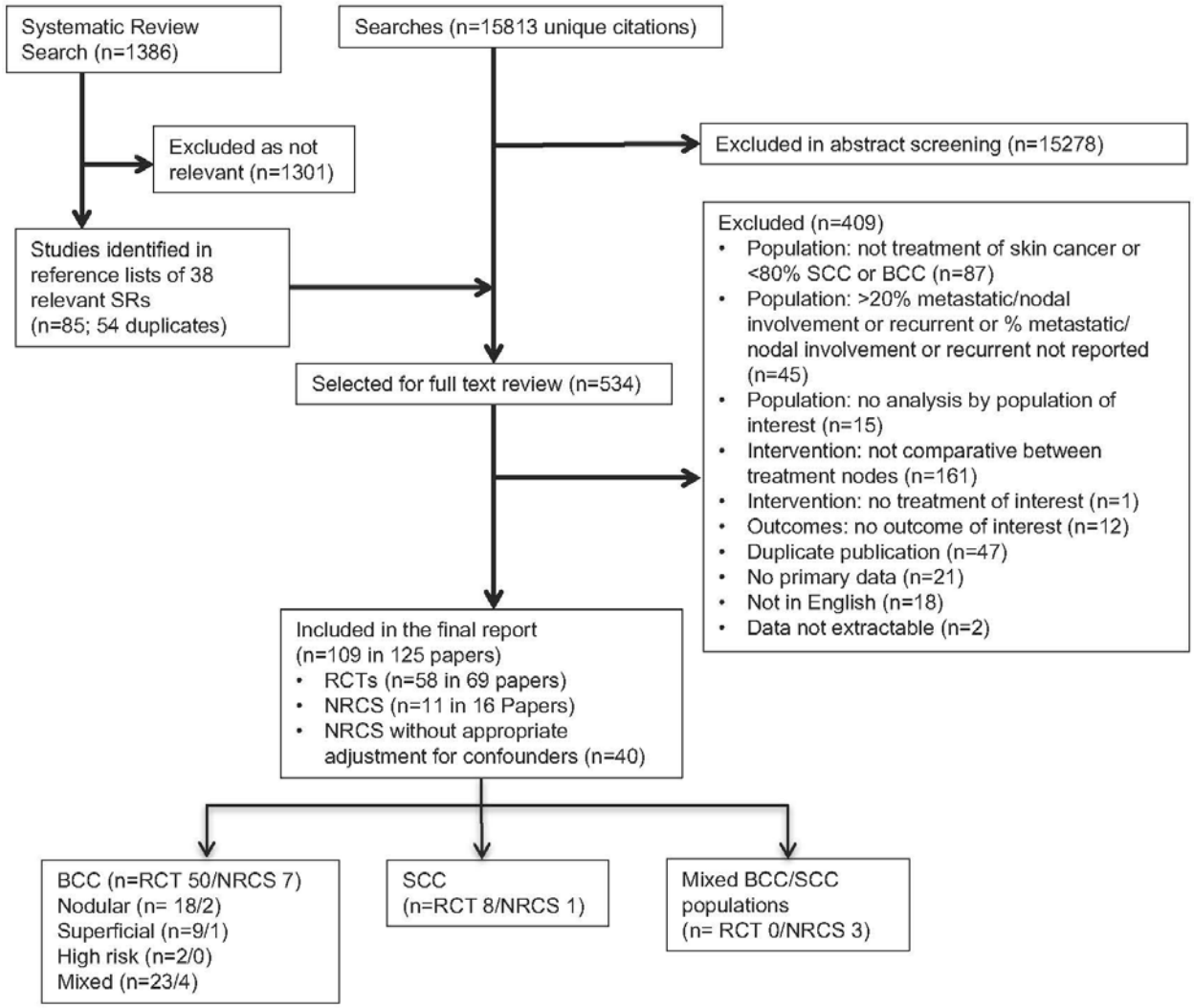
The 109 included studies (described in 125 papers) report 58 randomized controlled trials (RCTs) and 51 nonrandomized comparative studies (NRCSs). Two papers reported the results of two separate trials and were analyzed separately; another seven studies were reported in multiple papers. Among the 58 RCTs in 69 papers,[19, 20, 22, 42-105] 56 were reported in full papers, and two were reported only as conference abstracts.[42, 43, 45, 64]Eighteen reported industry funding[54, 56, 66, 68, 69, 74, 75, 79, 83, 85, 92, 94, 96-98, 100, 104], 5 used materials supplied by industry,[52, 55, 61, 62, 105] 165 explicitly reported no industry support,[19, 42, 49, 51, 53, 57-59, 70, 72, 73, 76, 81, 91, 99, 102] and 19 did not provide funding information [20, 43, 45-48, 50, 63, 64, 67, 71, 80, 82, 89, 90, 93, 101] (Appendix C).

Eleven of the NRCS contained either matched cohorts or adjustments for known confounders, and they were included in the analysis; the remaining 34 have been tabulated in Appendix G[106-140] Of the 11 NRCSs in 15 papers.[141-155] 2 reported industry funding,[143, 153] 6 explicitly reported no industry support,[142, 144-148, 150-152, 155] and 3 did not provide funding information[141, 149, 154] (See Appendix C). Results from NRCSs are presented at the end of each outcome section.

The studies primarily reported on basal cell carcinoma (BCC), with a minority reporting results for squamous cell carcinoma (SCC). Nearly all reported results for recurrence or cure rate outcomes and adverse events, and many reported results for cosmetic outcomes. Few studies reported results using validated instruments for quality of life, mental health, or patient satisfaction with treatment. Details about study design, baselines, and treatments are in Appendix C, D, and E, respectively. Risk of bias assessments are shown in Appendix F.

Because of the wide variety of adverse events reported (see Appendix H for a list of adverse events and how many studies reported each), we have limited the analysis to (1) adverse events that lead to treatment discontinuation, (2) any serious or severe adverse event (as defined by each study), (3) infections of the treatment site, and (4) pain after treatment.

Figure 4. Literature flow diagram



Note: Studies that enrolled both BCC and SCC populations are discussed in the BCC sections, because most enrolled lesions were BCCs.

SR = systematic review; SCC = squamous cell carcinoma; BCC = basal cell carcinoma; RCT = randomized controlled trial; NRCS = nonrandomized comparative study.

Basal Cell Carcinoma

The evidence graph in Figure 5 shows that there are 36 comparisons that have been observed between 29 interventions organized in 7 intervention categories.

This evidence graph suggests that limited conclusions can be drawn about which individual intervention is best (with respect to each outcome) for two reasons: 1) some interventions have never been compared with other interventions, directly or indirectly, and 2) the observed comparisons between individual interventions are relatively sparse.

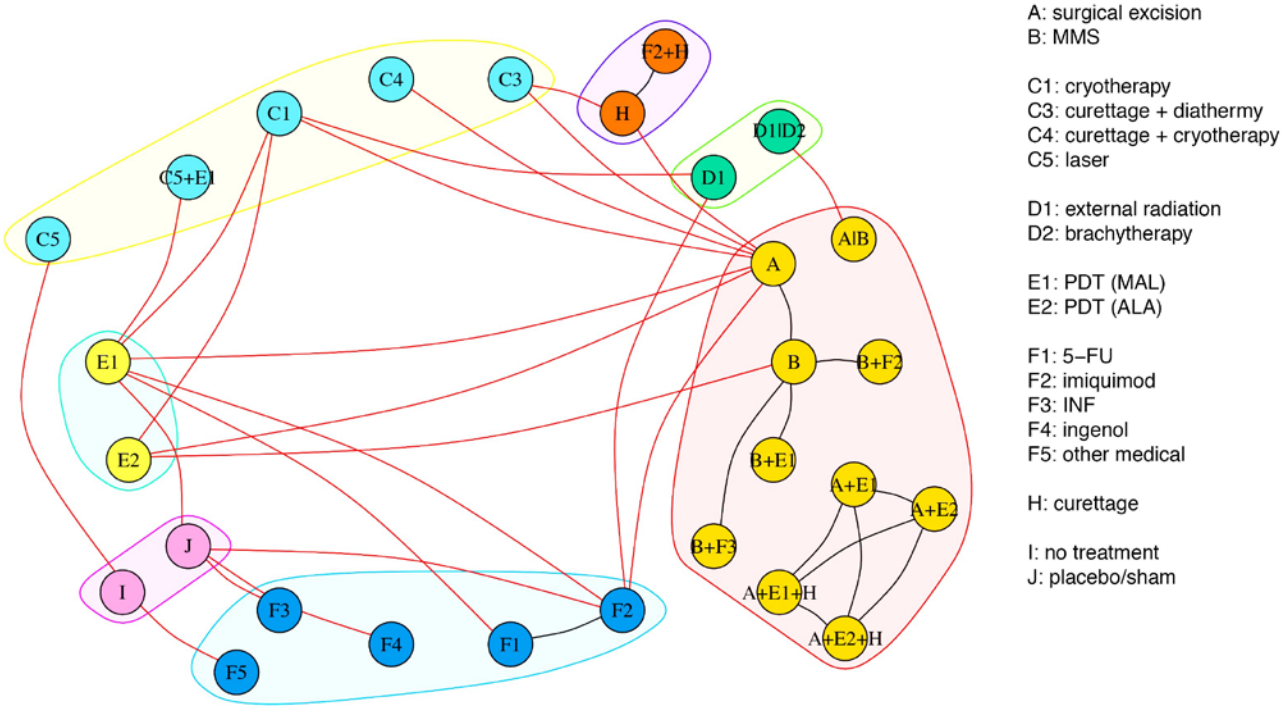
Groups of interventions that have never been compared with other groups are readily identified in the Figure, because they are represented as connected subgraphs. For example, one

connected subgraph comprises radiation therapy (external or brachytherapy, node D1|D2) versus surgery (surgical excision or Mohs micrographic surgery, node A|B). Another connected subgraph comprises laser ablation (C5) versus diclofenac and/or calcitriol (other medication – F5) and versus no treatment (I). Four such subgraphs exist, and no conclusions can be drawn between interventions that belong to different subgraphs.

For individual interventions, the observed comparisons are relatively sparse: there are only 35 observed comparisons in the figure, out of the 378 that are possible among the 28 treatments. Further, information on each comparison is provided by at most three RCTs, and for most comparisons by only a single RCT. The evidence is even more sparse when one considers the information that is actually available for specific outcomes. Figure 6 shows the evidence graphs for the outcomes for which we have the most data, namely recurrence, lack of histologic clearance, and lack of clinical clearance. For these outcomes, no RCT data exist for 14, 8, and 14 of the 29 interventions, respectively. Evidence on other outcomes (quality of life, cosmetic outcomes, and costs or resource use) is even more sparse, as discussed in the following sections.

The evidence remains sparse at the level of individual interventions even after considering results from the seven eligible NRCSs, which are described separately from the RCTs.

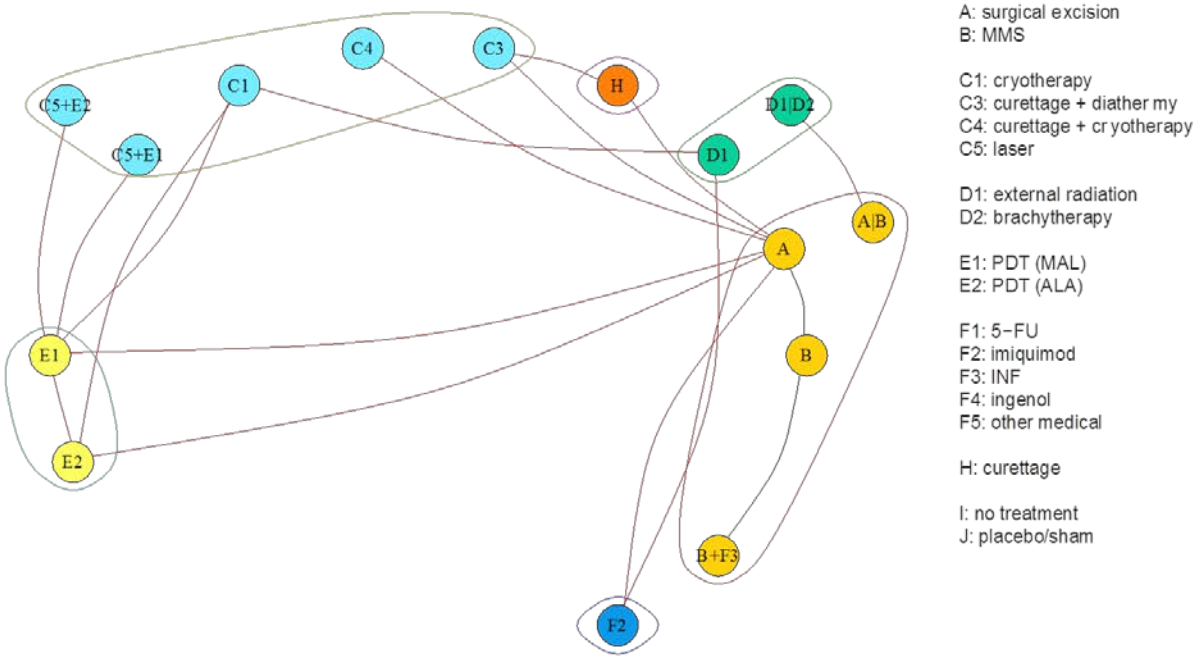
Figure 5. Evidence graph depicting compared treatments in RCTs of BCC lesions



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

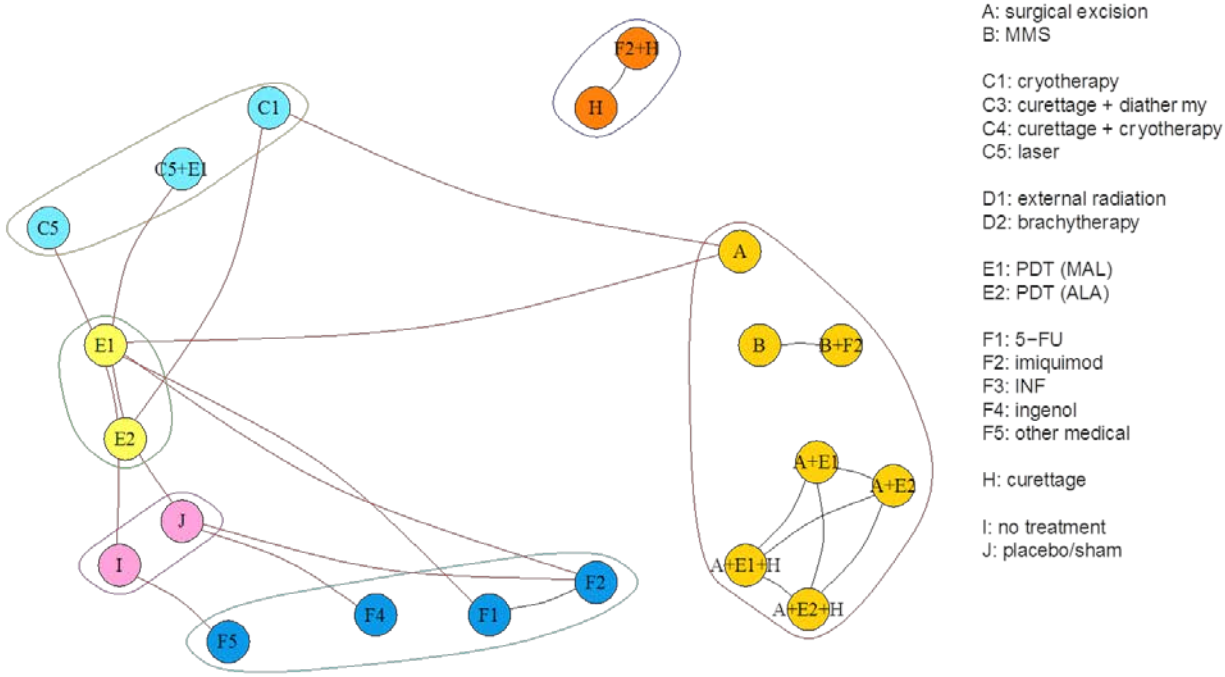
Figure 6. Evidence graphs for recurrence, histologic clearance, and clinical clearance from RCTs of BCC lesions

(A) Recurrence



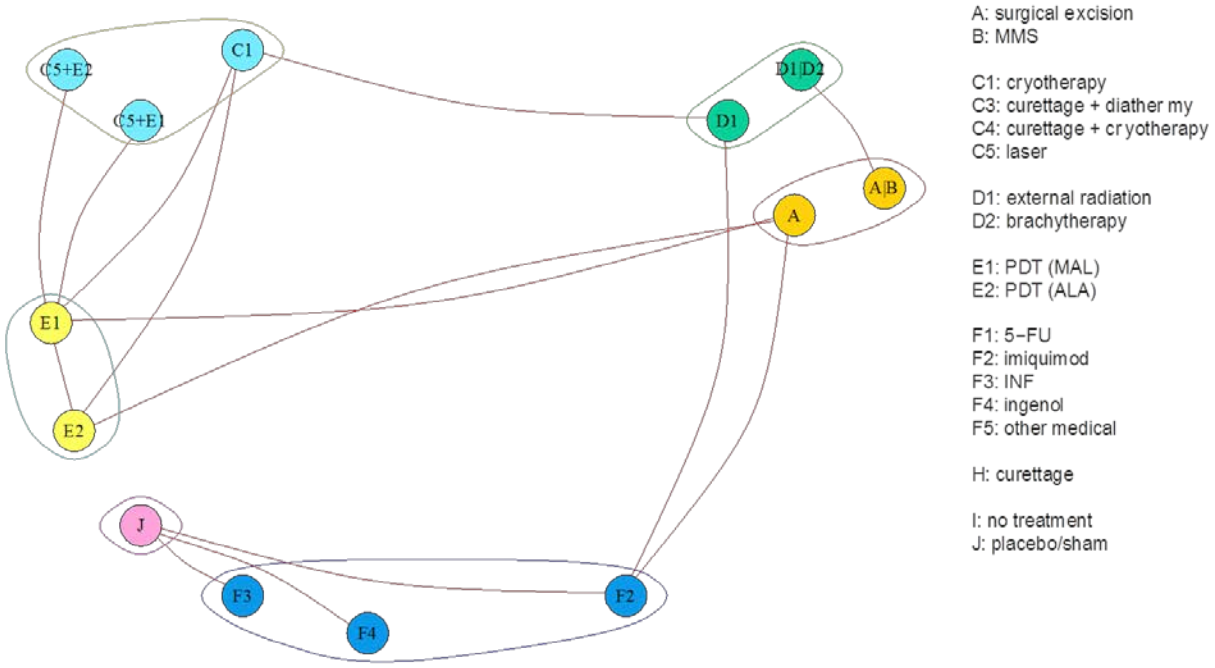
MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL= methyl aminolevulinate; FU = fluorouracil; INF = interferon

(B) Lack of Histologic Clearance



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

(C) Lack of Clinical Clearance



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

The characteristics of the included RCTs are summarized in Tables 3 through 6, for RCTs on superficial (n=9), nodular (n=18), high-risk (n=2), and mixed types (n=21) of BCC lesions. RCTs that report stratified results for different types of lesions are listed in the mixed table.

Across all trials, the mean or median age of enrollees ranged between 55 and 75.3 (median: 64, 25th-75th percentile: 61 to 67). The proportion of female patients ranged between 0 and 75 percent (median: 37, 25th-75th percentile: 30 to 43). When reported, the mean or median lesion area was between 30.1 and 205 mm^2, and the median maximum diameter was between 5.3 and 12 mm. The majority of RCTs included lesions in various body locations, and only a few reported results stratified by lesion location (discussed separately). Based on this information, the RCTs included patients and lesions are typically encountered in clinical practice, but the lack of information on treatment effect heterogeneity with respect to patient-level factors hinders extrapolation to specific patient subgroups. No RCT focused on patients who were immunocompromised or had substantially limited life expectancy.

In terms of design characteristics, 29 RCTs had two arms, 5 had three arms, and 15 had four or more; the latter were primarily phase II studies, examining the tolerability of various doses or schedules of topically applied medications or alternative photodynamic treatment protocols. Such phase II studies are included in the comparisons between interventions only when they include a no intervention or placebo/sham intervention arm. Their findings with respect to different doses or protocols for the same intervention are summarized separately. Analyzed sample sizes ranged between 18 and 694 (median: 70, 25th-75th percentile: 31 to 126.5); sample sizes per RCT arm ranged between 3 and 408.

Based on what was reported in the RCTs, we deemed that the allocation sequence was randomized using formal methods in 26 and successfully concealed in 25 RCTs, and that patients, providers, and outcome assessors were successfully blinded to the received treatments in 19, 13, and 19 RCTs, respectively. Our consensus assessment of the reported baseline characteristics across the compared arms in each RCT was that most RCTs (n=28) had arms that were likely balanced at baseline. In 41 RCTs fewer than 20 percent of patients had missing outcomes for any eligible outcome in any arm.

Table 3. Characteristics of RCTs of superficial BCCs

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Arits 2013 23683751	MAL-PDT	median 63	52	NR	head/neck excluding H-zone (12), extremities (29), trunk (59), upper extremities (16), lower extremities (13)	Yes	Yes	Yes	No	No	Yes	Yes
	Imiquimod	median 62	49	NR	head/neck excluding H-zone (12), extremities (27), trunk (61), upper extremities (13), lower extremities (14)							
	Fluorouracil	median 64	47	NR	head/neck excluding H-zone (15), extremities (24), trunk (60), upper extremities (13), lower extremities (11)							
Basset-Seguin 2008 18693158	MAL-PDT	62	33	NR	face/scalp (6), extremities (22), trunk/neck (72)	No	Yes	Yes	No	No	Unsure	Yes
	Cryotherapy	64	47	NR	face/scalp (4), extremities (20), trunk/neck (76)							
Beutner 1999 10570388	imiquimod 3x/week	NR	NR	NR	upper extremity (25), anterior upper trunk (25), posterior upper trunk (25), neck (25)	No	No	No	Unsure	Yes	Unsure	Yes
Geisse 2002 12196749	Imiquimod 3x/wk	62	NR	median 1.0 cm^2	neck/face/forehead (4), upper extremity (not	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
					hand) (15), trunk (73), lower extremity/thigh (not foot) (8)							
	Imiquimod 5x/wk	55	NR	median 0.6 cm^2	neck/face/forehead (3), upper extremity (not hand) (31), trunk (55), lower extremity/thigh (not foot) (10)							
	Imiquimod 1x/day	56	NR	median 0.7 cm^2	neck/face/forehead (7), upper extremity (not hand) (21), trunk (64), lower extremity/thigh (not foot) (7)							
	Imiquimod 2x/day	69	NR	median 1.0 cm^2	neck/face/forehead (8), upper extremity (not hand) (54), trunk (31), lower extremity/thigh (not foot) (8)							
	vehicle (control)	58	NR	median 0.8 cm^2	neck/face/forehead (9), upper extremity (not hand) (34), trunk (47), lower extremity/thigh (not foot) (9)							
Schleier 2007 25047438	ALA-thermogel PDT	69.9	46.15	NR	face (54.17), scalp (20.83), lip (2.78), eyelid (1.39), extremities (9.72), trunk/neck (11.11)	Yes	No	Yes	Yes	Yes	Yes	Yes
	Methyl-ALA-	71.8	36.36	NR	face (52.5), scalp (30), extremities							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
	thermogel PDT				(5), trunk/neck (12.5)							
Schulze 2005 15888150	imiquimod 5%	64.3	39	NR	cheek (1), forehead (0), extremities (including hand) (20), trunk/neck (70)	Yes	Yes	Yes	Yes	No	Unsure	No
	vehicle	64.5	39	NR	cheek (1), forehead (5), scalp (1), extremities (including hand) (30), trunk/neck (61)							
Siller 2010 20546215	Total (ingenol mebutate vs placebo)	59	27	9 mm	NR	Yes	Yes	Yes	Yes	Yes	Yes	Unsure
Sterry 2002 12452875 (superficial)	Imiquimod (2 days/ week) with occlusion	63	33	median 1.5 cm^2	extremities (29), trunk/neck (71)	Yes	Yes	No	No	No	Unsure	Yes
	Imiquimod (3 days/ week) with occlusion	58	35	median 1.2 cm^2	extremities (31), trunk/neck (69)							
	Imiquimod (2 days/ week)	69	33	median 1.0 cm^2	face (8). extremities (30), trunk/neck (62)							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
	without occlusion											
	Imiquimod (3 days/ week) without occlusion	61	44	median 1.0 cm^2	extremities (32), trunk/neck (64), genitals (4)							
Szeimies 2008 18624836	MAL-PDT	64.5	36.0	12.5 mm	face/scalp (11.1), extremities (28.9), trunk/neck (60)	Yes	Yes	Yes	No	No	No	Yes
	excision	63.1	31.3	12.6 mm	face/scalp (4.5) , extremities (25.0), trunk/neck (70.5)							

BCC = basal cell carcinoma; MMS = Mohs micrographic surgery, PDT = photodynamic therapy; ALA = 5-aminolevulinic acid, MAL = methyl aminolevulinate, FU = fluorouracil; INF = interferon; RCT = randomized controlled trial; NR = not reported; x/wk = times per week

*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm.

Table 4. Characteristics of RCTs of nodular BCC

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomization	2* Allocation Concealment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Abbade 2015	Surgical excision	NR	NR	NR	head and neck (100)	No	No	Yes	No	No	unsure	Yes
	MAL-PDT	NR	NR	NR	head and neck (100)							
Al-Niaimi 2015 26157307	PDT + MMS	61.4	66.7	200 mm^2	face (100)	No	Yes	Yes	No	No	Yes	No
	MMS	62.7	40	201 mm2	face (100)							
Berroeta 2007 17573890	Total (PDT vs. excision)	median 72	NR	NR	NR	Yes	Yes	unsure	No	No	Yes	Yes
Butler 2009 19018814	Vehicle group +MMS	75.3	43.8	30.1 mm2	face (100)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	imiquimod 5% Cream group +MMS	73.3	66.7	33.5 mm2	hands (100)							
Choi 2016 26551044	Er:YAG ablative fractional laser-primed MAL- PDT	NR	55	NR	NR	No	Yes	Yes	Yes	Yes	Yes	Yes
	MAL-PDT	NR	36.8	NR	NR							
Eigentler 2007 17610993	imiquimod 5% 8 weeks	median 65	27	8.2 mm	face (24.4), scalp (2.2), ear (8.9), trunk/neck (4.4), perioral (4.4), periorbital (8.9), nose (42), arm/shoulder	No	No	Unsure	No	unsure	unsure	Yes

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomization	2* Allocation Concealment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
					(4.4)							
	imiquimod 5% 12 weeks	median 63	33	9.6 mm	face (19.6), scalp (2.2), ear (10.9), trunk/neck (8.7), perioral (2.2), periorbital (6.5), nose (37), arm/shoulder (4.4), leg/hip (4.3)							
Foley 2009 20064185	methyl-aminolevulinatePDT	66	28.78	8.8 mm	face/scalp (25), extremities (20), Trunk 32 (43%) Neck 9 (12%)	Yes	Yes	unsure	Yes	Yes	Yes	Yes
	placebo PDT	67	20	9.0 mm	face/scalp (31), extremities (23), Trunk 34 (45%) Neck 1(1%)							
Haak 2015 24903544	MAL PDT	NR	37.5	median 8.5 mm	nose (37), forehead (31), cheek (6), oral area (13), periorbital area (13)	Yes	Yes	Yes	No	No	Yes	Yes
	AFXL MAL PDT	NR	68.8	median 7 mm	nose (56), forehead (19), cheek (13), oral area (6), periorbital area (6)							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomization	2* Allocation Concealment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Kuijpers 2006 16865869	ALA-PDT (total)	68.4	34.9	8.1 mm	forehead/temple+nose/paranasal (36.4), cheek/chin/lips (9.1), ears (9.1), extremities (9.1), trunk/neck (36.4)	Yes	Yes	unsure	No	No	Unsure	No
	MAL-PDT (total)	68.4	34.9	8.4 mm	forehead/temple+nose/paranasal (38.1), cheek/chin/lips (4.8), ears (14.3), extremities (4.8), trunk/neck (38.1)							
	ALA-PDT (debulking subgroup)	68.4	34.9	NR	NR							
	ALA-PDT (no debulking subgroup)	68.4	34.9	NR	NR							
	MAL-PDT (debulking subgroup)	68.4	34.9	NR	NR							
	MAL-PDT (no debulking subgroup)	68.4	34.9	NR	NR							
Kuijpers 2007 17451581	Curettage + Cryosurgery	67	43	5.4 mm	Forehead/temple, Cheek/chin, Periocular (80),	No	No	Yes	Unsure	Unsure	Yes	Yes

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomization	2* Allocation Concealment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
					Lips/mouth (4), Ears/periauricular (8), Neck, chest/back (8)							
	Surgical excision	67	43	5.3 mm	Forehead/temple, Cheek/chin, Periocular (76), Lips/mouth (6), Ears/periauricular (6), Neck, chest/back (12)							
Mosterd 2008 18717680	ALA-PDT	64	48.2	8.9 mm	face (53); "rest of the body" (47%)	Yes	Yes	Yes	Yes	No	No	No
	Surgical excision	65.1	50	9.3 mm	face (51); "rest of the body" (49%)							
Orenberg 1992 1430394	7.5 mg 5-FU	60	5	123.9 mm^2	face (30), extremities (30), trunk/neck (40)	unsure	unsure	No	yes	yes	yes	Yes
	15 mg 5-FU	60	5	76.4 mm^2	face (10), scalp (10), lip (10), ear (30), extremities (10), trunk/neck (30)							
Rhodes 2004 14732655	MAL PDT	69	38	NR	face/scalp (40), extremities (11), trunk/neck (49)	Yes	Yes	No	No	No	No	No
	excision	67	41	NR	face/scalp (58), extremities (9),							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomization	2* Allocation Concealment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
					trunk/neck (29)							
Shumack 2002 12224978 (12 weeks)	vehicle cream	NR	42	median 0.8 cm^2	face (17), trunk/neck (54.2), upper extremity (not hand) (25), lower extremity (not foot) (4)	No	No	No	Yes	unsure	unsure	Yes
	imiquimod 5% cream - Twice daily for 7 days per week	NR	75	median 0.8 cm2	face (25), trunk/neck (75)							
	imiquimod 5% cream - Once daily for 7 days per week	NR	10	median 0.7 cm2	face (29), trunk/neck (33), upper extremity (not hand) (19), lower extremity (not foot) (10)							
	imiquimod 5% cream - Once daily for 5 days per week	NR	35	median 0.7 cm2	face (48), trunk/neck (26), Upper extremity (not hand) (17), lower extremity (not foot) (9)							
	imiquimod 5% cream - Once daily for 3 days per week	NR	30	median 0.7 cm2	face (40), trunk/neck (35), upper extremity (not hand) (20), lower extremity (not foot) (5)							
Shumack 2002 12224978 (6	imiquimod 5% cream - Twice daily	NR	0	median 0.6 cm2	face (100)	Yes	unsure	No	Yes	unsure	unsure	Yes

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomization	2* Allocation Concealment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
weeks)	for 7 days per week											
	imiquimod 5% cream - Once daily for 3 days per week	63	13	median 0.8 cm2	face (28), trunk/neck (11.11), Upper extremity (not hand) (25), lower extremity (not foot) (13)							
	imiquimod 5% cream - Twice daily for 7 days per week	69	13	median 0.8 cm2	face (32), trunk/neck (39), Upper extremity (not hand) (26), lower extremity (not foot) (3)							
	imiquimod 5% cream - Once daily for 7 days per week	66	29	median 0.8 cm2	face (11), trunk/neck (48), Upper extremity (not hand) (26), lower extremity (not foot) (3)							
	imiquimod 5%	NR	40	NR	face (60), ear (10), unspecified other (30)	No	No	Unsure	unsure	unsure	No	Yes
	vehicle	NR	10	NR	face (50), ear (20), unspecified other (30)							
Sterry 2002 12452875 (nodular)	Imiquimod (2 days/wk) with occlusion	66	50	median: 0.6 cm2	Face (10), Scalp (1), extremities (2), trunk/neck (9)	Yes	Yes	Yes	No	No	Unsure	Yes
	Imiquimod (3 days/wk)	66	30	median: 0.7	Face (18), extremities (2),							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomization	2* Allocation Concealment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
	with occlusion			cm2	trunk/neck (3)							
	Imiquimod (2 days/wk) without occlusion	67	24	median : 1.0 cm2	Face (9), extremities (1), trunk/neck (10)							
	Imiquimod (3 days/wk) without occlusion	66	46	median : 0.6 cm^2	Face (11), extremities (5), trunk/neck (8)							
van der Geer 2012 22385074	Imiquimod + MMS	69	37	NR	H-zone (57), nose (23), ear 4 (11), scalp + frontal (23), other regions (cheek, temporal, chin) (43)	Yes	Yes	Yes	No	No	No	Yes
	no treatment + MMS	68	31	median 110 mm^2	H-zone (66), nose (26), ear (17), scalp + frontal (14), other regions (cheek, temporal, chin) (43)							
Wettstein 2013 23566745	Ringer's lactate (control group)	59	26.67	2.5 cm2	nose (46.2), cheek (23.1), frontal (7.7), ear (23.1)	Yes	Unsure	Yes	Yes	Yes	Unsure	Yes
	interferon alpha-2b	59	26.67	3.1 cm2	nose (50), cheek (10), frontal (20), ear (20)							

BCC = basal cell carcinoma; MMS = Mohs micrographic surgery, PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL= methyl aminolevulinate; FU = fluorouracil; INF = interferon; NR = not reported; RCT = randomized controlled trial; x/wk = times per week; AFXL = ablative fractional laser resurfacing

*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm.

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Table 5. Characteristics of RCTs of high-risk BCC lesions

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Alpsoy 1996 8708151	IFN alfa-2a	58.7	53	median 2.05 cm2	eyelid (27), nose (13), zygoma (27), forehead (13), cheek (13), trunk (7)	Yes	Yes	Unsure	Yes	Unsure	Unsure	Unsure
	IFN alfa-2b	63.6	53	median 1.82 cm2	eyelid (20), nose (7), zygoma (20), forehead (20), cheek (27), trunk (7)							
	IFN alfa-2a + IFN alfa-2b	60.3	40	median 1.9 cm2	eyelid (20), nose (13), zygoma (27), forehead (13), cheek (20), trunk (7)							
Migden 2015 25981810	Sonidegib 200	median 67	39	NR	head and neck (100)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Sonidegib 800	median 65	36	NR	head and neck (100)							

NR = not reported; IFN = interferon

*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm.

Table 6. Characteristics of RCTs of mixed types of BCC lesions

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Allen 1979 298425	cryotherapy	NR	NR	NR	NR	Yes	Yes	Unsure	Yes	Unsure	Unsure	Unsure
	radiotherapy	NR	NR	NR	NR							
Alpsoy 1996 8708151	IFN alfa-2a	58.7	53	median 2.05 cm2	eyelid (27), nose (13), zygoma (27), forehead (13), cheek (13), trunk (7)	Unsure	Unsure	Yes	Unsure	Unsure	Unsure	Yes
	IFN alfa-2b	63.6	53	median	eyelid (20),							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
				1.82 cm2	nose (7), zygoma (20), forehead (20), cheek (27), trunk (7)							
	IFN alfa-2a + IFN alfa-2b	60.3	40	median 1.9 cm2	eyelid (20), nose (13), zygoma (27), forehead (13), cheek (20), trunk (7)							
Avril 1997 9218740	surgery	66.5	54	11.1 mm	nose (53), cheek, pre- and retroauricular areas (21), eyelids, internal and external eye angles (19), forehead, temple, between eyebrows 36 (21), chin, cutaneous superior lip 10 (6), ear (3)	No	Yes	Yes	No	No	No	No
	radiotherapy	65.4	46	11.7 mm	nose (28), cheek, pre- and retroauricular areas (24), eyelids, internal and external eye angles (20), forehead, temple, between eyebrows (17), chin, cutaneous superior lip (7),							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
					ear (3)							
Bath-Hextall 2014 24332516	Imiquimod	NR	41	median 12 mm	face (37), trunk (38), neck (6), arm (6), leg (10), other (3)	Yes	Yes	Yes	No	No	Yes	No
	excision	NR	40	median 10 mm	face (33), trunk (39), neck (9), arm (7), leg (9), other (3)							
Beutner 1999 10570388	imiquimod 2x/day	NR	NR	NR	upper exremity (57), anterior upper trunk (14), neck (29)	No	No	No	Unsure	Yes	unsure	Yes
	imiquimod 1x/day	NR	NR	NR	upper extremity (50), anterior upper trunk (25), posterior upper trunk (25)							
	imiquimod 2x/week	NR	NR	NR	lower extremity (20), anterior upper trunk (40), posterior upper trunk (20), neck (20)							
	imiquimod 1x/week	NR	NR	NR	lower extremity (50), anterior upper trunk (25), posterior upper trunk (25)							
	vehicle (3 2x/day, 2 1x/day, 2 3x/week, 2 2x/week, 2 1x/week)	NR	NR	NR	face (9), upper extremity (46), anterior upper trunk (9), neck (9), posterior lower trunk (27)							
Brinkhuizen 2016 27067393	Diclofenac (results superficial/nodular)	63.0/78.5	25	61.7/49.5 mm2	extremities (47), trunk/neck (53)	Yes	Yes	No	No	No	Yes	Yes

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
	Calcitriol (results superficial/nodular)	65.5/68.5	22	54.2/59.7 mm2	trunk/neck (59), genetalia (41)							
	Diclofenac + Calcitriol (results superficial/nodular)	67.5/71	37.5	46.7/44.8 mm2	trunk/neck (50), genetalia (44)							
	No treatment (results superficial/nodular)	61.5/66	37.5	59.7/53.4 mm2	extremities (53), trunk/neck (47)							
Carija 2016 27516420	ALA-PDT	Median 71	13.3	255.4 mm2	extremities (3.6), trunk/neck (96.4)	No	No	Yes	unsure	Yes	Yes	Yes
	ALA-PDT + PDL	Median 71	13.3	216 mm2	extremities (23.5), trunk/neck (76.5)							
Cornell 1990 2229497	interferon	56	19	83 mm2	head and face (25), extermities (12), trunk/neck (63)	Yes	No	Yes	Yes	No	Yes	Yes
	placebo	57	14	75 mm2	head and face (17), extermities (14), trunk/neck (59)							
Edwards 1990 2107219	interferon gamma, 0.01	NR	NR	NR	NR	No	No	unsure	unsure	unsure	unsure	Yes
	interferon gamma, 0.05	NR	NR	NR	NR							
Edwards 1990 2383027	Interferon alfa-2b, 30 million IU	NR	NR	NR	NR	No	No	unsure	Yes	Yes	Yes	Yes
	Interferon alfa-2b, 10 million IU	NR	NR	NR	NR							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Eimpunth 2014	Laser vs. no treatment	NR	33	NR	NR	No Data	unsure	unsure	No	unsure	unsure	Yes
Garcia-Martin 2011 21242584	imiquimod 5%	73.1	33.3	7.6 mm	eyelid (100)	No	No	Yes	No	Unsure	Unsure	Yes
	radiotherapy	74.2	41.7	7.41 mm	eyelid (100)							
Geisse 2004 15097956	Imiquimod 5x/wk	58.4	37	NR	neck (4), trunk: anterior lower (1), trunk: anterior upper (17), trunk: posterior lower (7), trunk: posterior upper (24), lower extremity (excluding foot) (15), upper extremity (excluding hand) (31), chin (1), forehead (1)	Yes	Yes	No	Yes	Yes	Yes	Yes
	Vehicle 5x/wk or 7x/wk	58.7	38	NR	neck (1), trunk: anterior lower (1), trunk: anterior upper (20), trunk: posterior lower (6), trunk: posterior upper (20), lower extremity (excluding foot) (10.5), upper extremity (excluding hand) (39),							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
					cheek (1), chin (1), forehead (1)							
	Imiquimod 7x/wk	59.4	41	NR	neck (5), trunk: anterior lower 3, trunk: anterior upper (13), trunk: posterior lower (8), trunk: posterior upper (26), lower extremity (excluding foot) (11), upper extremity (excluding hand) (33), cheek (1), chin (1), forehead (1) Face: nose 1 (1%)							
Hall 1986 3514075	Radiotherapy	NR	NR	NR	face and neck (82), eyelid (6), trunk (12)	No	No	No	No	No	No	Unsure
	Cryotherapy	NR	NR	NR	face and neck (65), eyelid (17), trunk (17)							
Marks 2001 11312429	Imiquimod	61	27	NR	Upper extremities (32), upper trunk (28), head/neck/lower limbs (40)	No	No	unsure	No	unsure	unsure	Yes
Migden 2015 25981810	sonidegib 200	median 67	39	NR	head and neck (100)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	sonidegib 800	median 65	36	NR	head and neck (100)							
Miller 1997 8996264	5-FU	61	20	80 mm2	head (7), extremities (40),	No	No	unsure	Yes	Yes	Yes	No

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
					trunk/neck (52)							
Mosterd 2008 19010733	MMS	67.4	39.7	1.28 cm2	frontal/temporal (26), cheek/chin (9), (peri)nasal (34), lips/perioral (7), periocular (8), ears (4), periauricular (12)	Yes	Yes	Unsure	No	No	No	No
	Surgical excision	68.7	38.2	1.77 cm2	frontal/temporal (32), cheek/chin (8), (peri)nasal (30), lips/perioral (4), periocular (8), ears (8), periauricular (10)							
Salmanpoor 2012	Surgical excision	57.3	37	NR	face and scalp (100)	No	No	unsure	Unsure	Unsure	Unsure	Yes
	Curettage	57.3	37	NR	face and scalp (100)							
	Electodessication and curettage	57.3	37	NR	face and scalp (100)							
Thissen 2000 10940063	cryotherapy	NR	NR	NR	face (46), eyelid (4), ear (4), trunk/neck (6), forehead/temple (34), chin/perioral (6)	No	No	Yes	No	Unsure	Unsure	Yes
	surgical excision	NR	NR	NR	face (43), eyelid (8), trunk/neck (14), forehead/temple (25), chin/perioral (10)							

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Torres 2004 15606733	imiquimod, 2 weeks	NR	33.3	median 0.9 cm2	NR	Yes	No	Yes	Yes	Yes	Unsure	Yes
	imiquimod, 4 weeks	NR	41.7	median 0.8 cm2	NR							
	imiquimod, 6 weeks	NR	33.3	median 1.2 cm2	NR							
	vehicle controlled-pooled	NR	19.4	median 1.2 cm2	NR							
Tran 2012 22511036	PDL 15 j/cm2	NR	57	88 mm2	extremities (12), trunk/neck (88)	No	No	No	Yes	No	No	Yes
	PDL 7.5 j/cm2	NR	43	105 mm2	extremities (50), trunk/neck (50)							
	No treatment	NR	43	94 mm2	extremities (43), trunk/neck (57)							
Wang 2001 11298545	Total (ALA-PDT vs. Cryotherapy)	NR	50	NR	legs (11), arms (7), trunk (54), head/neck (28)	Unsure	Unsure	Unsure	No	No	Unsure	Yes

BCC = basal cell carcinoma; MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon; NR = not reported; PDL = pulse dye laser; x/wk = times per week

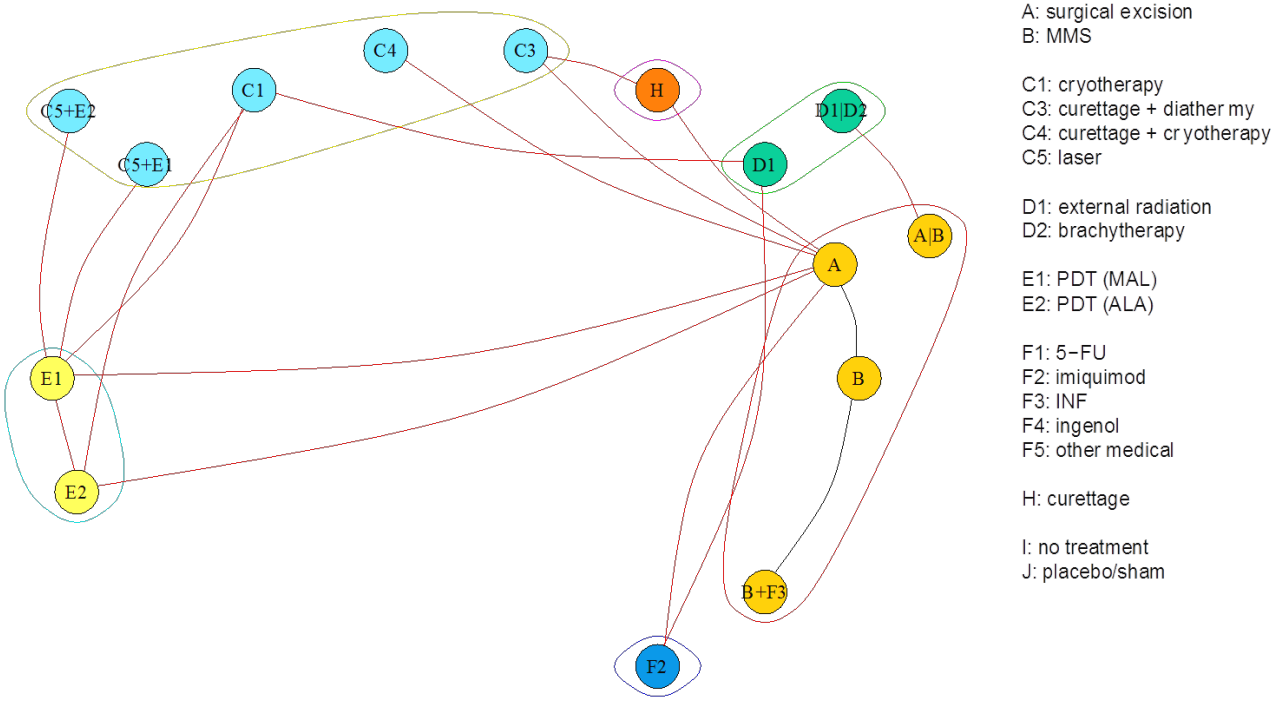
*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm.

Recurrence, All BCC Lesions

The evidence graph for recurrence with respect to individual treatments is sparse (Figure 6 (A) – reproduced in Figure 7 (A) for ease of reference), and comprises two connected subgraphs. Detailed results at the RCT-level are in the appendix.

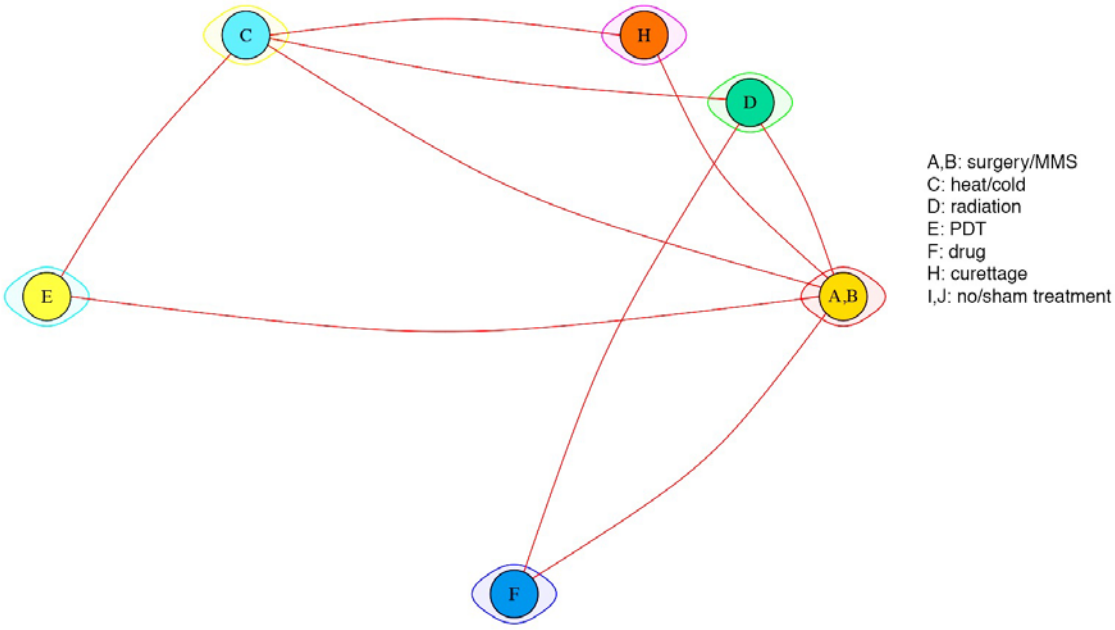
Figure 7. Evidence graph of RCTs evaluating recurrence in BCCs across (A) individual interventions and (B) types of interventions

(A)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

(B)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Note: The evidence graph for the individual treatments comprises 2 connected subgraphs defined by the following sets of nodes: A|B, D1|D2; and all remaining nodes.

Comparisons Across Intervention Categories

In total, 13 RCTs (1664 lesions) were included in this analysis.[19, 20, 42, 45, 50-52, 67, 70, 71, 85, 90, 104] Ten RCTs were deemed to be at low or moderate risk of bias. Cumulative sample sizes per comparison ranged from 27 to 347; for more details see Table 7.

Table 7. Sample information, recurrence (all BCC lesions, intervention categories)

Studies (total sample)	13 (1664)
Total sample by intervention	(A,B): 580; (E): 329; (D): 234; (F): 221; (C): 280; (H): 20
Total sample by intervention, (min, max)	20, 580
Data by comparison	(A,B--E): 3 (305); (A,B--D): 1 (347); (A,B--C): 2 (134); (A,B--H): 1 (44); (A—F): 1 (203); (E--C): 3 (355); (D--F): 1 (27); (D--C): 1 (93); (C--H): 1 (45)
Studies by comparison (min, max)	1, 3
Total sample by comparison (min, max)	27, 355
Followup median (min, max)	28 (3, 96) months

A = surgical excision; B = Mohs micrographic surgery; BCC=basal cell carcinoma; C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F2 = Imiquimod; H = curettage

Table 8 shows the relative odds ratios for recurrence across intervention categories. Overall, surgical treatments (A,B), radiation (D), and drugs (F), appear to be better than interventions that destroy lesions with heat or cold (C), photodynamic therapies (E), or curettage (H); and in many instances in the Table, statistically significantly so. There are no statistically significant

differences among the intervention categories in the former set (namely, [A,B], D, F) or among those in the latter set (namely, C, E, H), but almost universally, the confidence intervals are broad and cannot exclude large differences in the odds of recurrence in either direction.

In Table 8, shaded cells correspond comparisons that have been inferred from the analysis model but have not been examined in the included RCTs. For example, comparisons of drugs (F) versus other intervention categories are mostly indirect, and drugs have been compared head-to-head only with radiation (D). Indirect comparisons are more uncertain than those for which head-to-head data exist. The added uncertainty in indirect comparisons is partly reflected in the width of the respective 95 percent confidence intervals, which is (often much) broader for comparisons without direct data. For all comparisons that are empirically observed (all nonshaded cells in the Table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 8 (see Appendix I).

Table 8. Relative odds ratios for recurrence between intervention categories (all BCC lesions, Figure 7B)

Surgery/MMS (A,B)	*0.13 (0.05, 0.35)*	0.77 (0.21, 2.74)	*0.13 (0.05, 0.36)*	1.09 (0.05, 24.26)	*0.14 (0.03, 0.77)*
7.66 (2.85, 20.6)	Heat/cold (C)	*5.87 (2.02, 17.08)*	1 (0.48, 2.08)	8.33 (0.4, 171.71)	1.07 (0.23, 5.1)
1.3 (0.36, 4.66)	*0.17 (0.06, 0.5)*	Radiation (D)	*0.17 (0.06, 0.51)*	1.42 (0.06, 32.45)	0.18 (0.03, 1.05)
7.63 (2.79, 20.9)	1 (0.48, 2.07)	*5.85 (1.98, 17.31)*	PDT (E)	8.3 (0.4, 172.17)	1.07 (0.22, 5.14)
0.92 (0.04, 20.5)	0.12 (0.01, 2.48)	0.71 (0.03, 16.14)	0.12 (0.01, 2.5)	Drugs (F)	0.13 (<0.005, 3.6)
7.12 (1.29, 39.21)	0.93 (0.2, 4.42)	5.46 (0.95, 31.5)	0.93 (0.19, 4.48)	7.75 (0.28, 216.43)	Curettage (H)

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 9 offers complementary information from the same analysis; for each intervention category, it shows the mean recurrence rate across the included RCTs. Surgical treatments, radiation, and drugs RCT arms had on average lower recurrence rates (3.1% to 4.4%) compared to photodynamic therapy, curettage, and interventions that destroy lesions with heat or cold, which had average recurrence in the 20 to 23 percent range.

Table 9. Mean and forecasted recurrence rates by intervention category (all BCC lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Surgery/MMS (A,B)	3.4 (1.5, 7.6)	3.4 (0.9, 11.5)
Heat/cold (C)	21.2 (14.0, 30.7)	21.2 (8.2, 44.8)
Radiation (D)	4.4 (1.7, 10.5)	4.4 (1.2, 15.2)
PDT (E)	21.1 (13.6, 31.3)	21.1 (8.0, 45.2)
Drugs (F)	3.1 (0.2, 39.0)	3.1 (0.1, 42.8)
Curettage (H)	20.0 (5.4, 52.2)	20.0 (4.1, 59.6)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma; CI = confidence interval

Comparisons Across Individual Interventions

The results of the analyses of intervention categories are congruent with the corresponding results of the analyses of individual interventions. As evident from Figure 7, there are two connected subgraphs: a smaller one comprising the comparison between surgical treatments (surgical excision or MMS, [A,B]]) and external radiation of brachytherapy (D1|D2), and a larger one with all other interventions. In total, 14 RCTs (1772 lesions) were included in this analysis.[19, 20, 45, 50-52, 67, 70, 71, 81, 85, 90, 104, 105] They are described in Table 10.

Table 10. Sample information, recurrence (all BCC lesions, individual interventions)

	First subgraph[19, 20, 42, 45, 51, 52, 67, 70, 71, 81, 85, 90, 104, 105]	Second Subgraph[50]
Studies (total sample)	13 (1425)	1 (347)
Total sample by intervention	(A): 475; (E2): 149; (D1): 61; (F2): 15; (C1): 176; (C4): 38; (C3): 25; (H): 20; (B): 77; (E1): 206 (F2); 180; (B+F3): 9; (C5+E1): 16; (C5 + E2): 25	(A|B): 174; (D1|D2): 173
Total sample by intervention, (min, max)	9, 298	173, 174
Data by comparison	(A--E2): 1 (171); (A--C4): 1 (85); (A--C3): 1 (49); (A--H): 1 (44); (A--B): 1 (140); (A--E1): 2 (134); (A—F2): 1 (383); (E2--C1): 1 (83); (D1--F2): 1 (27); (D1--C1): 1 (93); (C1--E1): 1 (193); (C3--H): 1 (45); (B--B+F3): 1 (15); (E1--C5+E1): 1 (32); (E2—C5 + E2): 47	(A|B--D1|D2): 1 (347)
Studies by comparison (min, max)	1, 2	1, 1
Total sample by comparison (min, max)	15, 193	347, 347
Followup median (min, max)	28 (3, >120) months	41 (41, 41) months

A = surgical excision; B = Mohs micrographic surgery; BCC = basal cell carcinoma; C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F2 = Imiquimod; H = curettage

Tables 11 and 12 show the relative effects for the larger and smaller subgraphs, respectively. Because the comparisons across individual interventions are sparse, however, the confidence intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the compared interventions.

Table 13 shows, for each intervention, the mean recurrence rates across all RCTs; estimates for interventions in both subgraphs are listed in the table. One cannot compare statistically the estimated recurrence rates between an intervention in the first subgraph (e.g., cryotherapy [C1]) and the second subgraph (e.g., external radiation or brachytherapy [D1|D2]), because they come from disjoint analyses. The mean recurrence rates for individual interventions follow the same pattern as the corresponding recurrence rates for intervention categories. For example, the point estimates for the mean recurrence rate for surgical excision (A), MMS (B), and a combination of MMS and interferon (B+F3) ranged between 4.0 and 4.5 percent; and it was estimated at 3.4 percent for surgical interventions (A,B) in Table 8.

Table 11. Relative odds ratios for recurrence between individual interventions (all BCC lesions, Figure 7A, first subgraph)

Surgery (A)	1.04 (0.21, 5.23)	0.92 (0.04, 23.35)	*0.16 (0.05, 0.5)*	0.71 (0.11, 4.38)	*0.23 (0.07, 0.73)*	0.39 (0.06, 2.33)	*0.09 (0.01, 0.51)*	1.85 (0.34, 10.11)	*0.17 (0.05, 0.52)*	*0.11 (0.03, 0.35)*	1.49 (0.06, 37.27)	0.25 (0.05, 1.17)
0.96 (0.19, 4.82)	MMS (B)	0.89 (0.03, 25.27)	*0.16 (0.03, 0.85)*	0.68 (0.07, 6.92)	0.22 (0.03, 1.45)	0.37 (0.04, 3.34)	*0.08 (0.01, 0.74)*	1.78 (0.21, 14.78)	*0.16 (0.03, 0.88)*	*0.1 (0.02, 0.59)*	1.43 (0.05, 45.3)	0.24 (0.03, 1.97)
1.08 (0.04, 27.38)	1.13 (0.04, 32.17)	MMS + INF (B+F3)	0.18 (0.01, 4.31)	0.77 (0.02, 28)	0.25 (0.01, 7.05)	0.42 (0.01, 13.67)	0.09 (<0.005, 3.04)	2 (0.06, 62.36)	0.18 (0.01, 4.41)	0.12 (<0.005, 2.93)	1.61 (0.02, 129.86)	0.27 (0.01, 8.59)
6.14 (2, 18.85)	*6.4 (1.17, 34.91)*	5.67 (0.23, 138.61)	Cryotherapy (C1)	4.35 (0.63, 30.11)	1.4 (0.34, 5.84)	2.36 (0.48, 11.59)	0.54 (0.1, 2.77)	*11.35 (2.83, 45.48)*	1.01 (0.54, 1.9)	0.66 (0.28, 1.58)	9.14 (0.39, 213.14)	1.51 (0.28, 8.2)
1.41 (0.23, 8.71)	1.47 (0.14, 14.94)	1.3 (0.04, 47.52)	0.23 (0.03, 1.59)	Curettage and Diathermy (C3)	0.32 (0.04, 2.59)	0.54 (0.05, 5.92)	0.12 (0.01, 1.31)	2.61 (0.26, 26.39)	0.23 (0.03, 1.63)	0.15 (0.02, 1.09)	2.1 (0.06, 75.31)	0.35 (0.06, 2.13)
4.38 (1.37, 13.94)	4.56 (0.69, 30.25)	4.04 (0.14, 115.26)	0.71 (0.17, 2.97)	3.1 (0.39, 24.95)	Curettage and Cryotherapy (C4)	1.69 (0.23, 12.48)	0.38 (0.05, 2.74)	*8.1 (1.2, 54.76)*	0.72 (0.17, 3.06)	0.47 (0.11, 2.06)	6.52 (0.23, 182.96)	1.08 (0.17, 6.93)
2.6 (0.43, 15.7)	2.71 (0.3, 24.47)	2.4 (0.07, 78.64)	0.42 (0.09, 2.07)	1.84 (0.17, 20.09)	0.59 (0.08, 4.39)	Laser + PDT (MAL) (C5+E1)	0.23 (0.03, 2)	4.8 (0.61, 37.94)	0.43 (0.09, 1.94)	0.28 (0.05, 1.56)	3.87 (0.12, 122.7)	0.64 (0.07, 5.76)
11.44 (1.96, 66.7)	*11.92 (1.36, 104.37)*	10.56 (0.33, 339.17)	1.86 (0.36, 9.61)	8.11 (0.76, 85.93)	2.61 (0.36, 18.7)	4.4 (0.5, 38.73)	Laser + PDT (ALA) (C5+E2)	*21.15 (2.64, 169.72)*	1.89 (0.36, 10.04)	1.24 (0.25, 6.12)	17.02 (0.54, 532.11)	2.82 (0.32, 24.57)
0.54 (0.1, 2.96)	0.56 (0.07, 4.69)	0.5 (0.02, 15.54)	*0.09 (0.02, 0.35)*	0.38 (0.04, 3.88)	*0.12 (0.02, 0.84)*	0.21 (0.03, 1.64)	*0.05 (0.01, 0.38)*	Radiotherapy (D1)	*0.09 (0.02, 0.39)*	*0.06 (0.01, 0.28)*	0.8 (0.03, 21.66)	0.13 (0.02, 1.1)
6.06 (1.94, 18.94)	*6.31 (1.14, 34.96)*	5.59 (0.23, 137.95)	0.99 (0.53, 1.85)	4.29 (0.61, 30.09)	1.38 (0.33, 5.86)	2.33 (0.51, 10.58)	0.53 (0.1, 2.82)	*11.2 (2.53, 49.56)*	PDT (MAL) (E1)	0.65 (0.25, 1.73)	9.02 (0.38, 213.68)	1.49 (0.27, 8.21)
9.25 (2.88, 29.69)	*9.64 (1.7, 54.78)*	8.54 (0.34, 214.06)	1.51 (0.63, 3.59)	6.56 (0.92, 46.94)	2.11 (0.49, 9.18)	3.56 (0.64, 19.83)	0.81 (0.16, 4.01)	17.11 (3.53, 82.88)	1.53 (0.58, 4.04)	PDT (ALA) (E2)	13.77 (0.57, 333.54)	2.28 (0.41, 12.84)
0.67 (0.03, 16.82)	0.7 (0.02, 22.19)	0.62 (0.01, 49.98)	0.11 (<0.005, 2.55)	0.48 (0.01, 17.08)	0.15 (0.01, 4.31)	0.26 (0.01, 8.21)	0.06 (<0.005, 1.84)	1.24 (0.05, 33.44)	0.11 (<0.005, 2.63)	0.07 (<0.005, 1.76)	Imiquimod (F2)	0.17 (0.01, 5.24)
4.06 (0.85, 19.26)	4.23 (0.51, 35.17)	3.75 (0.12, 120.49)	0.66 (0.12, 3.58)	2.88 (0.47, 17.63)	0.93 (0.14, 5.95)	1.56 (0.17, 14.04)	0.35 (0.04, 3.09)	7.5 (0.91, 62.09)	0.67 (0.12, 3.68)	0.44 (0.08, 2.47)	6.04 (0.19, 190.85)	Curettage (H)

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

ALA = 5-aminolevulinic acid; BCC = basal cell carcinoma; FU = fluorouracil; INF = interferon; MAL = methyl aminolevulinate; MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Table 12. Relative odds ratios for recurrence between individual interventions (all BCC lesions, Figure 7A, second subgraph)

Surgical excision /MMS (A|B)	***0.12 (0.01, 0.96)***
8.39 (1.04, 67.8)	**External radiation/ brachytherapy (D1|D2)**

Note: Bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

BCC = basal cell carcinoma; MMS = Mohs micrographic surgery

Table 13. Mean recurrence rates by intervention (all BCC lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
First subgraph (Figure 7)		
Surgical excision (A)	4.2 (1.7, 9.7)	4.2 (0.8, 18.5)
MMS (B)	4.0 (0.9, 16.4)	4.0 (0.5, 24.9)
MMS+INF (B+F3)	4.5 (0.2, 51.4)	4.5 (0.2, 58.7)
Cryotherapy (C1)	21.0 (11.6, 35.1)	21.0 (5.3, 55.7)
Diathermy+curettage (C3)	5.8 (1.0, 27.2)	5.8 (0.6, 37.3)
Cryotherapy+curettage (C4)	15.9 (5.1, 40.0)	15.9 (2.8, 55.1)
Laser+PDT (MAL) (C5+E1)	10.1 (2.3, 35.1)	10.1 (1.4, 47.6)
Laser+PDT (ALA)	33.1 (9.7, 69.4)	33.1 (6.0, 79.5)
External radiation (D1)	2.3 (0.5, 9.1)	2.3 (0.3, 14.8)
PDT (MAL) (E1)	20.8 (11.0, 35.7)	20.8 (5.2, 55.8)
PDT (ALA) (E2)	28.6 (15.0, 47.6)	28.6 (7.5, 66.6)
Imiquimod (F2)	2.8 (0.1, 39.0)	2.8 (0.1, 46.2)
Curettage (H)	14.9 (3.6, 45.2)	14.9 (2.2, 58.2)
Second subgraph (Figure 7)		
Surgical excision or Mohs (A|B)	0.6 (0.1, 4.0)	NA
External radiation or brachytherapy (D1|D2)	4.6 (2.3, 9.0)	NA

ALA = 5-aminolevulinic acid; BCC = basal cell carcinoma; CI = confidence interval; FU = fluorouracil; INF = interferon; MAL = methyl aminolevulinate; MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Recurrence, Subgroup Analyses by Lesion Type

We conducted subgroup analyses by the type of BCC lesion. We report analyses comparing intervention categories, but not analyses comparing individual treatments. The latter are very sparse, and their results are very similar to the pertinent comparisons in Tables 9 and 10.

Many subgroup analyses per lesion type are possible; we describe here analyses in RCTs of lower-risk lesions (strata of predominantly [>80%] superficial BCCs, predominantly nodular BCCs, and superficial or nodular BCCs) overall, and broken down by lesion type; and of higher-risk lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).

Eleven RCTs (n=1234 lesions) included low risk BCCs (nodular and superficial subtypes). All results about comparisons among intervention categories are the same as in the previous section (Tables 7 and 8).

With respect to RCT strata of predominantly superficial lesions, a single RCT deemed to be at low risk of bias compared cryotherapy (C1, n=93) with PDT with MAL (E1, n=100).[51] A second RCT, also deemed to be at low risk of bias, compared surgery to drug therapy, in this case Imiquimod.[52] Results are shown in Tables 14 and 15. Both studies had a followup of 60 months. Briefly, there was no statistically significant difference between the two interventions in ether study, but based on the width of the 95% confidence intervals, one cannot exclude differences in the odds of the outcome as large as 80% in either direction.

Table 14. Relative odds ratios for recurrence between interventions (predominantly superficial BCC lesions)

Heat/cold (C) [Cryotherapy (C1)]	0.91 (0.46, 1.82)		
1.10 (0.55, 2.19)	**PDT (E) [PDT (MAL) (E1)]**		
		Surgery|MMS (A|B)	0.28 (0.06, 1.35)
		3.57 (0.74, 17.26)	**Drug (F)**

Note: Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT (MAL) = methyl aminolevulinate photodynamic therapy

Table 15. Mean recurrence rates by intervention category (predominantly superficial BCC lesions)

Intervention Type	Mean Recurrence Rate (95% CI)
Subgraph 1 (Figure 7)	
Heat/cold (C) [Cryotherapy (C1)]	20.4 (13.4, 29.8)
PDT (E) [PDT (MAL) (E1)]	22.0 (14.9, 31.2)
Subgraph 2 (Figure 7)	
Surgery|MMS (A|B)	2.1 (0.5, 8.1)
Drug (F)	7.2 (3.6, 18.8)

Note: Forecasted expected recurrence rates in groups of patients similar to the patients included in the analyzed RCTs are not given, because these results are from a fixed effects analysis

CI = confidence interval; MMS = Mohs micrographic surgery; PDT (MAL) = methyl aminolevulinate photodynamic therapy

Information about the samples for predominantly nodular lesions is in Table 16. The corresponding results are listed in Tables 17 and 18. These results are congruent with the corresponding results from the analyses in Tables 14 and 15.

Table 16. Sample information (predominantly nodular lesions)

	Studies [20, 45, 52, 67, 70, 85]
Studies (total sample)	6 (747)
Total sample by intervention	(A,B): 335; (E): 163; (C): 16; (D): 12; (F): 221
Total sample by intervention, (min, max)	12, 335
Data by comparison	(A,B--E): 3 (305); (E--C): 1 (32); (A—F): 383; (D--F): 1 (27)
Studies by comparison (min, max)	1, 3
Total sample by comparison (min, max)	27, 383
Followup median (min, max)	48 (12, 96)

A = surgical excision; B = Mohs micrographic surgery; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs

Table 17. Relative odds ratios for recurrence between interventions (predominantly nodular BCC lesions)

Surgery|MMS (A|B)	*0.04 (<0.005, 0.57)*	*0.23 (0.01, 9.06)*	*0.04 (0.01, 0.28)*	0.28 (0.03, 3.06)
25.53 (1.74, 374.42)	Heat or Cold (C)	5.77 (0.11, 295.02)	1 (0.09, 10.84)	7.1 (0.45, 111.9)
4.43 (0.11, 177.45)	0.17 (<0.005, 8.86)	Radiotherapy (D)	0.17 (0.01, 5.61)	1.23 (0.03, 52.02)
25.59 (3.61, 181.57)	1 (0.09, 10.9)	5.78 (0.18, 187.64)	PDT (E)	7.12 (0.91, 55.67)
3.6 (0.33, 39.57)	0.14 (0.01, 2.22)	0.81 (0.02, 34.36)	0.14 (0.02, 1.1)	Drug (F)

Note: Results from comparisons in the first and second subgraphs are shown in the upper left and lower right blocks in this Table. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 18. Mean and forecasted recurrence rates by intervention category (predominantly nodular BCC lesions)

Intervention Type	**Mean Percent (95% CI)**	**Forecast Percent (95% CI)**
First subgraph (Figure 7)		
Surgery/MMS (A,B)	0.9 (0.2, 4.4)	0.9 (0.1, 8.8)
Heat/cold (C)	18.7 (2.7, 66.0)	18.7 (1.5, 78.1)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Radiation (D)	3.8 (0.1, 52.2)	3.8 (0.1, 62.5)
PDT (E)	18.8 (7.3, 40.4)	18.8 (3.0, 63.8)
Drugs (F)	3.1 (0.6, 15.8)	3.1 (0.3, 27.5)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; Drugs, in this case represents Imiquimod; CI = confidence interval

Finally, with respect to high risk lesions, a single RCT compared surgical excision (A) with MMS (B) in histologically aggressive facial lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).[81] Although the average recurrence rate was smaller in the MMS arm (3.4% [95% CI 1.0% to 11.0%]) versus the surgical excision arm (4.8% [95% CI, 2.5% to 8.8%]), it was not significantly so (odds ratio for surgical excision versus MMS 1.43 [95% CI 0.35 to 5.95]).

Recurrence, Other Subgroup Analyses (Lesion Location, Lesion Size)

Table 19 summarizes results from two RCTs by lesion location and size. One RCT comparing surgical excision (A) versus MAL PDT (E) in predominantly nodular lesions[22, 85] examined subgroups defined by lesion diameter (<=10 mm versus 10 to 20 mm) and found no evidence of effect modification by lesion size at one through 5 years of follow up. Another RCT comparing cryotherapy (C) to radiation therapy (D) in low-risk lesions (mixed superficial and nodular BCCs) found no evidence of effect modification by lesion size (smaller than 10 mm, between 10 and 20 mm, and larger than 20 mm) or location (eyelids, face or neck, and trunk).[71]

Table 19. Subgroup results by lesion size and location for recurrence (BCC lesions)

Study	Comparison	Timepoint	Subgroup	n/N Arm 1 vs. n/N Arm 2	OR (95% CI); P-Value Within	P-Value Between
Rhodes 2004 14732655	Excision (A) vs MAL-PDT (E)	12 months	lesion diameter: 10-20 mm	0/14 vs. 1/19	0.43 (0.02, 11.23); p=1.00	NA
			lesion diameter: <= 10 mm	0/34 vs 1/29	0.28 (0.01, 7.02); p=0.46	
		24 months	lesion diameter: 10-20 mm	0/14 vs. 0/19	NA	NA
			lesion diameter: <= 10 mm	0/29 vs. 3/29	0.13 (0.01, 2.60); p=0.24	
		36 months	lesion diameter: 10-20 mm	1/14 vs. 1/19	1.38 (0.08, 24.23); p=1.00	NA
			lesion diameter: <= 10 mm	0/29 vs. 1/29	0.32 (0.01, 8.24); p=1.00	
		48 months	lesion diameter: 10-20 mm	1/14 vs. 0/19	4.33 (0.16, 114.58); p=0.42	NA
			lesion diameter: <= 10 mm	0/29 vs. 0/29	NA	
		60 months	lesion diameter: 10-20 mm	0/14 vs 0/19	NA	NA
			lesion diameter: <= 10 mm	0/29 vs 0/29	NA	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D)	12 months	Lesion location: eyelids	3/6 vs. 0/3	7.00 (0.25, 192.26); p=0.464	p= 0.97

Study	Comparison	Timepoint	Subgroup	n/N Arm 1 vs. n/N Arm 2	OR (95% CI); P-Value Within	P-Value Between
	therapy					
			Lesion location: face/neck	12/30 vs. 2/40	12.67 (2.56, 62.65); p<0.001	
			Lesion location: trunk	2/8 vs. 0/6	5.00 (0.20, 125.78); p=0.473	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D) therapy	12 months	Lesion diameter <10 mm	6/19 vs. 0/19	18.78 (0.97, 362.00); p=0.020	NA
			Lesion diameter 10-20 mm	9/23 vs. 2/25	7.39 (1.39, 39.27); p=0.016	
			Lesion diameter >20 mm	2/2 vs. 0/5	55.00 (0.83, 3650.69); p=0.048	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D) therapy	24 months	Lesion location: eyelids	3/6 vs. 0/3	7.00 (0.25, 192.26); p=0.464	NA
			Lesion location: face/neck	12/30 vs. 2/40	12.67 (2.56, 62.65); p<0.001	
			Lesion location: trunk	2/8 vs. 0/6	5.00 (0.20, 125.78); p=0.473	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D) therapy	12 months	Lesion diameter <10 mm	6/19 vs. 0/19	18.78 (0.97, 362.00) p=0.020	NA
			Lesion diameter 10-20 mm	9/23 vs. 2/25	7.39 (1.39, 39.27); p=0.016	
			Lesion diameter >20 mm	2/2 vs. 0/5	55.00 (0.83, 3650.69); p=0.048	

NA = not significant; PDT = photodynamic therapy; MAL = methyl aminolevulinate; OR = odds ratio; CI = confidence interval

Recurrence, Results From Nonrandomized Studies (BCC Lesions)

Two NRCSs reported on recurrence in populations with only BCC lesions. The first included 74 patients and reported on a matched population of 94 superficial (64%) and nodular (36%) BCCs 25 months after treatment. The study was rated as having a moderate risk of confounding bias because of lack of blinding, and unclear reporting. The mean age at baseline was 66 (range: 49 to 90), 47 percent of the population was female. Recurrence was similar across groups (4.2% in the ALA-PDT group vs. 4.3% in the surgical excision group; OR: 0.96 [95% CI 0.13 to 7.09]).[148] The second reported recurrence in 621 people (47% female) with BCC lesions (38.5% superficial, 17% nodular, and 44.5% infiltrative, micronodular, morpheaform, or sclerosing). This study was judged to have a high risk of confounding and selection bias because of lack of blinding, unclear distribution of dropouts, unclear results reporting, and uneven groups at baseline that were not accounted for in the analysis. Surgical excision had a higher rate of recurrence up to 5 years compared to Imiquimod (HR 2.13; 95% CI 1.28 to 3.53).[149]

Two NRCS reported on recurrence in populations with both BCCs and SCC lesions. One reported on 1174 patients with 1488 lesions selected from a private, university-affiliated clinic and a nearby Veterans Affairs clinic. This study was deemed to have a low risk of bias, with

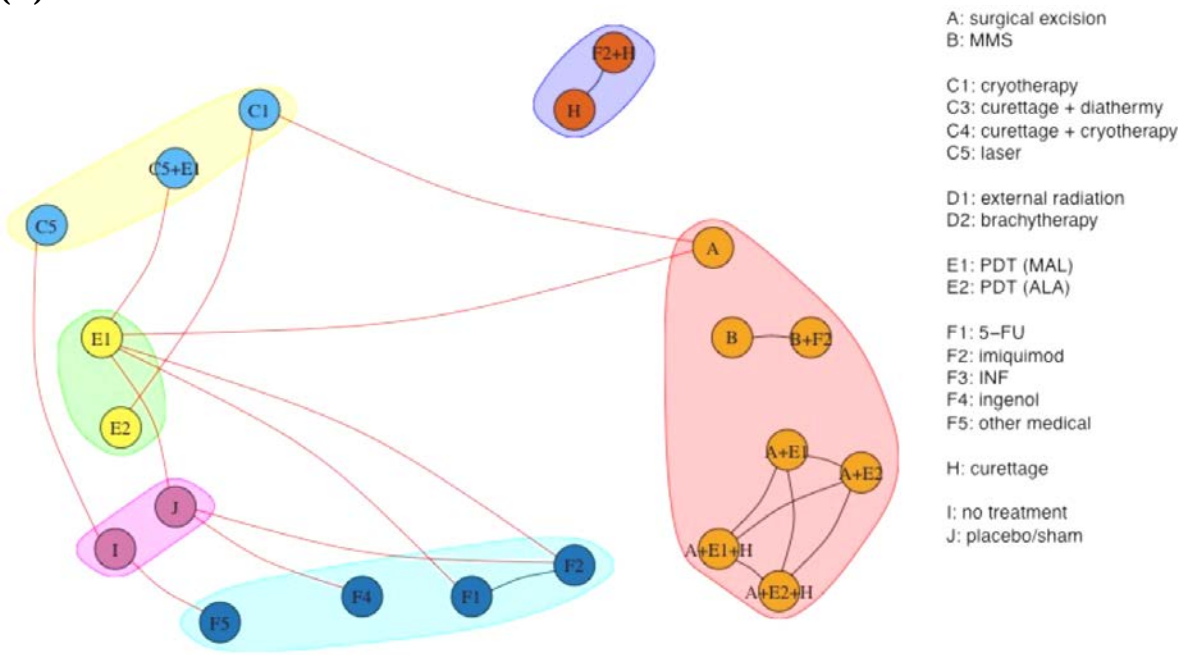
balanced groups, consecutive recruitment, blinding of outcome assessors, and adequate accounting for people lost to followup. Most (75%) of the lesions were BCCs; the other 25 percent were SCCs; 26 percent were female, 40 percent had a Fitzpatrick skin score of I or II, and 3 percent were immunocompromised due to prior solid-organ transplant. The lesions were treated by Mohs surgery (246; 65% in the H-zone of the face), surgical excision (251; 26% in H-zone of the face), and electrodessication and curettage (ED&C) (136; 11% in H-zone of the face). ED&C had the highest rate of recurrence after 5 years (4.9%), then excision (3.5%), and finally Mohs (2.1%). In a subsample of 240 pairs of tumors matched on propensity score, the difference in hazard of recurrence between Mohs and excision was not statistically significant (0.61; 95% CI 0.3, 1.24).[142, 144-147] A secondary analysis limited to 1483 lesions judged appropriate for Mohs surgery reported a similar nonsignificant 5-year adjusted hazard ratio for recurrence (0.6; 95% CI 0.3, 1.0),[156] The second NRCS reported on two doses and schedules of orthovoltage radiotherapy. The population consisted of 436 lesions in 385 elderly people, with BCCs (71%) and SCCs (29%). The mean age was 78, and 42 percent were female. A lower dose of radiation (3675 cGy) had a nonsignificantly higher recurrence rate than the higher dose (4500 cGy) (HR: 0.483; 95% CI 0.065 to 3.58).[151]

Lack of Histologic Clearance (All BCC Lesions)

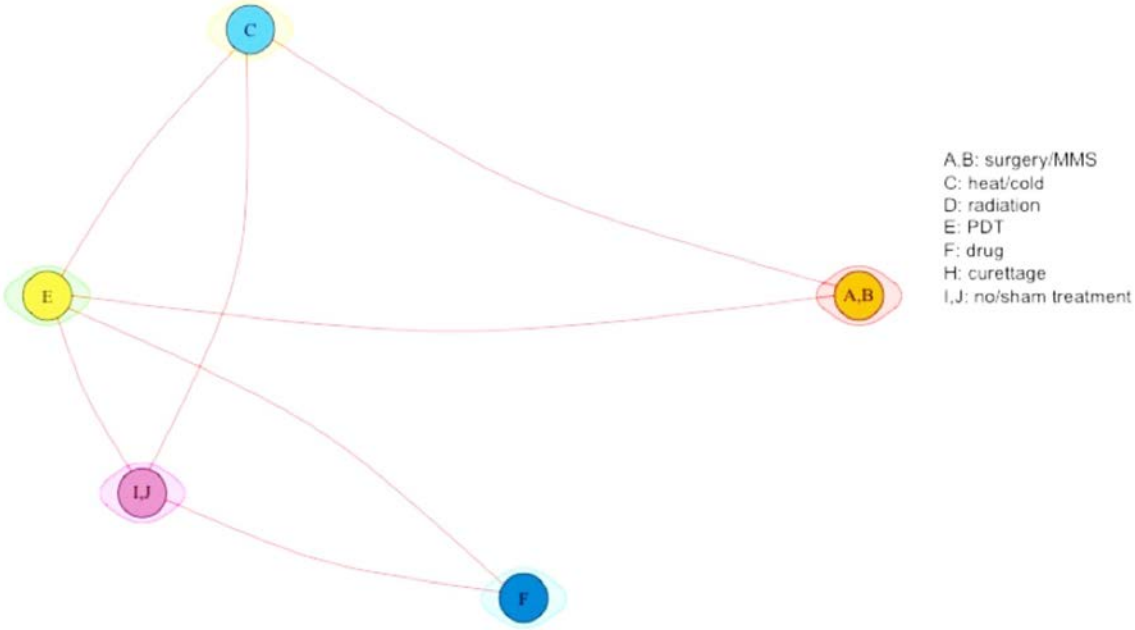
The evidence graph for lack of histologic clearance with respect to individual treatments is sparse (Figure 6 (B) – reproduced in Figure 8 (A) for ease of reference) and comprises 5 connected subgraphs. Detailed results at the RCT-level are in Appendix I.

Figure 8. Evidence graph of RCTs evaluating lack of histological clearance in BCCs across (A) individual interventions and (B) types of interventions

(A)



(B)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

Comparisons Across Intervention Categories

In total, 15 RCTs (1940 lesions) were included in this analysis.[45, 49, 54, 55, 64, 66, 68-70, 92-94, 99, 101, 104] Twelve RCTs were deemed to be at low or moderate risk of bias. Cumulative sample sizes per comparison ranged from 44 to 1196; for more details see Table 20.

Table 20. Sample information, lack of histological clearance (all BCC lesions, intervention categories)

Studies (total sample)	15 (1940)
Total sample by intervention	(F): 825; (I,J): 607; (A,B): 83; (C): 131; (E): 294
Total sample by intervention, (min, max)	83, 825
Data by comparison	(F--I,J): 7 (1196); (F--E): 1 (271); (I,J--C): 2 (44); (I,J--E): 1 (150); (A,B--C): 1 (96); (A,B--E): 1 (68); (C--E): 2 (115)
Studies by comparison (min, max)	1, 7
Total sample by comparison (min, max)	44, 1196
Followup median (min, max)	3 (1.5, 36) months

A = surgical excision; B = Mohs micrographic surgery; BCC = basal cell carcinoma; C = heat/cold; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Table 21 shows the relative odds ratios for lack of histologic clearance across intervention categories. Overall, surgical treatments (A,B) were statistically significantly better than any other intervention category in terms of histological clearance. No or sham treatment (I,J) was statistically significantly worse that all other treatments. Among the other intervention categories, the odds ratios favor PDT (E) over interventions that destroy lesions with heat or cold (C), and the latter (C) over drugs (F), but these differences are not statistically significant. Further, the confidence intervals for the comparisons between the latter three treatments are broad and cannot exclude large effects in either direction.

In the table, shaded cells correspond to comparisons that have been inferred from the analysis model, but that have not been examined in the included RCTs. For example, comparisons of surgical treatments (A,B) or interventions that destroy lesions with heat or cold (C) versus drugs (F) or placebo (I,J) are indirect, through PDT (E) as the common comparator. Indirect comparisons are more uncertain that those for which head-to-head data exist. The added uncertainty in the indirect comparisons is partly reflected in the width of the respective 95 percent confidence intervals, which is (often much) broader for comparisons without versus with direct data. For all comparisons that have been empirically observed (all nonshaded cells in the table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 17 (see Appendix I).

Table 21. Relative odds ratios for lack of histologic clearance between intervention categories (all BCC lesions, Figure 8B)

Surgery/MMS (A,B)	***0.04 (<0.005, 0.77)***	0.05 (<0.005, 1.03)	***0.02 (<0.005, 0.41)***	***<0.005 (<0.005, 0.04)***
27.5 (1.3, 579.51)	**Heat/cold (C)**	1.36 (0.22, 8.45)	0.6 (0.11, 3.16)	***0.07 (0.01, 0.34)***
20.11 (0.97, 418.64)	0.73 (0.12, 4.54)	**PDT (E)**	0.44 (0.09, 2.25)	***0.05 (0.01, 0.24)***
45.91 (2.42, 870.68)	1.67 (0.32, 8.83)	2.28 (0.44, 11.74)	**Drugs (F)**	**0.11 (0.03, 0.45)**
418.6 (22.48, 7793.78)	***15.25 (2.98, 77.94)***	***20.81 (4.18, 103.57)***	***9.12 (2.2, 37.76)***	**No/sham treatment (I,J)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 22 offers complementary information from the same analysis. For each intervention category, it shows the mean fraction of lesions without histologic clearance across the included RCTs. It also forecasts the expected fractions with lack of histologic clearance in each intervention category in groups of patients similar to the patients included in the analyzed RCTs. The average number of lesions with no histological clearance was 1.2 percent in the surgery arms, between 19.5 and 35.6 percent in other active intervention categories, and 83.5 percent for no or sham (placebo) treatment.

Table 22. Mean and forecasted lack of histologic clearance fractions by intervention category (all BCC lesions)

Intervention Type	Mean Lack of Histological Clearance Fraction Percent (95% CI)	Forecasted Lack of Histological Clearance Fraction Percent (95% CI)
Surgery/MMS (A,B)	1.2 (0.1, 15.9)	1.2 (<0.5, 36.7)
Heat/cold (C)	24.9 (8.2, 55.0)	24.9 (1.6, 87.1)
PDT (E)	19.5 (6.4, 46.4)	19.5 (1.2, 83.0)
Drugs (F)	35.6 (16.5, 60.8)	35.6 (2.9, 91.0)
No/sham treatment (I,J)	83.5 (65.5, 93.1)	83.5 (21.8, 98.9)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; CI = confidence interval

Comparisons Across Individual Interventions

The results of the analyses of individual interventions are congruent with the analyses intervention categories are congruent with the corresponding results. As is evident from Figure 8, there are five connected subgraphs. Separate analyses are conducted for each connected subgraph. In total, 19 RCTs (2170 lesions) were included in these analyses, as summarized in the Table 23

Table 23. Sample information, lack of histological clearance (all BCC lesions, individual interventions)

	First subgraph[45, 49, 54, 66, 68-70, 92-94, 99, 104]	Second subgraph[73]	Third subgraph[55, 64, 101]	Fourth subgraph[96]	Fifth subgraph[5, 6, 100]
Studies (total sample)	12 (2010)	1 (43)	3 (76)	1 (20)	2 (97)
Total sample by intervention	(F2): 761; (J): 575; (A): 83; (C1): 87; (E2): 44; (E1): 250; (F1): 146; (F4): 48; (C5+E1): 16	(A+E1): 11; (A+E1+H): 10; (A+E2): 11; (A+E2+H): 11	(C5): 28; (I): 32; (F5): 16	(F2+H): 10; (H): 10	(B): 50; (B+F2): 47
Total sample by intervention, (min, max)	16, 761	10, 11	16, 32	10, 10	47, 50
Data by comparison	(F2--J): 5 (1110); (F2--E1): 1 (271); (F2--F1): 1 (291); (J--E1): 1 (150); (J--F4): 1 (54); (A--C1): 1 (96); (A--E1): 1 (68); (C1--E2): 1 (83); (E1--F1): 1 (272); (E1--C5+E1): 1 (32)	(A+E1--A+E1+H): 1 (21); (A+E1--A+E2): 1 (22); (A+E1--A+E2+H): 1 (22); (A+E1+H--A+E2): 1 (21); (A+E1+H--A+E2+H): 1 (21); (A+E2--A+E2+H): 1 (22)	(C5--I): 2 (44); (I--F5): 1 (32)	(F2+H--H): 1 (20)	(B--B+F2): 2 (97)
Studies by comparison (min,	1, 5	1, 1	1, 2	1, 1	2, 2

	First subgraph[45, 49, 54, 66, 68-70, 92-94, 99, 104]	Second subgraph[73]	Third subgraph[55, 64, 101]	Fourth subgraph[96]	Fifth subgraph[5, 6, 100]
max)					
Total sample by comparison (min, max)	32, 1110	21, 22	32, 44	20, 20	97, 97
Followup median (min, max)	3 (3, 36) months	2.5 (2.5, 2.5) months	2 (1.5, 2) months	2 (2, 2) months	1.5 (0.5, 2.5) months

A = surgical excision; B = Mohs micrographic surgery; BCC = basal cell carcinoma; C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; C5 = laser; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F1 = 5-FU; F2 = Imiquimod; F4 = Ingenol; H = curettage; J = placebo

Table 24 has results on the relative effects for the largest subgraph. Table 25 has the corresponding results for the other subgraphs: the one for the comparison of surgical excision with PDT with MAL or ALA, with or without curettage (A+E1 versus A+E2 versus, A+E1+H versus A+E2+H); and the one for the comparison between laser ablation (C5) versus diclofenac and/or calcitriol (other medication – F5) and versus no treatment (I). Table 26 shows the relative effects for the last two subgraphs, namely the one for the comparison between curettage alone (H) versus curettage and imiquimod (H+F2); and the one for the comparison between MMS (B) and MMS with imiquimod (B+F2). In all three tables, comparisons across individual observations are sparse. The confidence intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the compared interventions. The exception is for comparisons between surgical treatments and no intervention, which are statistically significant despite the wide confidence interval, because the relative effect is very large.

Table 27 shows, for each intervention, the mean fractions for lack of histologic clearance across all RCTs. Estimates for interventions in all five subgraphs are listed in the table. One should not compare statistically these fractions across the subgraphs, because they come from disjoint analyses. In general, the mean fractions for lack of histologic clearance for individual interventions are in congruence with the corresponding fractions estimated for intervention categories. For example, in the first subgraph, the average recurrence rates for PDT with MAL (E1) and ALA (E2) were 18.2 percent (95% CI 5.1 to 48.0) and 25.0 percent (95% CI 2.0 to 84.0), respectively, and the corresponding result from the analysis between intervention categories was 19.5 percent (95% CI 6.4 to 46.4). The mean number of lesions with no histological clearance for the three medical interventions, namely 5-FU (F1), imiquimod (F2), and ingenol (F4), ranged between 5.5 and 77.1 percent, but the respective confidence intervals were very wide, and the corresponding odds ratios in Table 24 were not statistically significant.

Table 24. Relative odds ratios for lack of histological clearance between individual interventions (all BCC lesions, Figure 8A, largest subgraph)

(A) Surgery	0.11 (<0.005, 3.3)	0.02 (<0.005, 1.08)	0.05 (<0.005, 1.19)	0.04 (<0.005, 1.81)	0.21 (<0.005, 10.47)	***0.04 (<0.005, 0.83)***	***<0.005 (<0.005, 0.18)***	***<0.005 (<0.005, 0.05)***
9.31 (0.3, 285.72)	**(C1) Cryotherapy**	0.19 (0.01, 6.43)	0.5 (0.04, 6.05)	0.34 (0.01, 10.68)	1.93 (0.06, 61.81)	0.39 (0.04, 4.11)	0.03 (<0.005, 1.06)	***0.02 (<0.005, 0.23)***
49.8 (0.93, 2678.92)	5.35 (0.16, 184.09)	**(C5+E1) Laser + PDT (MAL)**	2.69 (0.11, 67.1)	1.8 (0.03, 99.7)	10.35 (0.19, 576.29)	2.1 (0.09, 47.08)	0.18 (<0.005, 9.86)	0.12 (0.01, 2.66)
18.52 (0.84, 407.72)	1.99 (0.17, 23.98)	0.37 (0.01, 9.28)	**(E1) PDT (MAL)**	0.67 (0.03, 15.3)	3.85 (0.17, 88.57)	0.78 (0.13, 4.86)	0.07 (<0.005, 1.51)	**0.04 (0.01, 0.27)**
27.67 (0.55, 1386.65)	2.97 (0.09, 94.42)	0.56 (0.01, 30.77)	1.49 (0.07, 34.14)	**(E2) PDT (ALA)**	5.75 (0.11, 298.48)	1.17 (0.06, 23.88)	0.1 (<0.005, 5.11)	0.07 (<0.005, 1.35)
4.81 (0.1, 242.47)	0.52 (0.02, 16.52)	0.1 (<0.005, 5.38)	0.26 (0.01, 5.98)	0.17 (<0.005, 9.03)	**(F1) 5-FU**	0.2 (0.01, 4.18)	***0.02 (<0.005, 0.89)***	***0.01 (<0.005, 0.24)***
23.66 (1.2, 464.54)	2.54 (0.24, 26.54)	0.48 (0.02, 10.63)	1.28 (0.21, 7.93)	0.86 (0.04, 17.46)	4.92 (0.24, 101.09)	**(F2) Imiquimod**	0.08 (<0.005, 1.73)	***0.06 (0.01, 0.28)***
279.18 (5.58, 13970.12)	30 (0.95, 951.08)	5.61 (0.1, 310.02)	15.07 (0.66, 343.77)	10.09 (0.2, 520.18)	***58.02 (1.12, 3007.15)***	11.8 (0.58, 240.42)	**(F4) Ingenol**	0.67 (0.03, 13.6)
414.45 (21.31, 8061.19)	***44.53 (4.32, 459.3)***	8.32 0.38, 184.46)	**22.38 (3.66, 136.75)**	14.98 (0.74, 302.98)	***86.14 (4.23, 1754.46)***	***17.52 (3.51, 87.41)***	1.48 (0.07, 29.96)	**(J) Placebo/sham**

PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, BCC=basal cell carcinoma. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

Table 25. Relative odds ratios for lack of histological clearance between individual interventions (all BCC lesions, Figure 8, other subgraphs)

(A_plus_E1) Surgery + PDT (MAL)	2.29 (0.32, 16.51)	1 (0.18, 5.68)	2.57 (0.36, 18.33)
0.44 (0.06, 3.16)	**(A_plus_E1_plus_H) Surgery + PDT (MAL) + curettage**	0.44 (0.06, 3.16)	1.13 (0.13, 9.94)
1 (0.18, 5.68)	2.29 (0.32, 16.51)	**(A_plus_E2) Surgery + PDT (MAL)**	2.57 (0.36, 18.33)
0.39 (0.05, 2.77)	0.89 (0.1, 7.86)	0.39 (0.05, 2.77)	**(A_plus_E2_plus_H) Surgery + PDT (MAL) + curettage**

(C5) laser	***0.02 (<0.005, 0.56)***	***0.17 (0.03, 0.9)***
43.95 (1.77, 1090.16)	**(F5) Other medical**	7.49 (0.29, 196.65)

		5.87 (1.11, 31.13)	0.13 (0.01, 3.51)	**(I) No treatment**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; BCC = basal cell carcinoma

Table 26. Relative odds ratios for lack of histological clearance between individual interventions (all BCC lesions, Figure 8A, 2 more subgraphs)

(F2_plus_H) **Imiquimod + curettage**	0.17 (0.01, 1.88)		
6.00 (0.53, 67.65)	**Curettage (H)**		
		MMS (B)	***11.11 (2.66, 46.36)***
		0.09 (0.02, 0.38)	**(B_plus_F2)** **MMS + imiquimod**

Note: Results are given as odds ratios (95% confidence intervals). Bold-italic indicates statistical significance.

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; BCC = basal cell carcinoma

Table 27. Mean and forecasted lack of histological clearance fractions by intervention category (all BCC lesions)

Intervention Type	Mean Lack of Histological Clearance Fraction (95% CI)	Forecasted Lack of Histological Clearance Fraction (95% CI)
First subgraph		
Surgical excision (A)	1.2 (0.1, 15.8)	1.2 (<0.5, 36.3)
Cryotherapy (C1)	10.1 (1.4, 46.4)	10.1 (0.4, 76.9)
Laser (C5+E1) + PDT (MAL)	37.5 (3.2, 91.5)	37.5 (1.1, 96.9)
PDT (MAL) (E1)	18.2 (5.1, 48.0)	18.2 (1.0, 82.5)
PDT (ALA) (E2)	25.0 (2.0, 84.4)	25.0 (0.7, 94.2)
5-FU (F1)	5.5 (0.4, 48.7)	5.5 (0.1, 73.9)
Imiquimod (F2)	22.2 (8.3, 47.3)	22.2 (1.5, 84.3)
Ingenol (F4)	77.1 (17.2, 98.2)	77.1 (6.5, 99.4)
Placebo (J)	83.3 (61.9, 93.9)	83.3 (21.1, 98.9)
Second subgraph		
Surgery + PDT (MAL) (A+E1)	36.4 (14.3, 66.1)	NA
Surgery + PDT (MAL) + curettage (A+E1+H)	20.0 (5.0, 54.1)	NA
Surgery + PDT (ALA) (A+E2)	36.4 (14.3, 66.1)	NA
Surgery + PDT (ALA) + curettage (A+E2+H)	18.2 (4.6, 50.7)	NA
Third subgraph		
Laser (C5)	43.5 (26.1, 62.8)	NA
Other medical (diclofenac and/or calcitriol) (F5)	97.1 (66.4 99.8)	NA
No treatment (J)	80.5 (58.8, 92.2)	NA
Fourth subgraph		
Imiquimod + curettage (F2+H)	10.0 (1.4, 46.7)	NA
Curettage (H)	40.0 (15.8, 70.3)	NA
Fifth subgraph		
MMS (B)	92.0 (75.8, 97.7)	NA
MMS + imiquimod (B+F2)	51.0 (37.0, 64.9)	NA

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; BCC = basal cell carcinoma; CI = confidence interval; NA=forecasts are not available for the 4 smaller subgraphs, because they were analyzed with a fixed effects model

Incomplete Excision, All BCC Lesions

Two RCTs reported incomplete excision outcomes in mixed BCC populations. In the first study, the average age was 68 (SD 12), and 39.7 percent were female. The average lesion size was 1.28 cm^2 (SD 1.36) in the group randomized to receive Mohs surgery (n=198) and 1.77 cm^2 (SD 1.28) in the surgical excision without intraoperative evaluation group (n=199). In this study, about half of the BCCs were classified as aggressive. After the first excision, 35 of 199 lesions (17.6%) were found to have been incompletely excised in the surgical excision without intraoperative margin assessment group; whereas none were found in the Mohs surgery group (0/198). Thirty-one of the lesions in the excision group were reexcised and of these four were found to have been incompletely excised (12.9%). In the aggressive lesions, the incomplete excision rate was 21 of 88 (23.9%) in the surgical excision group; none in the Mohs group (n=105).[81]

The second RCT reported incomplete excision and number of repeat procedures in people who had either surgical excision without intraoperative assessment of the margins or curettage and cryosurgery for BCCs on their face (90%) or trunk/neck (10%). The mean age was 67 (range 34 to 92), and 43 percent were women. In the curettage and cryosurgery group there were 51 lesions, all nodular, with an average diameter of 5.4 mm (SD 2.9). In the surgical excision arm, there were 49 lesions, 92 percent nodular and 8 percent superficial, with an average diameter of 5.3 mm (SD 2.6). There were no incomplete excisions in the curettage and cryosurgery group; and there were three in the surgical excision group (6%). There were no repeat procedures in the curettage and cryosurgery group and four in the surgical excision group.[19]

Lack of Histological Clearance, Subgroup Analyses by Lesion Type

We conducted subgroup analyses by the type of BCC lesion. We report analyses comparing groups of interventions, but not analyses comparing individual treatments. The latter are very sparse, and their results are very similar to the pertinent comparisons in Tables 24, 25, and 26.

Many subgroup analyses per lesion type are possible. In this section, we describe analyses in RCTs of lower-risk lesions (strata of predominantly [>80%] superficial BCCs, predominantly nodular BCCs, and superficial or nodular BCCs) overall, and broken down by lesion type, as well as higher-risk lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).

Fifteen RCTs (n=1972 lesions) included low-risk BCCs (nodular and superficial subtypes).[45, 49, 54, 55, 64, 66, 68-70, 92-94, 99, 101, 104] Their results are very similar to the findings in Tables 22 and 23 in the previous section.

With respect to RCT strata of predominantly superficial lesions, six RCTs (n=1300 lesions) compared PDT (E) versus drugs (F) versus no or sham treatment.[49, 55, 68, 69, 92, 94] Table 28 provides details about the comparisons between these six RCTs. The results are shown in Tables 29 and 30. Briefly, there was no statistically significant difference between the two active intervention categories, but both were statistically significantly better than no or sham treatment.

Table 28. Sample information, lack of histological clearance (superficial lesions)

Studies (total sample)	6 (1300)
Total sample by intervention	(E): 126; (F): 693; (I,J): 481
Total sample by intervention, (min, max)	126, 693

Data by comparison	(E--F): 1 (271); (F--I,J): 5 (1029)
Studies by comparison (min, max)	1, 5
Total sample by comparison (min, max)	271, 1029
Followup median (min, max)	3 (2, 36) months

A = surgical excision; B = Mohs micrographic surgery; C = heat/cold; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Table 29. Relative odds ratios for lack of histological clearance between intervention categories (predominantly superficial BCC lesions)

PDT (E)	0.19 (<0.005, 9.84)	***0.01 (<0.005, 0.36)***
5.17 (0.1, 263.01)	**Drugs (F)**	***0.03 (<0.005, 0.36)***
150.98 (2.78, 8187.95)	***29.21 (2.81, 303.6)***	**No/sham treatment (I,J)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 30. Mean fraction of lesions without histological clearance by intervention category (predominantly superficial BCC lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
PDT (E)	7.9 (0.2, 75.9)	7.9 (0.1, 93.1)
Drugs (F)	30.8 (8.4, 68.3)	30.8 (0.9, 95.6)
No/sham treatment (I,J)	92.9 (69.8, 98.7)	92.9 (20.2, 99.9)

PDT = photodynamic therapy; BCC = basal cell carcinoma; CI = confidence interval

With respect to the five RCT strata of predominantly nodular lesions (n=374),[45, 55, 66, 70, 93] details on the comparisons are in Table 31. The corresponding results are listed in Tables 32 and 33. These results are qualitatively similar to the corresponding results from the analyses in Tables 22 and 23.

Table 31. Sample information, lack of histological clearance (nodular lesions)

Studies (total sample)	5 (374)
Total sample by intervention	(F): 84; (I,J): 115; (A,B): 35; (E): 124; (C): 16
Total sample by intervention, (min, max)	16, 124
Data by comparison	(F--I,J): 2 (124); (I,J--E): 1 (150); (A,B--E): 1 (68); (E--C): 1 (32)
Studies by comparison (min, max)	1, 2
Total sample by comparison (min, max)	32, 150
Followup median (min, max)	3 (2, 12) months

A = surgical excision; B = Mohs micrographic surgery; C = heat/cold; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Table 32. Relative odds ratios for lack of histological clearance between intervention categories (nodular BCC lesions)

Surgery/MMS (A,B)	0.02 (<0.005, 1.48)	0.04 (<0.005, 1.79)	***0.01 (<0.005, 0.44)***	***<0.005 (<0.005, 0.14)***
42.6 (0.67, 2692.89)	**Heat/cold (C)**	1.9 (0.14, 26.18)	0.39 (0.02, 6.78)	0.14 (0.01, 1.99)
22.45 (0.56, 903.83)	0.53 (0.04, 7.27)	**PDT (E)**	0.21 (0.02, 1.76)	***0.08 (0.01, 0.48)***
108.35 (2.29, 5127.73)	2.54 (0.15, 43.87)	4.83 (0.57, 40.95)	**Drugs (F)**	0.36 (0.04, 3.13)
298.54 (7.35, 12122.67)	7.01 (0.5, 97.88)	***13.3 (2.1, 84.38)***	2.76 (0.32, 23.73)	**No/sham treatment (I,J)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma.

Table 33. Mean and forecasted lack of histological clearance fractions by intervention category (nodular BCC lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Surgery/MMS (A,B)	1.4 (<0.5, 31.0)	1.4 (<0.5, 44.0)
Heat/cold (C)	37.5 (5.8, 85.5)	37.5 (2.7, 92.8)
PDT (E)	24.0 (8.0, 53.6)	24.0 (2.7, 78.1)
Drugs (F)	60.4 (21.8, 89.3)	60.4 (9.6, 95.6)
No/sham treatment (I,J)	80.8 (52.9, 94.0)	80.8 (26.9, 98.0)

MMS= Mohs micrographic surgery; PDT=photodynamic therapy; BCC=basal cell carcinoma; CI=confidence interval

Incomplete Excision (a Related Outcome) in High-Risk BCCs

We identified one RCT that measured the distinct, yet related, outcome of incomplete excision in 172 lesions, about half of which were on the face, the rest were elsewhere on the body. This study compared surgical excision (A) with MMS (B) in histologically aggressive facial lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation). The average age was 65 years (standard deviation 13), and 43.3 percent were female. The average lesion diameter was 9.1 mm (standard deviation 4.1). In the 88 lesions that had surgical excision without intraoperative margin assessment, two had an incomplete excision. This outcome was not applicable to the other arm of the study (ALA-PDT).[20]

Lack of Histological Clearance, Other Subgroup Analyses (Lesion Location, Lesion Size, Sex, Age)

Table 34 shows results on subgroup analyses for two RCTs that reported treatment effects in subgroups of interest. The first RCT enrolled patients with predominantly superficial BCCs and found significant differences in treatment effects across a number of subgroups that include age, gender, lesion location, and lesion size.[49, 87, 88] The second RCT reported subgroup results for lack of histological clearance in predominantly nodular BCC. There was no significant difference between or within subgroups based on lesion location or size.[66]

Table 34. Subgroup results for lack of histological clearance in superficial BCCs

Study	Comparison	Timepoint	Subgroup	n/N Arm 1 vs. n/N Arm 2	OR (95% CI); P-Value Within	P- Value Between
Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	age: <= 60 years old	25/81 vs. 8/77	3.85 (1.61, 9.20); p=0.002	p=0.032
			age: > 60 years old	27/115 vs. 23/112	1.19 (0.63, 2.23); p=0.633	
Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	females	29/103 vs. 9/92	3.61 (1.61, 8.13); p=0.002	p=0.029
			males	23/93 vs. 22/97	1.12 (0.57, 2.19); p=0.865	
Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	lesion location: head/neck	9/24 vs. 4/20	2.40 (0.61, 9.47); p=0.321	p=0.047
			lesion location: trunk	36/115 vs. 12/116	3.95 (1.93, 8.08); p<0.001	
			lesion location: lower extremities	2/26 vs. 6/28	0.31 (0.06, 1.68); p=0.253	
			lesion location: upper extremities	5/31 vs. 3/25	1.41 (0.30, 6.58); p=0.720	
Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	lesion area: <= 60 mm2	23/106 vs. 18/90	1.11 (0.55, 2.22); p=0.861	p=0.043
			lesion area: > 60 mm2	27/86 vs. 12/96	3.20 (1.50, 6.83); p=0.002	
Foley 2009 20064185	PDT (MAL) (E1) vs. sham PDT (J)	3 months	lesion location: extremities	5/15 vs. 12/17	0.21 (0.05, 0.93); p=0.074	p=0.437
			lesion location: face/scalp	3/19 vs. 18/23	0.05 (0.01, 0.25); p<0.001	
			lesion location: neck	4/9 vs. 1/1	0.27 (0.01, 8.46); p=1.000	
			lesion location: trunk	8/32 vs. 24/34	0.14 (0.05, 0.41); p<0.001	
Foley 2009 20064185	PDT (MAL) (E1) vs. sham PDT (J)	3 months	lesion diameter: <10 mm	15/64 vs. 43/61	0.13 (0.06, 0.28); p<0.001	p=0.939
			lesion diameter: 10-20 mm	5/11 vs. 12/14	0.14 (0.02, 0.94); p=0.081	

NA = not significant; PDT = photodynamic therapy; BCC = basal cell carcinoma; MAL = methyl aminolevulinate; OR = odds ratio; CI = confidence interval

Lack of Histological Clearance, Results From Nonrandomized Studies (BCC Lesions)

We identified six NRCSs reporting lack of histological clearance in BCC or mixed BCC and SCC lesions.[143, 150-154] These are summarized narratively below.

The first NRCS included 12 patients with one superficial BCC each. After an initial excision surgery, six patients received imiquimod and six received placebo. The study was deemed to be at a high risk of confounding bias, because the arms were not balanced (there were only six patients per arm); both the dermatologist and pathologist were blinded, and the study followed all participants to the end. The mean lesion area was 52 mm^2, and the lesions were located on the trunk or neck (67%) or forearm (33%). The mean age was 61 (range 52 to 78), and 33 percent

were female. All lesions in the vehicle group had residual tumor at excision, as did four of the six treated with imiquimod.[154]

The second NRCS reported lack of clinical and histological clearance in 74 patients with one nodular BCC each, receiving different doses of vismodegib. The risk of bias of this study was judged to be moderate because of lack of blinding and inadequate baselines reporting that lead to ambiguity about how well balanced the arms were. The lesion diameter ranged from 1 to 3 cm, and all were located in the scalp, head, neck, trunk, or limbs. The mean age was 63.6 (SD 12; range 40 to 89), and 22 percent were female; 99 percent were white. Twenty-four lesions were treated with vismodegib for 12 weeks then were excised; twenty-five were treated with vismodegib for 12 weeks then had a 24-week observation period before excision; and 25 were treated with vismodegib for 16 weeks then were excised. The 12-week groups had a much higher and statistically significant rate of lack of clinical clearance than the 16-week group (OR 10.42; 95% CI 1.22 to 89.13). However, the lack of histological clearance was much closer between the two doses, and not significant (OR 1.57; 95% CI 0.49 to 5.01).[153]

The third NRCS reported on lack of histological clearance in 56 people with 56 nodular BCCs, who received ALA-PDT with or without surface preparation with a CO2 laser. This study was judged to have moderate to low risk of bias, primarily because of lack of blinding. The mean age was 62, and 43 percent were females. Most of the lesions (87.5%) were on the head (not H-zone or adjacent to the eyes or ears) or neck. The group with the surface preparation had a lower rate of lack of histological clearance than the group without surface preparation (OR 0.23; 95% CI 0.07 to 0.75).[150]

The fourth NRCS reported on a matched population of 40 patients treated with different doses of brachytherapy (36.6 versus 42 Gy). This study was deemed to be at a moderate risk of confounding bias, primarily for lack of blinding and unclear reporting of baselines. The mean age was 75, 45 percent were female, and all had a Fitzpatrick skin score of I (47.5%) or II (52.5%). Forty-five percent of the BCCs were superficial, while 55 percent were nodular; 75 percent were on the head and neck and 25 percent on the trunk or extremities. The lower dose (36.6 Gy) had a higher rate of lack of histological clearance at up to a year than the higher dose (42 Gy), but this difference was not significant (OR 2.11; 95% CI 0.18 to 25.35).[143]

The fifth NRCS reports on 20 BCC lesions (43% superficial/multicentric, 47.5% nodular, 9.5% infiltrative/micronodular/morpheaform/sclerosing; 90.5% on the trunk/neck and 9.5% on the extremities) treated with pulse dye laser and 20 matched lesions that received no treatment. This study was deemed to be at a moderate risk of confounding bias, primarily for lack of blinding and unclear reporting of baselines. At surgical excision, approximately 2 weeks after the last treatment, 7 of the 20 lesions treated with pulse dye laser showed lack of histological clearance, compared to 18 of the lesions not treated (OR 0.06; 95% CI 0.01 to 0.34).[152]

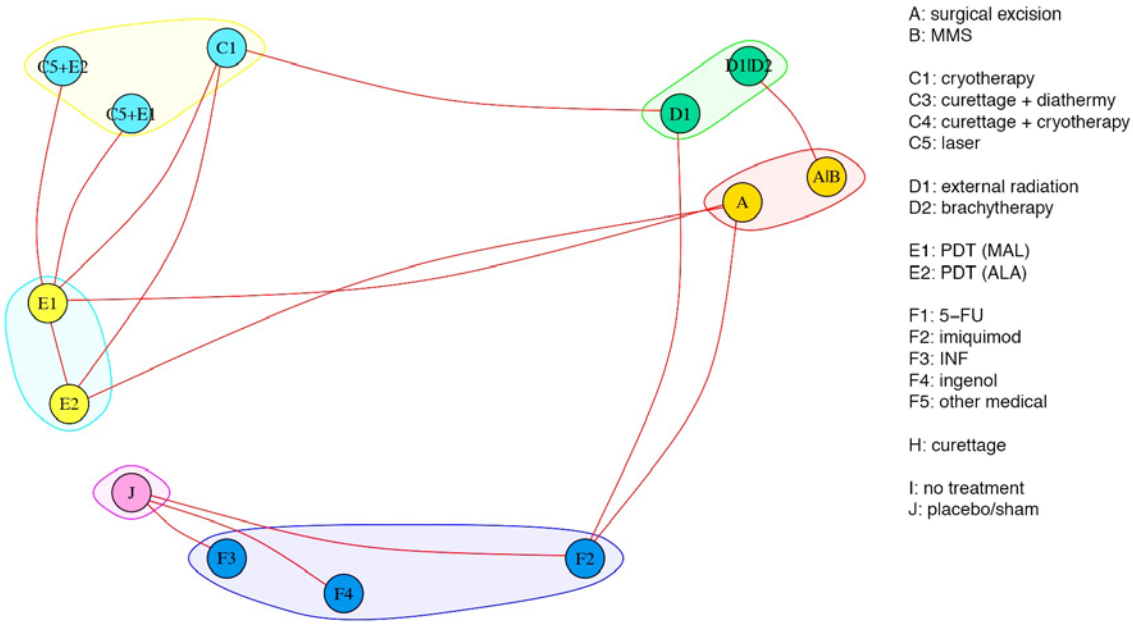
Finally, the sixth NRCS included both BCCs (71%) and SCCs (29%), and compared two doses of external radiation therapy. In the lower-dose (37 Gy) group 14 of 236 lesions (5.9%) were not histologically clear compared to none of 149 (0%) in the higher-dose (45 Gy) group. There was no adjusted analysis available for this outcome.[151]

Lack of Clinical Clearance, All BCC Lesions

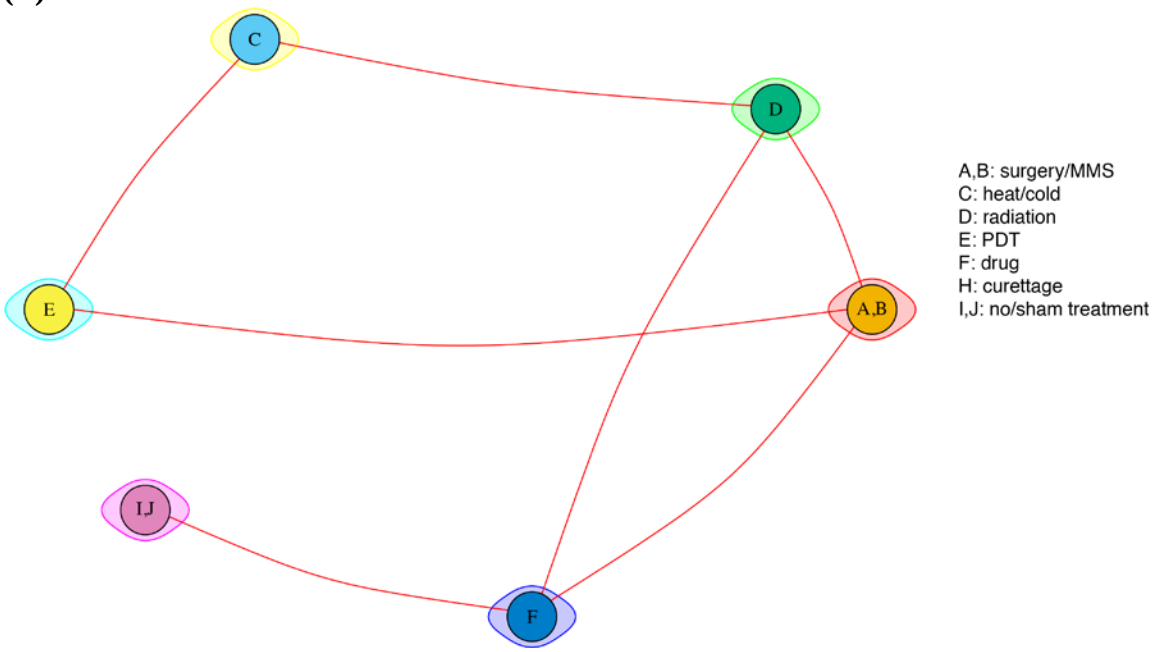
The evidence graph for lack of clinical clearance with respect to individual treatments is sparse (Figure 6 (C) – reproduced in Figure 9 (A) for ease of reference), and comprises 3 connected subgraphs. Detailed results at the RCT-level are in Appendix I.

Figure 9. Evidence graph of RCTs evaluating lack of clinical clearance in BCCs across (A) individual interventions and (B) types of interventions

(A)



(B)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

Comparisons Across Intervention Categories

In total, 15 RCTs (1846 lesions) were included in this analysis.[42, 47, 50-53, 58, 59, 67, 70, 85, 92, 94, 98, 104] Twelve RCTs were deemed to be at low or moderate risk of bias. Cumulative sample sizes per comparison ranged from 27 to 380; for more details see Table 35.

Table 35. Sample information, lack of clinical clearance (all BCC lesions, intervention categories)

Studies (total sample)	15 (1846)
Total sample by intervention	(D): 201; (F): 379; (A,B): 460; (C): 223; (I,J): 129; (E): 404
Total sample by intervention, (min, max)	129, 460
Data by comparison	(D--F): 1 (27); (D--A,B): 1 (347); (D--C): 1 (31); (F--A,B): 1 (212); (F--I,J): 3 (379); (A,B--E): 3 (380); (C--E): 4 (420)
Studies by comparison (min, max)	1, 4
Total sample by comparison (min, max)	27, 420
Followup median (min, max)	6 (3, 41) months

A = surgical excision, B = Mohs micrographic surgery; BCC=basal cell carcinoma; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Table 36 shows the relative odds ratios for lack of clinical clearance across intervention categories. Overall, no or sham treatment (I,J) was statistically significantly worse than all active treatments. Surgical treatments (A,B) were statistically significantly better than PDT (E) and drugs (F) All other comparisons were statistically not significant; however, the confidence intervals were wide and could not exclude even large differences between the comparators.

In the Table, shaded cells correspond comparisons that have been inferred from the analysis model, but that have not been examined in the included RCTs. For example, comparisons of surgical treatments (A,B) versus drugs (F) are indirect. Indirect comparisons are more uncertain that those for which head-to-head data exist. The added uncertainty about indirect comparisons is partly reflected in the width of the respective 95% confidence intervals, which is (often much) broader for comparisons without versus with direct data. For all comparisons that are empirically observed (all nonshaded cells in the Table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 36 (see Appendix I).

Table 36. Relative odds ratios for lack of clinical clearance between intervention categories (all BCC lesions, Figure 9B)

Surgery|MMS (A|B)	0.23 (0.05, 1.11)	0.64 (0.08, 5.11)	***0.18 (0.05, 0.7)***	***0.16 (0.03, 0.87)***	***0.01 (<0.005, 0.04)***
4.29 (0.9, 20.48)	**Heat/cold (C)**	2.74 (0.36, 20.9)	0.78 (0.28, 2.2)	0.68 (0.13, 3.56)	***0.03 (<0.005, 0.17)***
1.57 (0.2, 12.55)	0.37 (0.05, 2.79)	**Radiation (D)**	0.29 (0.04, 2.08)	0.25 (0.03, 2.09)	***0.01 (<0.005, 0.1)***
5.48 (1.44, 20.89)	1.28 (0.46, 3.58)	3.5 (0.48, 25.44)	**PDT (E)**	0.86 (0.18, 4.1)	***0.03 (0.01, 0.2)***
6.35 (1.15, 35.1)	1.48 (0.28, 7.8)	4.05 (0.48, 34.21)	1.16 (0.24, 5.51)	**Drugs (F)**	***0.04 (0.01, 0.14)***
171.32 (23.53, 1247.4)	***39.94 (5.86, 272.09)***	***109.33 (10.37, 1152.42)***	***31.28 (5, 195.56)***	***26.99 (7.26, 100.4)***	**No/sham treatment (I|J)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy.

Table 37 offers complementary information from the same analysis. For each intervention category, it shows the mean fraction of lesions without clinical clearance across the included RCTs. It also forecasts expected fractions with each intervention category in groups of patients similar to the patients included in the analyzed RCTs. The average percentage of lesions with no clinical clearance was 2.9 percent in surgical treatment arms, between 4.5 and 16.5 percent in other active intervention categories, and 84.2 percent for no or sham treatment.

Table 37. Mean and forecasted lack of clinical clearance fractions by intervention category (all BCC lesions)

Intervention Type	Mean Lack of Clinical Clearance Fraction Percent (95% CI)	Forecasted Lack of Clinical Clearance Fraction Percent (95% CI)
Surgery|MMS (A|B)	3.0 (0.8, 10.7)	3.0 (0.2, 38.7)
Heat/cold (C)	11.9 (4.2, 29.1)	11.9 (0.7, 71.1)
Radiation (D)	4.7 (0.8, 23.4)	4.7 (0.2, 55.8)
PDT (E)	14.7 (6.1, 31.3)	14.7 (1.0, 74.9)
Drugs (F)	16.6 (5.3, 41.6)	16.6 (1.0, 79.6)
No/sham treatment (I|J)	84.3 (52.5, 96.3)	84.3 (19.2, 99.2)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; CI = confidence interval; BCC = basal cell carcinoma

Comparisons Across Individual Interventions

The results of the analyses of intervention categories are congruent with the corresponding results of analyses of individual interventions. As evident from Figure 9, there are 2 connected subgraphs for this outcome. Separate analyses are conducted for each connected subgraph. In total, 14 RCTs (1734 lesions) were included in these analyses, as summarized in Table 38.

Table 38. Sample information, lack of clinical clearance (all BCC lesions, individual interventions)

	First subgraph[42, 47, 51-53, 58, 59, 67, 70, 85, 92, 94, 98, 104]	Second subgraph[50]
Studies (total sample)	14 (1449)	1 (347)
Total sample by intervention	(D1): 28; (F2): 213; (C1): 152; (F3): 118; (J): 129; (E2): 93; (A): 286; (E1): 311; (F4): 48; (C5+E1): 37; (C5 + E2): 34	(A|B): 174; (D1|D2): 173
Total sample by intervention, (min, max)	28, 311	173, 174
Data by comparison	(D1--F2): 1 (27); (D1--C1): 1 (31); (F2--J): 1 (166); (F2--A): 1 (212); (C1--E2): 1 (83); (C1--E1): 1 (201); (F3--J): 1 (159); (J--F4): 1 (54); (E2--A): 1 (40); (A--E1): 2 (340); (E1--C5+E1): 2 (74); (E2—C5 + E2): 1 (62)	(A|B--D1|D2): 1 (347)
Studies by comparison (min, max)	1, 2	1, 1
Total sample by comparison (min, max)	27, 340	347, 347
Followup median (min, max)	6 (3, 12) months	41 (41, 41) months

A = surgical excision; B = Mohs micrographic surgery; BCC=basal cell carcinoma; C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; C5 = laser; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F1 = 5-FU; F2 = Imiquimod; F3 = Interferon; F4 = Ingenol; H = curettage; J = placebo

Table 39 has results on the relative effects for the largest subgraph. Table 40 has the corresponding results for the comparison of surgical excision or MMS (A|B) with external radiation therapy or brachytherapy (D1|D2). In Table 39 comparisons across individual observations are sparse; the majority of the pairwise comparisons are inferred from indirect data. The confidence intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the comparators. The comparison in Table 40 was not statistically significant; the confidence interval was wide and could not exclude large differences between the comparators.

Table 41 shows, for each intervention, the mean fractions for lack of clinical clearance across all RCTs. Estimates for interventions in all three subgraphs are listed in the table. One should not statistically compare these fractions across the subgraphs, because they come from disjoint analyses. In general, the mean fractions of lack of clinical clearance for individual interventions are in congruence with the corresponding fractions estimated for intervention categories.

Table 39. Relative odds ratios for lack of clinical clearance between individual interventions (all BCC lesions, Figure 9A, largest subgraph)

Surgery (A)	*0.17 (0.04, 0.65)*	0.6 (0.13, 2.72)	0.28 (0.07, 1.22)	0.45 (0.03, 6.02)	*0.2 (0.06, 0.7)*	0.41 (0.14, 1.18)	0.36 (0.08, 1.74)	0.27 (0.05, 1.42)	*0.07 (0.01, 0.45)*	*0.06 (0.01, 0.29)*
5.95 (1.53, 23.14)	Cryotherapy (C1)	3.56 (0.84, 15.01)	1.68 (0.34, 8.28)	2.67 (0.23, 31.74)	1.21 (0.39, 3.77)	2.44 (0.7, 8.51)	2.16 (0.41, 11.44)	1.61 (0.28, 9.21)	0.44 (0.07, 2.84)	0.35 (0.07, 1.88)
1.67 (0.37, 7.6)	0.28 (0.07, 1.18)	Laser + PDT (MAL) (C5+E1)	0.47 (0.07, 2.99)	0.75 (0.05, 10.88)	*0.34 (0.14, 0.84)*	0.69 (0.14, 3.29)	0.61 (0.1, 3.69)	0.45 (0.07, 2.95)	*0.12 (0.02, 0.9)*	*0.1 (0.02, 0.6)*
3.53 (0.82, 15.24)	0.59 (0.12, 2.92)	2.11 (0.33, 13.37)	Laser + PDT (ALA) (C5+E2)	1.59 (0.1, 25.01)	0.72 (0.14, 3.65)	1.45 (0.51, 4.16)	1.28 (0.19, 8.56)	0.96 (0.13, 6.85)	0.26 (0.03, 2.09)	0.21 (0.03, 1.41)
2.22 (0.17, 29.75)	0.37 (0.03, 4.44)	1.33 (0.09, 19.26)	0.63 (0.04, 9.9)	External radiation (D1)	0.45 (0.04, 5.67)	0.91 (0.07, 12.11)	0.81 (0.06, 10.4)	0.6 (0.04, 8.25)	0.16 (0.01, 2.47)	0.13 (0.01, 1.72)
4.93 (1.43, 17.02)	0.83 (0.26, 2.6)	*2.95 (1.2, 7.28)*	1.4 (0.27, 7.12)	2.22 (0.18, 27.9)	PDT (MAL) (E1)	2.02 (0.55, 7.48)	1.79 (0.36, 8.8)	1.33 (0.25, 7.1)	0.36 (0.06, 2.2)	0.29 (0.06, 1.44)
2.44 (0.85, 7.01)	0.41 (0.12, 1.43)	1.46 (0.3, 7)	0.69 (0.24, 1.98)	1.1 (0.08, 14.53)	0.49 (0.13, 1.82)	PDT (ALA) (E2)	0.88 (0.17, 4.57)	0.66 (0.12, 3.7)	0.18 (0.03, 1.15)	*0.14 (0.03, 0.75)*
2.75 (0.58, 13.2)	0.46 (0.09, 2.46)	1.65 (0.27, 10.02)	0.78 (0.12, 5.21)	1.24 (0.1, 15.97)	0.56 (0.11, 2.75)	1.13 (0.22, 5.85)	Imiqumod (F2)	0.74 (0.35, 1.59)	*0.2 (0.06, 0.63)*	*0.16 (0.1, 0.28)*
3.7 (0.7, 19.48)	0.62 (0.11, 3.56)	2.21 (0.34, 14.44)	1.05 (0.15, 7.51)	1.66 (0.12, 22.82)	0.75 (0.14, 3.99)	1.52 (0.27, 8.54)	1.34 (0.63, 2.87)	INF (F3)	*0.27 (0.09, 0.87)*	*0.22 (0.13, 0.38)*
13.59 (2.24, 82.53)	2.29 (0.35, 14.85)	*8.14 (1.11, 59.66)*	3.85 (0.48, 30.95)	6.12 (0.41, 92.23)	2.76 (0.45, 16.72)	5.58 (0.87, 35.77)	4.93 (1.58, 15.4)	3.68 (1.16, 11.69)	Ingenol (F4)	0.81 (0.29, 2.24)
16.86 (3.47, 82.04)	2.84 (0.53, 15.08)	*10.09 (1.66, 61.51)*	4.77 (0.71, 32.06)	7.59 (0.58, 98.98)	3.42 (0.69, 16.86)	*6.93 (1.33, 36.11)*	*6.12 (3.61, 10.4)*	*4.56 (2.64, 7.88)*	1.24 (0.45, 3.45)	Placebo (J)

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates a significant result. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; INF = Interferon; BCC = basal cell carcinoma; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon.

Table 40. Relative odds ratios for lack of clinical clearance between individual interventions (all BCC lesions, Figure 9A, remaining subgraphs)

Surgery or MMS (A|B)	0.16 (0.01, 3.27)
6.16 (0.31, 123.87)	**External radiation or brachytherapy (D1|D2)**

BCC = basal cell carcinoma

Table 41. Mean and forecasted lack of clinical clearance fractions by individual intervention (all BCC lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
First subgraph (Figure 9)		
Surgical excision (A)	0.5 (0.2, 1.8)	0.5 (0.0, 9.8)
Cryotherapy (C1)	3.1 (1.0, 9.4)	3.1 (0.2, 38.2)
Laser + PDT (MAL) (C5+E1)	0.9 (0.2, 3.4)	0.9 (0.0, 16.2)
Laser + PDT (ALA)	1.8 (0.4, 7.5)	1.8 (0.1, 29.1)
External radiation (D1)	1.2 (0.1, 11.5)	1.2 (0.0, 31.1)
PDT (MAL) (E1)	2.6 (0.9, 7.1)	2.6 (0.1, 32.9)
PDT (ALA) (E2)	1.3 (0.4, 4.2)	1.3 (0.1, 20.6)
Imiquimod (F2)	1.6 (0.4, 5.2)	1.6 (0.1, 24.0)
IFN(F3)	1.6 (0.4, 5.9)	1.6 (0.1, 25.4)
Ingenol (F4)	5.5 (1.5, 18.4)	5.5 (0.3, 54.9)
No/sham treatment (J)	6.6 (2.0, 19.7)	6.6 (0.4, 58.6)
Second subgraph (Figure 9)		
Surgical excision or MMS (A|B)	0.3 (0.0, 4.4)	NA
External radiation or brachytherapy (D1|D2)	1.7 (0.6, 5.2)	NA

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; INF = interferon; BCC = basal cell carcinoma; CI = confidence interval; NA = not applicable

Lack of Clinical Clearance, Subgroup Analyses by Lesion Type

We conducted subgroup analyses by the type of BCC lesion. We report analyses comparing groups of interventions, but not analyses comparing individual treatments. The latter are very sparse, and their results are similar to the pertinent comparisons in Tables 39 and 40.

Many subgroup analyses per lesion type are possible; we describe here analyses in RCTs of lower-risk lesions (strata of predominantly [>80%] superficial BCCs, predominantly nodular BCCs, and superficial or nodular BCCs) overall, and broken down by lesion type, along with analyses of higher-risk lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).

All 14 RCTs reporting results on lack of clinical clearance enrolled patients with low-risk BCCs (nodular and superficial subtypes; n=1922).[47, 50-53, 58, 59, 67, 70, 85, 92, 94, 98, 104] Thus, for the lower-risk BCCs subgroup the results are practically the same as in the previous section (Tables 36 and 37).

Table 42 summarizes characteristics of the five RCTs of patients with predominantly superficial BCC lesions (n=868).[51, 52, 92, 94, 98] Tables 43 and 44 show the results. Most comparisons in Table 43 are indirect, and the confidence intervals for these differences are too broad to allow drawing conclusions..

Table 42. Sample information, lack of clinical clearance (superficial BCC lesions)

Studies (total sample)	5 (868)
Total sample by intervention	(F): 246; (I,J): 88; (A,B): 215; (E): 221; (C): 98

Total sample by intervention, (min, max)	88, 246
Data by comparison	(F--I,J): 2 (220); (F--A,B): 1 (212); (A,B--E): 1 (235); (E--C): 1 (201)
Studies by comparison (min, max)	1, 2
Total sample by comparison (min, max)	201, 235
Followup median (min, max)	3 (3, 36) months

A = surgical excision; B = Mohs micrographic surgery; BCC=basal cell carcinoma; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Table 43. Relative odds ratios for lack of clinical clearance between intervention categories (superficial BCC lesions)

Surgery/MMS (A,B)	0.13 (<0.005, 10.81)	0.12 (<0.005, 5.06)	0.02 (<0.005, 0.79)	<0.005 (<0.005, 0.02)
7.71 (0.09, 642.49)	**Heat/cold (C)**	0.94 (0.01, 59.67)	0.19 (<0.005, 9.58)	<0.005 (<0.005, 0.28)
8.16 (0.2, 337.33)	1.06 (0.02, 66.93)	**PDT (E)**	0.2 (0.01, 4.49)	<0.005 (<0.005, 0.14)
40.1 (1.27, 1269.18)	5.2 (0.1, 259.27)	4.91 (0.22, 108.22)	**Drugs (F)**	0.02 (<0.005, 0.53)
2071.45 (41.73, 102817.08)	268.7 (3.6, 20036.53)	253.71 (7.01, 9177.18)	51.65 (1.88, 1415.99)	**No/sham treatment (I,J)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons. Results are given as odds ratios (95% confidence intervals).

BCC=basal cell carcinoma; MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Table 44. Mean and forecasted lack of clinical clearance fractions by intervention category (superficial BCC lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Surgery/MMS (A,B)	0.7 (<0.5, 10.7)	0.7 (<0.5, 34.6)
Heat/cold (C)	5.1 (0.2, 61.3)	5.1 (<0.5, 85.5)
PDT (E)	5.4 (0.5, 38.5)	5.4 (0.1, 76.5)
Drugs (F)	21.9 (3.8, 66.4)	21.9 (0.6, 92.6)
No/sham treatment (I,J)	93.5 (50.0, 99.5)	93.5 (17.6, 99.9)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma; CI = confidence interval

Table 45 provides details on the comparisons of six RCTs of predominantly nodular lesions (n=434). Results are given in Tables 46 and 47.[52, 53, 58, 67, 70, 85] These results very uncertain, and are based on at most two studies per comparison. The confidence intervals for differences between the intervention categories are generally very broad.

Table 45. Sample information, lack of clinical clearance (superficial BCC lesions)

Studies (total sample)	6 (434)
Total sample by intervention	(D): 12; (F): 113; (A,B): 161; (E): 111; (C): 37
Total sample by intervention, (min, max)	12, 161
Data by comparison	(D--F): 1 (27); (F--A,B): 1 (188); (A,B--E): 2 (145); (E--C): 2 (74)
Studies by comparison (min, max)	1, 2

Total sample by comparison (min, max)	27, 188
Followup median (min, max)	8 (3, 36) months

A = surgical excision; B = Mohs micrographic surgery; BCC=basal cell carcinoma; C = heat/cold; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Table 46. Relative odds ratios between intervention categories for lack of clinical clearance (nodular BCC lesions)

Surgery/MMS (A,B)	2.06 (0.38, 11.25)	1.79 (0.03, 97.08)	0.28 (0.09, 0.87)	1.98 (0.15, 26.6)
0.49 (0.09, 2.65)	Heat/cold (C)	0.87 (0.01, 53.43)	0.13 (0.04, 0.49)	0.96 (0.06, 16.76)
0.56 (0.01, 30.25)	1.15 (0.02, 70.67)	Radiotherapy (D)	0.15 (<0.005, 8.16)	1.11 (0.03, 44.12)
3.63 (1.16, 11.4)	7.48 (2.06, 27.14)	6.5 (0.12, 344.91)	PDT (E)	7.19 (0.52, 99.37)
0.5 (0.04, 6.77)	1.04 (0.06, 18.11)	0.9 (0.02, 36.04)	0.14 (0.01, 1.92)	Drugs (F)

Note: RCTs of predominantly nodular lesions. Cells shaded gray indicate that the estimate is based only on indirect comparisons. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 47. Mean fractions of lesions with no clinical clearance by intervention category (nodular BCC lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Surgery/MMS (A,B)	7.6 (1.5, 31.6)	7.6 (0.2, 74.7)
Heat/cold (C)	3.9 (0.6, 20.6)	3.9 (0.1, 60.6)
Radiotherapy (D)	4.4 (0.1, 66.7)	4.4 (0.0, 86.1)
PDT (E)	23.0 (6.0, 58.5)	23.0 (0.9, 90.8)
Drugs (F)	4.0 (0.4, 32.7)	4.0 (0.1, 69.1)

Note: RCTs of predominantly nodular lesions.

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma; CI = confidence interval

Lack of Clinical Clearance, Other Subgroup Analyses (Lesion Location, Lesion Size)

Table 48 shows results on subgroup analyses for three RCTs that reported treatment effects in subgroups of interest, two in patients with predominantly superficial BCCs[51, 98] and one in patients with predominantly nodular BCCs.[22, 85] Neither lesion location nor size were associated with differences in the treatment effect beyond what is expected by chance. Only one outcome was statistically significant at a 0.05 level: surgical excision (A) performed better than PDT with MAL (E1) for lesions on the trunk and neck at 3 months; however by 12 months, this finding was no longer significant.[98]

Table 48. Subgroup results for lack of clinical clearance in BCC lesions

Study	Comparison	Timepoint	Subgroup	n/N Arm 1 vs. n/N Arm 2	OR (95% CI); P-Value Within	P- Value Between
Szeimies 2008 18624842	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion location: face/scalp	0/4 vs. 0/15	N/A	NA
			lesion location: trunk/neck	1/83 vs. 7/76	0.12 (0.01, 1.00) ; p=0.028	
			lesion location: extremities	0/31 vs. 3/37	0.16 (0.01, 3.15); p=0.245	
Szeimies 2008 18624837	Surgical excision (A) vs. PDT (MAL) (E1)	12 months	lesion location: face/scalp	0/4 vs. 4/15	0.28 (0.01, 6.42); p=0.530	NA
			lesion location: trunk/neck	0/82 vs. 3/69	0.12 (0.01, 2.27); p=0.093	
			lesion location: extremities	0/31 vs. 4/34	0.11 (0.01, 2.08); p=0.115	
Rhodes 2004 14732655	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion location: extremities	0/5 vs. 0/5	NA	NA
			lesion location: face/scalp	1/32 vs. 1/21	0.65 (0.04, 10.91); p=1.000	
			lesion location: trunk/neck	0/15 vs. 4/27	0.17 (0.01, 3.35); p=0.279	
Szeimies 2008 18624840	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion diameter: 7-14 mm	1/70 vs. 7/85	0.16 (0.02, 1.35); p=0.073	NA
			lesion diameter: 15-20 mm	0/43 vs. 3/43	0.13 (0.01, 2.66); p=0.241	
Rhodes 2004 14732655	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion diameter: 6-14mm	1/43 vs 4/40	0.21 (0.02, 2.00); p=0.191	p=0.994
			lesion diameter: 15-19mm	0/6 vs. 1/11	0.54 (0.02, 15.30); p=1.000	
			lesion diameter: 20-30mm	0/3 vs. 0/2	NA	
Basset-Seguin 2008 18693159	Cryotherapy (C1) vs. PDT (MAL) (E1)	3 months	lesion diameter: 5-10mm	3/41 vs. 1/44	3.39 (0.34, 34.02); p=0.349	NA
			lesion diameter: 11-19 mm	2/41 vs. 1/43	2.15 (0.19, 24.70); p=0.611	
			lesion diameter: >= 20 mm	0/16 vs. 1/16	0.31 (0.01, 8.28); p=1.000	

NA = not significant; PDT = photodynamic therapy; MAL = methyl aminolevulinate; BCC = basal cell carcinoma; CI = confidence interval

Lack of Clinical Clearance, Results From Nonrandomized Studies (BCC Lesions)

None of the eligible NRCSs reported data on lack of clinical clearance.

Various Outcomes in Patients With High-Risk BCC Lesions Treated With Hedgehog Inhibitors

Hedgehog inhibitors, including vismodegib and sonidegib (F5, other drugs), are a group of systemic medications that are primarily used for advanced or metastatic BCC. Comparisons of outcomes in these high-risk populations with studies that include lower-risk BCCs are not clinically meaningful and so we report these separately.

One RCT (n=230) compared 2 doses (200 vs. 800 mg per os daily) of sonidegib for locally advanced BCC not amenable to surgery (n=194) or radiation or metastatic BCC for which other options had been exhausted (n=36). Median age was 67 and 65, respectively, and over 90 percent were white. In the locally advanced group, 2 of 66 (3%) participants in the 200 mg arm achieved a complete response compared with none of 128 (0%) in the 800 mg arm. The number of participants experiencing any adverse event was high in both arms (75/79 [95%] in the 200 mg arm, 150/150 [100%] in the 800 mg arm.[75]

Patient-Reported Cosmetic Outcomes, All BCC Lesions

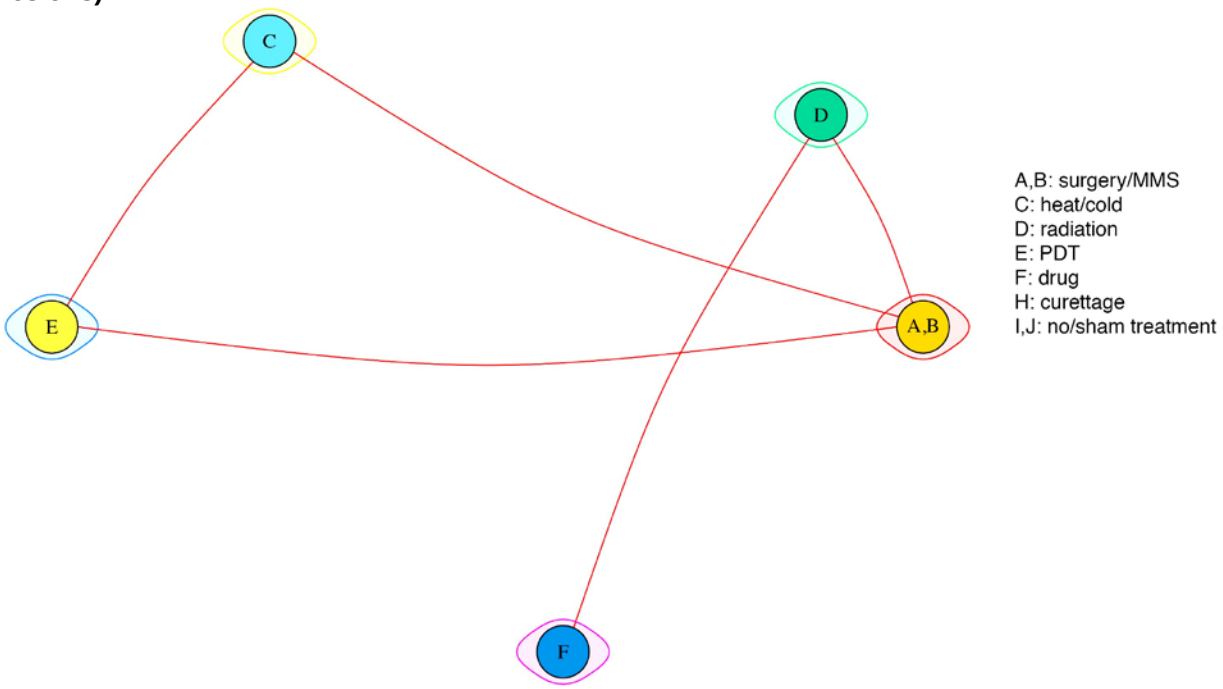
For this outcome we describe only results between intervention categories, because data are sparse for the comparison of individual observations. In total, seven RCTs (752 lesions) were included in this analysis.[50, 51, 67, 70, 85, 98, 99] Five RCTs were deemed to be at low or moderate risk of bias. The evidence graph in Figure 10 shows the observed comparisons based on RCTs that report patient assessments of "at least good" cosmetic outcome. The evidence graph is sparsely connected. Patients assessed cosmetic outcomes using different scales in each RCT, though often on scales of that included poor, fair, good, and excellent or similar. We provide analyses for an "at least good" cosmetic outcome. Details about the comparisons between these RCTs are in Table 49.

Table 49. Sample information, patient-reported cosmetic outcomes (all BCC lesions, intervention categories)

Studies (total sample)	7 (752)
Total sample by intervention	(D): 125; (F): 15; (A,B): 309; (C): 113; (E): 190
Total sample by intervention, (min, max)	15, 309
Data by comparison	(D--F): 1 (27); (D--A,B): 1 (244); (A,B--C): 1 (96); (A,B--E): 2 (254); (C--E): 2 (131)
Studies by comparison (min, max)	1, 2
Total sample by comparison (min, max)	27, 254
Followup median (min, max)	4 (3, 48) months

A = surgical excision; B = Mohs micrographic surgery; BCC = basal cell carcinoma; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Figure 10. Evidence graph of RCTs comparing patient-assessed cosmetic outcomes (all BCC lesions)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 50 shows the results of the comparisons between intervention categories based on a network meta-analysis. Most comparisons are indirect (denoted by shaded cells) and have wide confidence intervals. For comparisons with head-to-head data (denoted by unshaded cells) the numbers in the table are very similar whether information from indirect comparisons is included or excluded. Five of 10 comparisons are statistically significant.

Table 50. Relative odds ratios between intervention categories for at least good cosmetic outcome as assessed by patients (all BCC lesions, Figure 10)

Surgery/MMS (A,B)	**5.2 (1.37, 19.79)**	***2.1 (1.18, 3.72)***	***0.17 (0.06, 0.46)***	0.49 (0.02, 14.01)
0.19 (0.05, 0.73)	**Heat/cold (C)**	0.4 (0.1, 1.67)	***0.03 (0.01, 0.13)***	0.09 (<0.005, 3.01)
0.48 (0.27, 0.85)	2.48 (0.6, 10.25)	**Radiation (D)**	***0.08 (0.02, 0.25)***	0.23 (0.01, 6.69)
6 (2.16, 16.69)	***31.19 (7.54, 128.97)***	***12.58 (3.95, 40.03)***	**PDT (E)**	2.95 (0.09, 93.05)
2.03 (0.07, 58.01)	10.58 (0.33, 336.76)	4.27 (0.15, 121.7)	0.34 (0.01, 10.7)	**Drugs (F)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 51 shows the average percentage of patients with at least good cosmetic outcomes in the RCTs, based on the same network meta-analysis as Table 50. Drugs (F) and PDT (E) are associated with highest percentages, followed surgical treatments (A,B), radiation (D), interventions that use heat or cold to destroy the lesion (C).

Table 51. Mean and forecasted fractions of lesions with at least good cosmetic outcome as assessed by patients (all BCC lesions)

Intervention Type	Mean Percent (95% CI)	Mean Percent (95% CI)
Surgery/MMS (A,B)	88.8 (73.7, 95.7)	88.8 (44.3, 98.8)
Heat/cold (C)	60.5 (32.4, 83.0)	60.5 (12.7, 94.2)
Radiation (D)	79.1 (55.2, 92.1)	79.1 (26.8, 97.5)
PDT (E)	97.9 (93.1, 99.4)	97.9 (81.1, 99.8)
Drugs (F)	94.2 (37.5, 99.8)	94.2 (25.0, 99.9)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma; CI = confidence interval

Observer-Reported Cosmetic Outcomes, All BCC Lesions

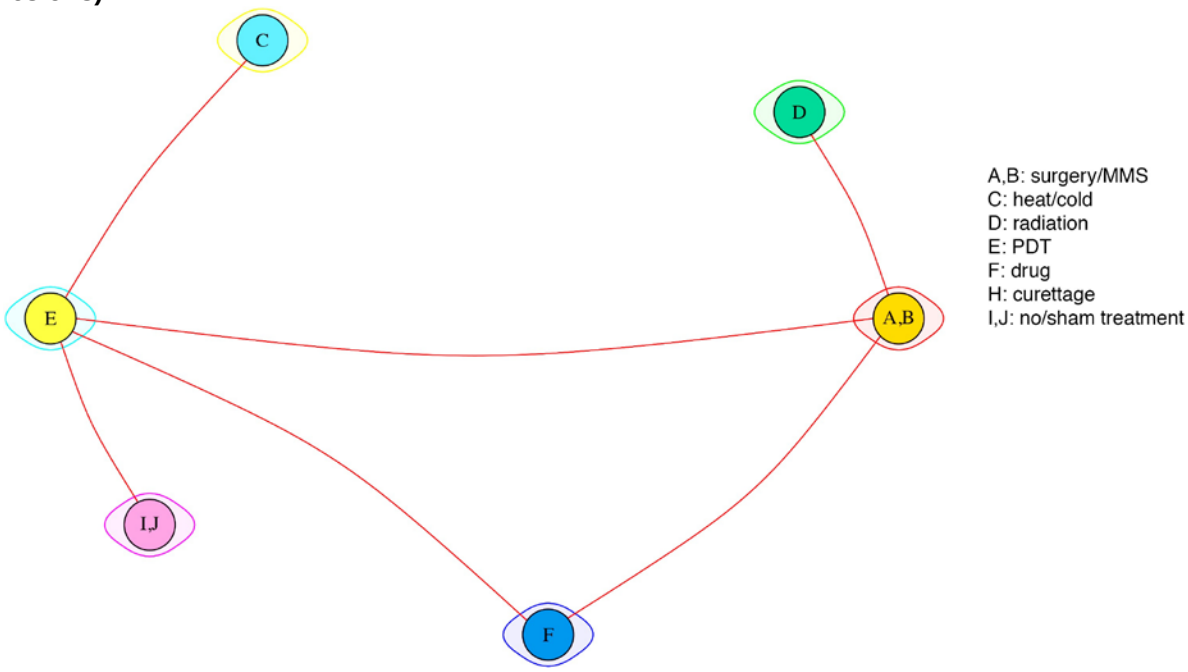
We describe only the results between intervention categories, because data are sparse for the comparison of individual observations. In total, 10 RCTs (1460 lesions) were included in this analysis.[49-52, 66, 70, 85, 98, 104] Nine RCTs were deemed to be at low or moderate risk of bias. The evidence graph in Figure 11 shows the observed comparisons based on RCTs that report observers' (investigators' or providers') assessments of "at least good" cosmetic outcome. The cosmetic outcome was assessed using different scales in each RCT, though often on scales of that included poor, fair, good, and excellent or similar. We provide analyses for an "at least good" cosmetic outcome. The evidence graph is sparsely connected. Details about the comparisons between these RCTs are in Table 52.

Table 52. Sample information, observer-reported cosmetic outcomes (all BCC lesions, intervention categories)

Studies (total sample)	10 (1460)
Total sample by intervention	(A,B): 426; (D): 113; (C): 109; (E): 443; (F): 354; (I,J): 15
Total sample by intervention, (min, max)	15, 443
Data by comparison	(A,B--D): 1 (244); (A,B--E): 2 (235); (A,B--F): 1 (344); (C--E): 4 (209); (E--F): 1 (370); (E--I,J): 1 (58)
Studies by comparison (min, max)	1, 4
Total sample by comparison (min, max)	58, 370
Followup median (min, max)	12 (12, 60) months

A = surgical excision; B = Mohs micrographic surgery; BCC=basal cell carcinoma; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

Figure 11. Evidence graph of RCTs comparing observer-assessed cosmetic outcomes (all BCC lesions)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy

Table 53 has the results of the comparisons between intervention categories based on a network meta-analysis. Most comparisons are indirect (denoted by shaded cells) and have wide confidence intervals. For comparisons with head-to-head data (denoted by unshaded cells), the numbers in the table are very similar whether information from indirect comparisons is included or excluded. Overall, the results are compatible with the corresponding results for patient-rated cosmetic outcomes. Specifically, four out of 15 comparisons are statistically significant: For example, based only on indirect data, surgical interventions (A,B) are favored over radiation (D), and based on direct and indirect data, PDT (E) is favored over surgical interventions (A,B).

Table 53. Relative odds ratios between intervention categories for at least good cosmetic outcome as assessed by an observer (all BCC lesions, Figure 11)

Surgery/MMS (A,B)	0.42 (0.12, 1.47)	3.57 (0.83, 15.36)	***0.16 (0.06, 0.40)***	0.38 (0.12, 1.18)	0.14 (0.01, 2.04)
2.37 (0.68, 8.25)	**Heat/cold (C)**	***8.45 (1.42, 50.4)***	0.37 (0.13, 1.06)	0.90 (0.22, 3.64)	0.33 (0.02, 5.11)
0.28 (0.07, 1.21)	***0.12 (0.02, 0.71)***	**Radiation (D)**	***0.04 (0.01, 0.22)***	***0.11 (0.02, 0.61)***	***0.04 (<0.005, 0.76)***
6.39 (2.5, 16.35)	2.70 (0.94, 7.74)	***22.81 (4.56, 114.26)***	**PDT (E)**	2.43 (0.81, 7.33)	0.89 (0.06, 12.23)
2.63 (0.85, 8.14)	1.11 (0.27, 4.48)	***9.38 (1.63, 54.02)***	0.41 (0.14, 1.24)	**Drugs (F)**	0.36 (0.02, 5.78)
7.22 (0.49, 106.52)	3.05 (0.2, 47.44)	***25.76 (1.31, 505.2)***	1.13 (0.08, 15.59)	2.75 (0.17, 43.61)	**No/sham treatment (I,J)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. Results are given as odds ratios (95% confidence intervals).

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

Table 54 shows the average percentage of patients with at least good cosmetic outcomes in the RCTs, based on the same network meta-analysis as Table 53. The mean percentage of lesions with cosmetic outcome rated as good or excellent ranged between 74.3 and 89.8 percent for interventions that destroy the lesion with heat or cold (C), drugs (F), PDT (E) and no or sham treatment (I,J), and was 55.0 percent for surgical treatments (A,B). Radiation (D) had the smallest percentage of at least good cosmetic outcome. The confidence intervals for these proportions are wide. Refer to Table 53 for a pairwise comparison between these treatments.

Table 54. Mean fractions of lesions with at least good cosmetic outcome as assessed by an observer (all BCC lesions)

Intervention Type	Mean Fraction Percent (95% CI)	Forecasted Fraction Percent
Surgery/MMS (A,B)	55.0 (34.7, 73.8)	55.0 (15.1, 89.3)
Heat/cold (C)	74.3 (51.5, 88.8)	74.3 (28.0, 95.6)
Radiation (D)	25.5 (7.1, 60.7)	25.5 (3.3, 77.3)
PDT (E)	88.7 (78.9, 94.2)	88.7 (54.2, 98.1)
Drugs (F)	76.3 (52.8, 90.2)	76.3 (29.6, 96.1)
No/sham treatment (I,J)	89.8 (40.1, 99.1)	89.8 (28.3, 99.5)

MMS = Mohs micrographic surgery; PDT = photodynamic therapy; CI = confidence interval

Evidence From NRCSs

Three NRCS reported investigator-evaluated results for cosmetic outcomes.[143, 148, 151]

The first one compared surgical excision (A) and PDT with ALA (E2). It reported investigator-evaluated cosmetic outcomes in a matched population of 94 superficial (64%) and nodular (36%) BCCs in 74 patients at 12 months after treatment. The study was rated as having a moderate risk of bias due to lack of blinding and unclear reporting. The mean age was 66, with an age range of 49 to 90, 47 percent of the population was female. The group that received ALA-PDT reported significantly better cosmetic results on a 4-level scale of poor to excellent (OR 10.2; 95% CI 4.0 to 26.1).[148]

A second NRCS reported whether an investigator saw pigmentation changes or alopecia in a small matched population of 40 patients treated with different doses of brachytherapy (36.6 versus 42 Gy). The risk of bias of this study was determined to be moderate, primarily for lack of blinding and unclear reporting of baselines. The mean age was 75, 45 percent were female, and all had a Fitzpatrick skin score of I (47.5%) or II (52.5%). Forty-five percent of the BCCs were superficial, while 55 percent were nodular; 75 percent were on the head and neck and 25 percent on the trunk or extremities. The lower dose had one fewer patient with pigmentation changes or alopecia (OR 0.81, 95% CI 0.23 to 2.86), but this difference was not significant.[143]

The third NRCS reported investigator-evaluated results for cosmetic outcomes to a median of 31.8 months after treatment, with two different doses and schedules of orthovoltage radiotherapy. The risk of bias was determined to be low with well-balanced arms, outcome assessors blinded, and full followup. The population consisted of 436 lesions in 385 elderly people, with BCCs (71%) and SCCs (29%). The mean age was 78, and 42 percent were female. A lower dose of radiation (37 Gy) had a slightly better cosmetic outcomes on a 4-level scale of poor to excellent than the higher dose (45 Gy), but this difference was not significant (RR: 1.048, 95% CI0.170 to 6.473).[151]

Quality of Life, All BCC Lesions

One RCT[65] and one NRCS[142, 144-147, 156] reported eligible results. The former informs on the comparison between surgical excision (A) and MMS (B), and the latter on the comparison between excision (A), MMS (B), and electrodessication and curettage (C3).

Evidence From RCTs

The RCT reported on both quality of life and anxiety in a population of 408 primary BCCs (BCC) in 374 people, randomized to surgical excision (A; n=204) or MMS (B; n=204). The mean age of patients was 67.7. The majority of tumors were located in the H-zone (93%) with the highest distribution in the frontal/temporal area (31%). Approximately half of all lesions had an aggressive histological subtype (47% BCC). Differences in tumor location or subtype were not significantly different between treatment groups. The Quality of life (emotional reactions, energy, pain, sleep, social isolation, and physical mobility) and level of anxiety of patients were measured at baseline and 6 months posttreatment, using the Nottingham Health Profile and the State-trait Anxiety Inventory, respectively. Both questionnaires were administered by a single researcher, and only patients with a single BCC were evaluated for these outcomes. At baseline and 6 months posttreatment, patients in both treatment groups showed good "health-related quality life" and a "minimum level of anxiety," with no observable statistically significant differences between the two groups for any measure.[65]

Evidence From NRCSs

The NRCS reported skin-specific quality of life in three domains: symptoms, emotion, and functioning in 1174 patients with 1488 lesions at two sites, a private, university-affiliated dermatology clinic (where majority of patients were recruited) and a nearby Veterans Affairs clinic. This study was deemed to have a low risk of bias, with balanced groups, consecutive recruitment, blinding of outcome assessors, and adequate accounting for people lost to followup. Most (75%) of the lesions were BCCs; the other 25 percent were SCCs; 26 percent were female, 40 percent had a Fitzpatrick skin score of I or II, and 3 percent were immunocompromised due to prior solid-organ transplant. The lesions were treated by MMS (B; n=246; 65% in H-zone of the face), surgical excision (A; n=251; 26% in H-zone of the face), and electrodessication and curettage (ED&C) (C3; n=136; 11% in H-zone of the face).[142, 144-147]

Table 55 shows the propensity-matched net differences between arms for improvement from baseline for each of the three reported Skindex domains (symptoms, emotions, and function) each measured on a scale from 0 (never bothered) to 100 (always bothered). The authors used a shortened, 16-item version of the Skindex (the current Skindex has 29-items), which they had previously validated in a similar population.[157, 158]

The unadjusted results in a large population showed large and significant differences, primarily in favor of Mohs and surgical excision as compared to ED&C, but no difference in improvement was observed comparing excision and Mohs surgery in any of the Skindex domains.[145] However, these results are subject to residual confounding. The propensity-matched results include a smaller population, and thus, while they show potentially large differences, the differences cannot be distinguished from chance.[142, 144-147]

Table 55. Quality of life measured with Skindex

Outcome	Arm	N/arm	Baseline Score Mean (SD)	Comparison	Net Difference at 2 Years (95% CI)	N Propensity-Matched Pairs
QoL: Skindex Symptoms	ED&C	136	19.6 (23.6)	excision vs ED&C	-1.6 (-9.8, 6.7)	51
	excision	251	21.7 (23.2)	Mohs vs ED&C	9.2 (-2.1, 20.5)	24
	Mohs	246	21.8 (23.5)	Mohs vs excision	4.0 (-3.1, 11.1)	81
QoL: Skindex Emotions	ED&C	136	33.0 (28.0)	excision vs ED&C	13.2 (3.3, 23.1)	51
	excision	251	38.9 (30.4)	Mohs vs ED&C	23.6 (10.1, 37.2)	24
	Mohs	246	46.3 (27.0)	Mohs vs excision	3.4 (-3.8, 10.7)	81
QoL: Skindex Functioning	ED&C	136	12.1 (21.7)	excision vs ED&C	3.1 (-3.5, 9.8)	51
	excision	251	15.1 (24.6)	Mohs vs ED&C	3.7 (-4.6, 12.0)	24
	Mohs	246	14.0 (21.1)	Mohs vs excision	4.2 (-2.3, 10.8)	81

ED&C = electrodessication and curettage; QoL = Quality of Life; CI = confidence interval; SD = standard deviation

Mental Health, All BCC Lesions

A single RCT reported information on anxiety measured with the State-Trait Anxiety Inventory at 6 months, for a population of 408 primary BCCs (BCC) in 374 people randomized to surgical excision (A; n=204) or MMS (B; n=204). No statistically significant differences were found between the comparators. This RCT is summarized in some more detail in the Quality of Life section, under Evidence from RCTs.[65]

Patient Satisfaction, All BCC Lesions

We did not identify eligible RCTs with results for this outcome.

Mortality, All BCC Lesions

Three RCTs[22, 49, 81, 85, 87, 88] and 1 NRCS[151] reported results on all cause mortality.

Evidence From RCTs

The first RCT reported mortality between 1 and 3 years in 501 people with 1 superficial BCC lesion each for the comparison of PDT with MAL (E1), 5-FU (F1), and imiquimod (F2). The risk of bias for this study was low, with randomization and allocation concealment adequately reported, blinding of outcome assessors, high similarity of groups at baseline, and low loss to followup. The median age was 63 (range 26 to 91), 49 percent were women, and most lesions were on the trunk (60%), extremities (27%), and face excluding the H-zone (13%). All-cause mortality was recorded for 5 of 196 (2.6%) patients in the PDT with MAL (E1) arm, 2 of 198 (1.0%) in the 5-FU arm (F1), and 4 of 189 (2.1%) in the imiquimod arm (F2).[49, 87, 88]

The second RCT compared surgical excision (A) (n=49) to PDT with MAL (E1) (n=52). The average age was 68 (range 38 to 95), and 40 percent were female. Most (88%) had Fitzpatrick skin types II (46.5%) and III (41.5%). The risk of bias for this study was judged to be relatively

high because the groups were not similar at baseline, there was no blinding, and there was a high loss to followup after a year. Mortality at 1 and 2 years was not statistically significantly different in the excision (2/46, 4.3%) and MAL-PDT groups (2/50, 4.0%).[22, 85]

The third RCT compared surgical excision (A) without intraoperative evaluation of the excised margins (n=199) versus MMS (B) (n=198). It reported results for long-term mortality in people with unspecified BCCs on the face, about half of which were classified as an "aggressive histological subtype" between 18 months and 5 years. The average age was 68 (SD 12), and 39.7 percent were female. The average lesion size was 1.28 cm^2 (SD 1.36) in the MMS arm and 1.77 cm^2 (SD 1.28) in the surgical excision arm. The risk of bias was judged to be moderate to high because of lack of baseline details given, lack of blinding, and high loss to followup. Thirty-six (18%) died in the MMS arm as compared to 34 (17%) in the excision arm. None of the deaths were deemed to be related to the tumor or the treatment.[81]

Evidence From NRCSs

One NRCS reported results for long-term mortality, from 12 to a median of 31.8 months after treatment with two doses of external radiation (orthovoltage range) therapy. It was deemed that there was low risk of confounding or measurement bias based on the fact that arms were well-balanced, outcome assessors were blinded, and no patients were lost to followup. The population consisted of 436 lesions in 385 elderly people, with BCCs (71%) and SCCs (29%). The mean age was 78, and 42 percent were female. The 45 Gy dose of radiation had a lower mortality (16.1%) than the 37 Gy dose group (30.5%), but the mean age in the lower dose group was significantly higher (81.3 vs. 73.3 years). Once adjusted for age, number of lesions per patient, histology, severity, and lesion site, the difference in mortality was not significant (Adjusted HR: 0.662; 95% CI 0.387 to 1.131).[151]

Costs and Resource Use, All BCC Lesions

No RCTs informed on U.S. costs or on use of resources.

One NRCS reported cost and resource use outcomes in patients.[155] It compared surgical excision (A), MMS (B), and electrodessication and curettage (C3). Among the 936 examined lesions, 80 percent (n=748) were BCC and 20 percent (n=188) were SCCs. The risk of confounding bias of this study was determined to be low with differences at baseline controlled for in multivariate analysis, and no loss to followup. Females accounted for 59.4 percent of the population. Overall, 60.1 percent (n=563) of tumors in the study sample presented on the head and neck. Of these, the majority (56.3%) was treated by MMS; the majority (69.3%) of tumors presenting on the trunk and extremities were treated with electrodessication and curettage (ED&C). Similarly, 31.5% (295) of tumors presented in the H-zone, with the majority (80%) of these treated with MMS, compared to a majority (36.8% and 36.2%) of tumors not in the H-zone treated with ED&C and surgical excision, respectively. Differences in histology of the tumors and tumor diameter across treatment types were not observed to be statistically significant.

In both adjusted and unadjusted analyses of total surgical care, there was a statistically significant difference ($p<0.001$) in costs by treatment type. MMS treatments were observed to have the highest primary procedure and follow-up visit costs compared to excision (by, on average, $857 in adjusted analyses). Excision had the second highest costs for both primary procedure and follow-up visit, and ED&C had the lowest. Also, in both adjusted and unadjusted analyses, total fees for all surgical care were significantly higher for large tumors (>10 mm) and

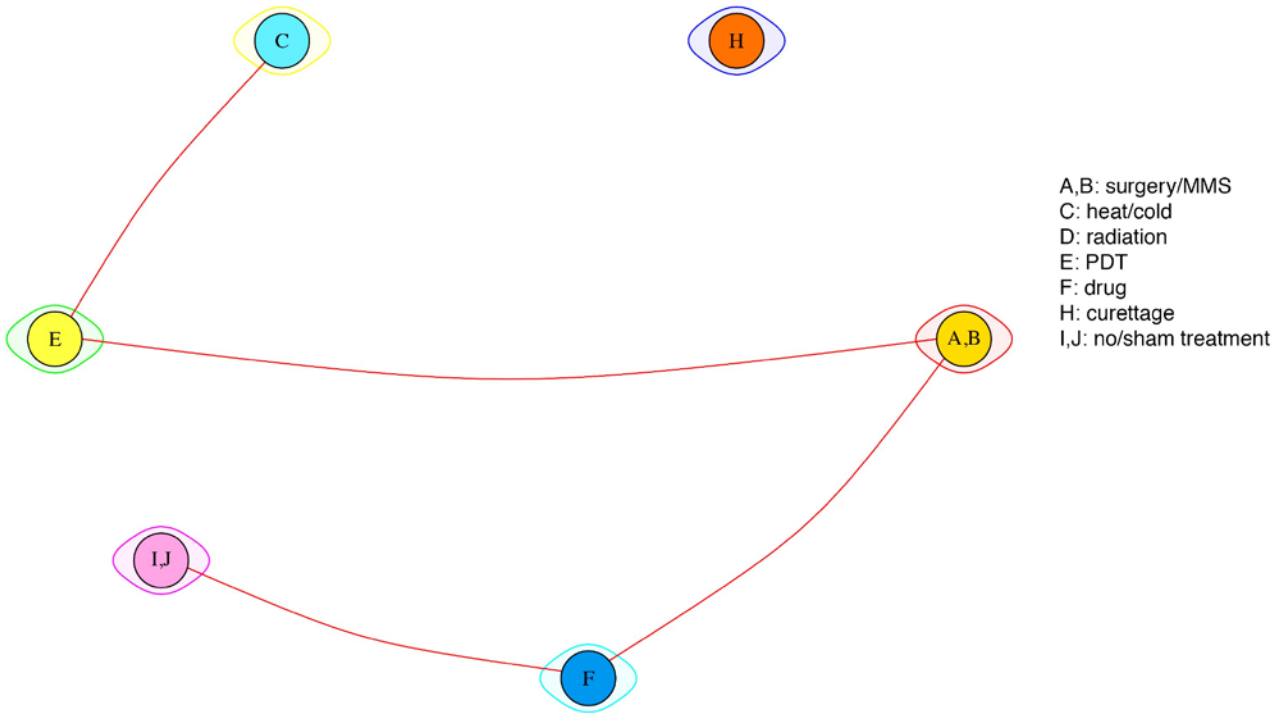
for H-zone locations. Independent predictors of higher total costs were determined using multivariate regression log models and included presentation of tumor at the head or neck, greater than 10mm lesion diameter, and repair with flap or graft. However, the study did not take fees related to recurrence into account.[155]

Adverse Events, All BCC Lesions

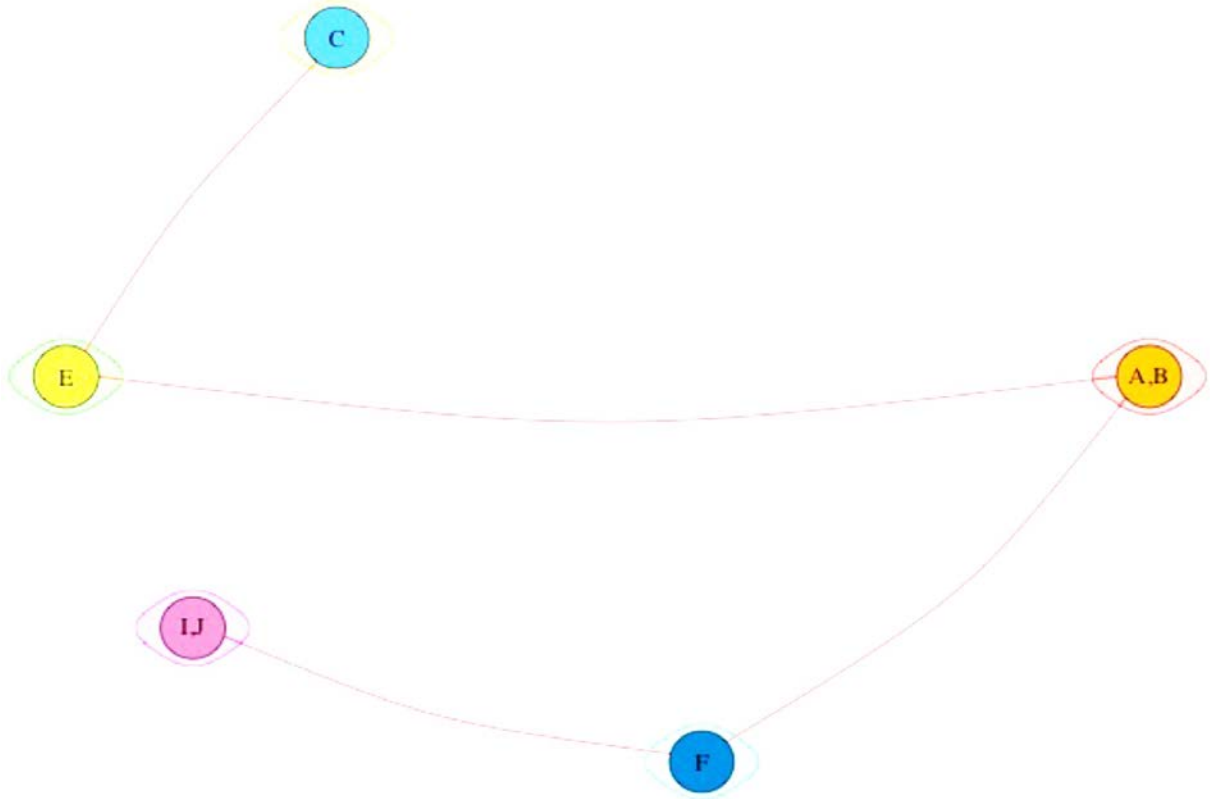
In this section we describe only results between intervention categories, because data are sparse for the comparison of individual observations. Figure 12 shows the evidence graph for the comparison of the frequency of adverse events leading to discontinuation, serious adverse events, pain after treatment completion, and infection of the treated site. Reporting of adverse events was not consistent across RCTs. Appendix I enumerates other types of adverse events that were reported.

Figure 12. Evidence graph of RCTs comparing frequency of adverse events (all BCC lesions)

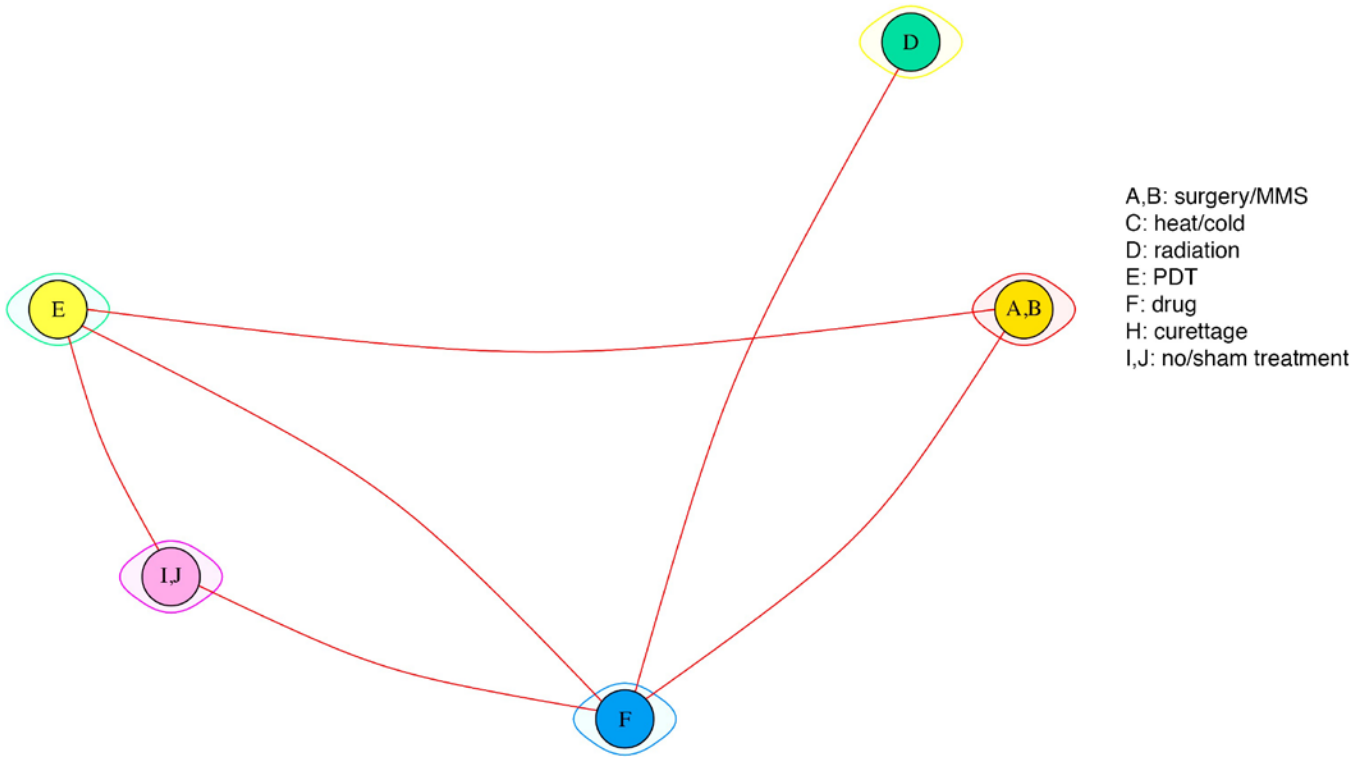
(A) Leading to treatment discontinuation



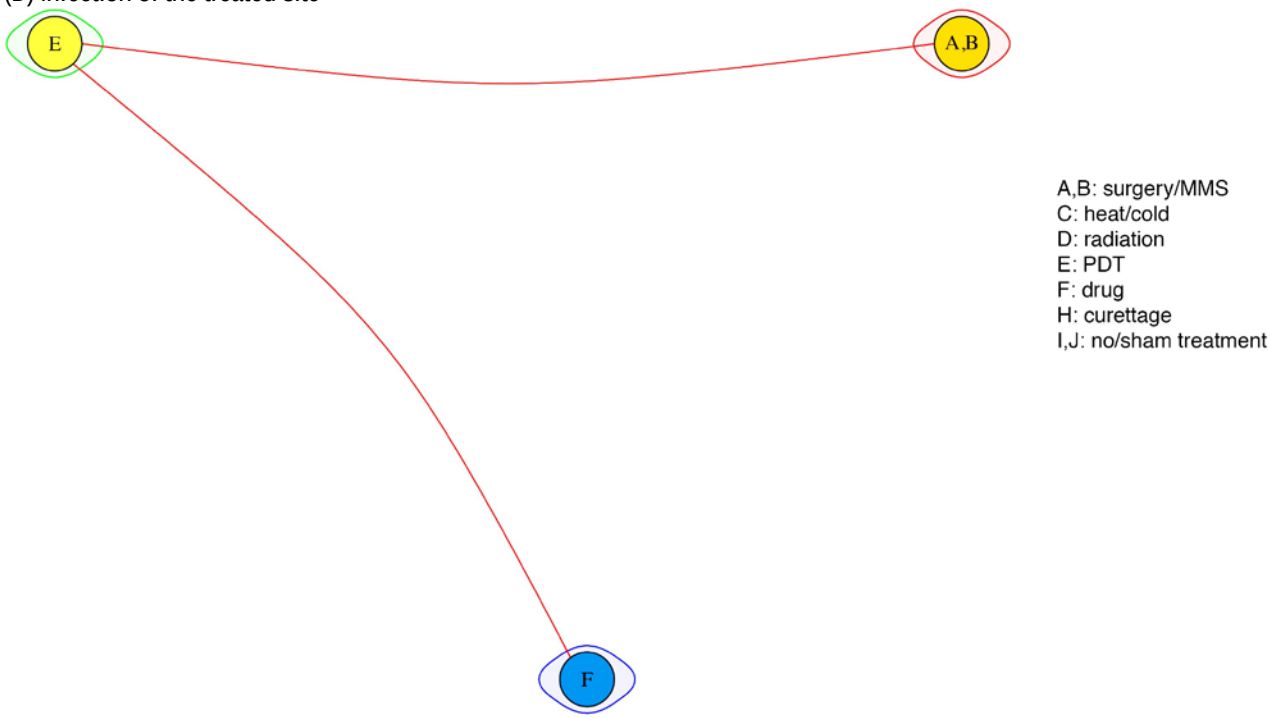
(B) Serious adverse events



(C) Pain (after treatment completion)



(D) Infection of the treated site



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; BCC = basal cell carcinoma

The evidence graphs in Figure 12 are sparsely connected. For parsimony, we do not report relative effects for comparisons of the frequency of each type of adverse event. Table 56 has details about the comparisons by type of adverse event.

Table 56. Sample information, adverse events (all BCC lesions, intervention categories)

	Adverse events leading to treatment discontinuation[51, 52, 55, 68, 85, 92, 94]	Serious adverse events[20, 49, 52, 55, 58, 94, 98]	Pain after treatment[49, 52, 54, 55, 66, 67, 69, 85, 93, 94, 98]	Infection of treated site[49, 85, 98]
Studies (total sample)	7 (1733)	7 (1395)	12 (1612)	3 (682)
Total sample by intervention	(A,B): 287; (E): 120; (F): 782; (I,J): 486; (C): 58	(A,B): 413; (E): 397; (F): 523; (I,J): 44; (C): 18	(D): 12; (F): 705; (I,J): 176; (E): 340; (A,B): 351	(E): 348; (F): 189; (A,B): 145
Total sample by intervention, (min, max)	58, 782	18, 523	12, 705	145, 348
Data by comparison	(A,B--E): 1 (118); (A,B--F): 1 (483); (E--C): 1 (118); (F--I,J): 4 (1014)	(A,B--E): 2 (369); (A,B--F): 1 (483); (E--F): 1 (385); (E--C): 1 (34); (F--I,J): 2 (124)	(D--F): 1 (27); (F--I,J): 5 (379); (F--E): 1 (339); (F--A,B): 1 (439); (I,J--E): 1 (131); (E--A,B): 2 (297)	(E--F): 1 (385); (E--A,B): 2 (297)
Studies by comparison (min, max)	1, 4	1, 2	1, 5	1, 2
Total sample by comparison (min, max)	118, 1014	34, 483	27, 439	297, 385
Followup median (min, max)	[during treatment]	12 (1, 60) months	3 (0.5, 12) months	3 (1, 12) months

A = surgical excision; B = Mohs micrographic surgery; BCC = basal cell carcinoma; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

We report mean fractions of adverse events per intervention category, based on a joint analysis of all RCTs reporting the same outcome. Most likely, adverse events were defined differently across studies, but these definitions were often not clearly described. Results for adverse events, as defined by each study, are in Table 57 and come from different analyses.

Drugs had the highest frequency of adverse events leading to treatment discontinuation was (4.9%; 95% CI, 2.0 to 20.1); for other interventions, it was less than 1.2 percent. Surgical interventions and PDT are one-time procedures and cannot be “discontinued”; for parsimony of exposition, however, in the descriptive analyses in Table 57 we assigned 0 discontinuation events to these interventions.

The frequency of adverse events characterized as “serious” by the investigators was smaller than 3.6 percent for all intervention categories.

Pain after treatment was most commonly encountered for surgical interventions (21.5%) and for PDT (20.7%), and was least common with sham treatments (2.9%).

Infections at the treatment site were described in 5.5 percent of lesions with surgical treatments (95% CI 28 to 10.7), and were reported in less than 1 percent for PDT (E) and drugs

(F). No information on infections was available for treatments that destroy lesions with heat or cold (C) or for no (or sham) treatment.

Table 57. Mean fractions of adverse events, using each RCT's definitions (all BCC lesions)

Intervention Type	Leading to Discontinuation (Figure 12A)		Serious* (Figure 12B)	Pain After Treatment (Figure 12C)		Infection of the Treated Site* (Figure 12D)
	Mean	Forecast	Mean	Mean	Forecast	Mean
Surgery/MMS (A,B)	Not defined**	Not defined**	0.6 (0.1, 2.7)	21.5 (8.1, 46.2)	21.5 (1.7, 81.5)	5.5 (2.8, 10.7)
Heat/cold (C)	0.9 (0.0, 20.1)	0.9 (0.0, 29.0)	2.6 (0.1, 36.7)	12.9 (0.8, 73.1)	12.9 (0.3, 87.5)	NA
PDT (E)	Not defined**	Not defined**	0.7 (0.1, 3.0)	20.7 (8.2, 43.3)	20.7 (1.6, 80.3)	0.5 (0.1, 2.4)
Drugs (F)	4.9 (2.0, 11.6)	4.9 (0.6, 29.2)	2.2 (0.8, 6.4)	9.9 (4.4, 20.9)	9.9 (0.7, 61.6)	0.5 (0.1, 3.7)
No/sham treatment (I,J)	1.0 (0.2, 4.4)	1.0 (0.1, 9.8)	2.4 (0.3, 17.8)	2.9 (0.9, 9.4)	2.9 (0.2, 33.5)	NA

Note: Results are given as percent and 95% confidence interval.

MMM = Mohs micrographic surgery; PDT = photodynamic therapy; RCT = randomized controlled trial; BCC = basal cell carcinoma

* No forecasts for these outcomes (fixed effects analyses only); NA: not applicable.

** Surgical interventions and PDT are one-time procedures and cannot be "discontinued"; for parsimony of exposition, however, in the descriptive analyses in the Table we assigned 0 discontinuation events to these interventions.

Evidence From NRCSs

Results on the frequency of adverse events are reported in three NRCSs.[151, 153, 154]

The first NRCS reported on adverse events in 12 patients with 1 superficial BCC each. The mean lesion area was 52 mm^2, and the lesions were located on the trunk or neck (67%) or forearm (33%). This study was deemed to have high risk of confounding bias, because of baseline imbalance. The mean age was 61 (range 52 to 78), and 33% were female. Six lesions were treated with imiquimod (F2) and six with a vehicle (J). More people in the vehicle arm (3 of 6) reported application site adverse events than in the imiquimod arm (2 of 6) during treatment, both erythemas.[154]

The second NRCS reported on adverse events in 74 patients with 1 nodular BCC each, receiving different doses of vismodegib (F5, other drug). It was deemed that this study was at moderate risk of confounding bias; it was not blinded, and it was not possible to assess for baseline (im)balance, because pertinent information was not reported. The lesion diameter ranged from 10 to 30 mm, and all were located in the scalp, head, neck, trunk or limbs. The mean age was 63.6 (SD 12; range 40 to 89), and 22 percent were female; 99 percent were white. Twenty-four lesions were treated with vismodegib for 12 weeks then were excised; twenty-five were treated with vismodegib for 12 weeks then had a 24-week observation period before excision; and 25 were treated with vismodegib for 16 weeks then were excised. Just about everyone (99%) reported at least one adverse event, including muscle spasms (76%), alopecia (58%), and changes in tasting, namely dysgeusia (50%) and ageusia (30%).[153]

The third NRCS reported results for any adverse events, from 12 to a median of 31.8 months after treatment with two doses of (orthovoltage) radiation therapy (D1). The risk of bias was

determined to be low; arms were well-balanced at baseline, outcome assessors were blinded, and no patients were lost to followup. The lower-dose group (36 Gy) had fewer adverse events (5.9% as compared to 4.0% in the 45 Gy group), but no adjusted analysis was available for this outcome.[151]

Dose Response Analyses for Drugs, All BCC Lesions

Table 58 summarizes analyses from phase II or phase II/III trials on different doses or application schedules for drugs (F), stratified by whether the patients had superficial, nodular, or a mix of superficial and nodular BCC lesions in 16 studies.[48, 54, 61-63, 68, 69, 74, 76, 82, 93, 94, 97, 100, 101] Results cannot be combined across these studies in a straightforwardly interpretable way. Overall, the general pattern was that, with increasing intensity of treatment (higher doses or more applications) there was an apparent increase in the frequency of adverse events; but it is not always clearly reported whether this was statistically significant or not.

Special Populations

No studies reported comparative results in special populations of interest, specifically patients at the end of life or immunocompromised patients.

Table 58. Summary of phase II or II/III trials comparing different doses or intensities of application schedules for drugs (all BCC lesions)

PMID Author	Arm1 (n)	Arm2 (n)	Arm3 (n)	Arm4 (n)	Arm5 (n)	Arm6 (n)	Arm7 (n)	Authors' Conclusion
Superficial Lesions								
12196749 Geisse	Vehicle (32)	Imiquimod 5% 3x/wk (29)	Imiquimod 5% 5x/wk (26)	Imiquimod 5% 1x/day (31)	Imiquimod 5% 2x/day (10)			"There was a positive association between dosing frequency and complete response rate; higher response rates were associated with more frequent dosing…An acceptable safety profile was seen in 3 of the 4 imiquimod dosing regimens. Only the most frequent dosing regimen, twice daily for 12 weeks, presented a safety profile that was judged not acceptable because of severe local skin reactions at the treatment site."[69]
15097956 Geisse	Vehicle 5x/wk (175)	Vehicle 7x/wk (171)	Imiquimod 5% 5x/wk (178)	Imiquimod 5% 7x/wk (170)				"The results from these Phase III studies confirm that imiquimod has higher complete clearance rates than vehicle cream for each of the active treatment groups. Additionally, there was not a statistically significant or clinically meaningful difference in complete clearance rate noted between the imiquimod 5/week and 7/week (73% composite and 79% histologic) treatment groups."[69]
11312429 Marks	Imiquimod 5% 1x/day (33)	Imiquimod 5% 2x/day (3)	Imiquimod 5% 1x/day 3x/wk (33)	Imiquimod 5% 2x/day 3x/wk (30)				"There was a dose-response gradient varying from 3 of 3 (100%) in the twice-every-day regimen group to 23/33 (69.7%) in the once-daily 3 times/week regimen group…This study confirms previous work suggesting that imiquimod 5% cream is likely to be of value in the treatment of sBCC."[74]
20546215 Siller	Vehicle (12)	Ingenol mebutate 0.0025% Days 1 and 2 (8)	Ingenol mebutate 0.01% Days 1 and 2 (8)	Ingenol mebutate 0.05% Days 1 and 2 (8)	Ingenol mebutate 0.0025% Days 1 and 8 (8)	Ingenol mebutate 0.01% Days 1 and 8 (8)	Ingenol mebutate 0.05% Days 1 and 8 (8)	The study was not powered to detect differences in treatment concentration and schedule, but the clinical and histological response was more common in 0.05% 1&2 day application compared to other doses or 0.05% 1&8 day application.[94]
12452875 Sterry	Imiquimod 5% 2x/wk without occlusion (24)	Imiquimod 5% 2x/wk with occlusion (21)	Imiquimod 5% 3x/wk without occlusion	Imiquimod 5% 3x/wk with occlusion				"The complete response rate increased as dosing frequency increased, both with and without occlusion. However, the only statistically significant difference in response rate was seen when comparing the 2 days per week with occlusion and 3 days per week with occlusion groups (P = 0.004)."[97]
Nodular lesions								
17610993 Eigentler	Imiquimod 5% 3x/wk for 8 weeks (45)	Imiquimod 5% 3/wk for 12 weeks (45)						"There were no significant differences between the treatment arms with respect to efficacy and tolerability."[63]
1430394 Orenberg	5-FU 7.5 mg	5-FU 15 mg						"Application of Fisher's exact test showed no differences in response between the treatment groups."[82]
12224977	Vehicle	Imiquimod	Imiquim	Imiquimo	Imiquimo			"An increase in the complete response rate was seen with

PMID Author	Arm1 (n)	Arm2 (n)	Arm3 (n)	Arm4 (n)	Arm5 (n)	Arm6 (n)	Arm7 (n)	Authors' Conclusion
Shumack 12 weeks	(24)	5% 1x/day 3x/wk (20)	od 5% 1x/day 5x/wk (23)	d 5% 1x/day 7x/wk (21)	d 5% 2x/day 7x/wk			increasing dosing frequency. This increase was statistically significant (P.001) based on the Cochran-Armitage test for trend (2-sided)."[93]
12224977 Shumack 6 weeks	Imiquimod 5% 1x/day 3x/wk (32)	Imiquimod 5% 2x/day 3x/wk (31)	Imiquim od 5% 1x/day 7x/wk (35)	Imiquimo d 5% 2x/day 7x/wk (1)				"The highest complete response rate was seen in the once-daily dosing group. No statistically significant dose-response trend was detected."[93]
12452875 Sterry	Imiquimod 5% 2x/wk without occlusion (24)	Imiquimod 5% 2x/wk with occlusion (21)	Imiquim od 5% 3x/wk without occlusio n	Imiquimo d 5% 3x/wk with occlusion				"No significant differences of complete response rate were detected between the four treatment groups (P = 0.700)."[97]
Mixed lesions								
8708151 Alpsoy	IFN alfa-2b (15)	IFN alfa-2a plus IFN alfa-2b (15)					Mixed	"IFN alfa provides a safe and effective treatment for nodular and superficial BCC…The effectiveness is not increased by combining IFN alfa-2a and 2b."[48]
10570388 Beutner	Imiquimod 5% 2x/day (7)	Imiquimod 5% 1x/day (4)	Imiquim od 5% 3x/wk (4)	Imiquimo d 5% 2x/wk (5)	Imiquimo d 5% 1x/wk (4)		Mixed	"The response of BCC to imiquimod noted in this pilot study appears to be excellent."[54]
2107219 Edwards	IFN gamma 900,000 IU (14)						Mixed	"Although 76% of our subjects had one or more side effects, these were generally minor and were not dose related. It is likely that higher doses of interferon gamma injected intralesionally into basal cell carcinomas would produce a higher, perhaps clinically important, cure rate but might not result in a significant increase in side effects."[62]
2383027 Edwards	IFN alfa-2b 30 million IU 3x (32)						Mixed	"Side effects were similar for both single and repeated dosage groups, and were those common to interferon… Side effects were similar for both single and repeated dosage groups, and were those common to interferon."[61]
8996264 Miller	5-FU 0.5 ml 1x/wk for 6 wk (21)	5-FU 1.0 ml 2x/wk for 3 wk (18)	5-FU 0.5 ml 2x/wk for 3 wk (19)	5-FU 0.5 ml 2x/wk for 4 wk (21)	5-FU 0.5 ml 3x/wk for 2 wk (17)		Mixed	"The intralesional administration of 5-FU/epi gel proved to be safe and effective in treating nodular and superficial BCCs. All regimens appeared to work well and there were no statistically significant differences among them."[76]
15606733 Torres	Mohs plus Imiquimod 5% 5x/wk for 2 wk (12)	Mohs plus Imiquimod 5% 5x/wk for 4 wk (12)	Mohs plus Imiquim od 5% 5x/wk for 6 wk				Mixed	"The application of 5% imiquimod cream before excision with Mohs micrographic surgery significantly reduced the size of the target tumor and resulted in a smaller surgical defect from the Mohs micrographic surgery excision (compared to vehicle groups)…the study was not designed and the sample sizes were not large enough to adequately characterize an imiquimod dose–duration

PMID Author	Arm1 (n)	Arm2 (n)	Arm3 (n)	Arm4 (n)	Arm5 (n)	Arm6 (n)	Arm7 (n)	Authors' Conclusion
			(12)					response curve."[100]
22511036 Tran	PDL 15 J/cm^2 (7)	PDL 7.5 J/cm^2 (7)					Mixed	Neither dose was statistically significantly different from the control group. "The results of our pilot study suggest that BCCs and SCCIS can be cleared in a single treatment using a pulsed-laser in a stacked pulse setting. However, given the small sample size of this pilot study, further larger scale studies will be needed to determine statistical significance and long-term recurrence rate and to further validate these findings."[101]

PDL = pulsed-dye laser; BCC = basal cell carcinoma; SCCIS = squamous cell carcinoma; x/wk = times per week; FU = fluorouracil; IFN = interferon

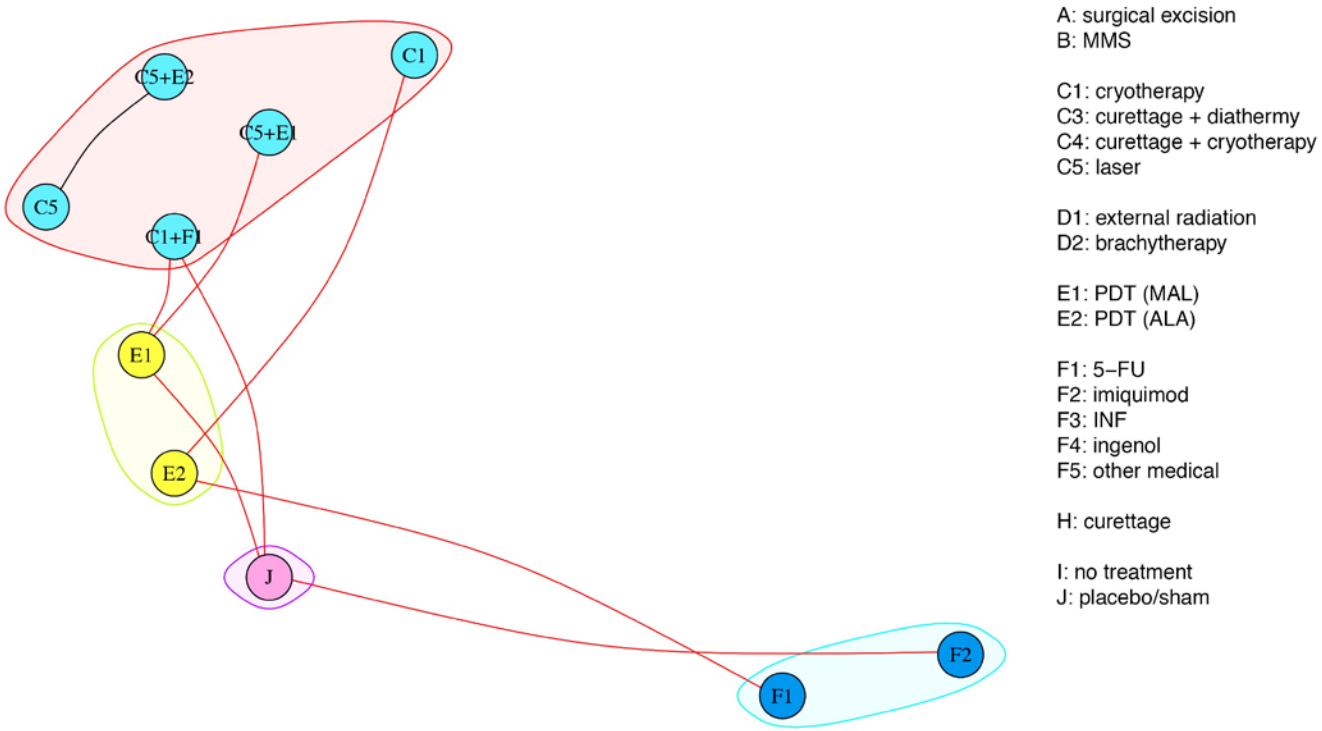
Squamous Cell Carcinoma

The evidence graph in Figures 13 and 14 depict eight comparisons between 10 interventions organized in four intervention categories. Comparisons between individual interventions are sparse, suggesting that limited, if any, conclusions can be drawn about which individual treatment is best for each outcome. Figure 13 has two connected subgraphs. The smallest one compares a laser-based preparation of the lesion for PDT treatment (C5+E2) versus PDT alone (E2), and the other comprises all other treatments. Information on each comparison is provided by at most three RCTs, and for most comparisons, by a single RCT.

The evidence is sparser when one considers the information that is actually available for specific outcomes. Figure 15 shows the corresponding evidence graphs for the outcomes for which we have the most data, namely recurrence, lack of histologic clearance, and lack of clinical clearance. RCT data exists for only 7, 4, and 8 of the 28 interventions, respectively. Evidence on other outcomes (quality of life, cosmetic outcomes, costs or resource use) is even sparser.

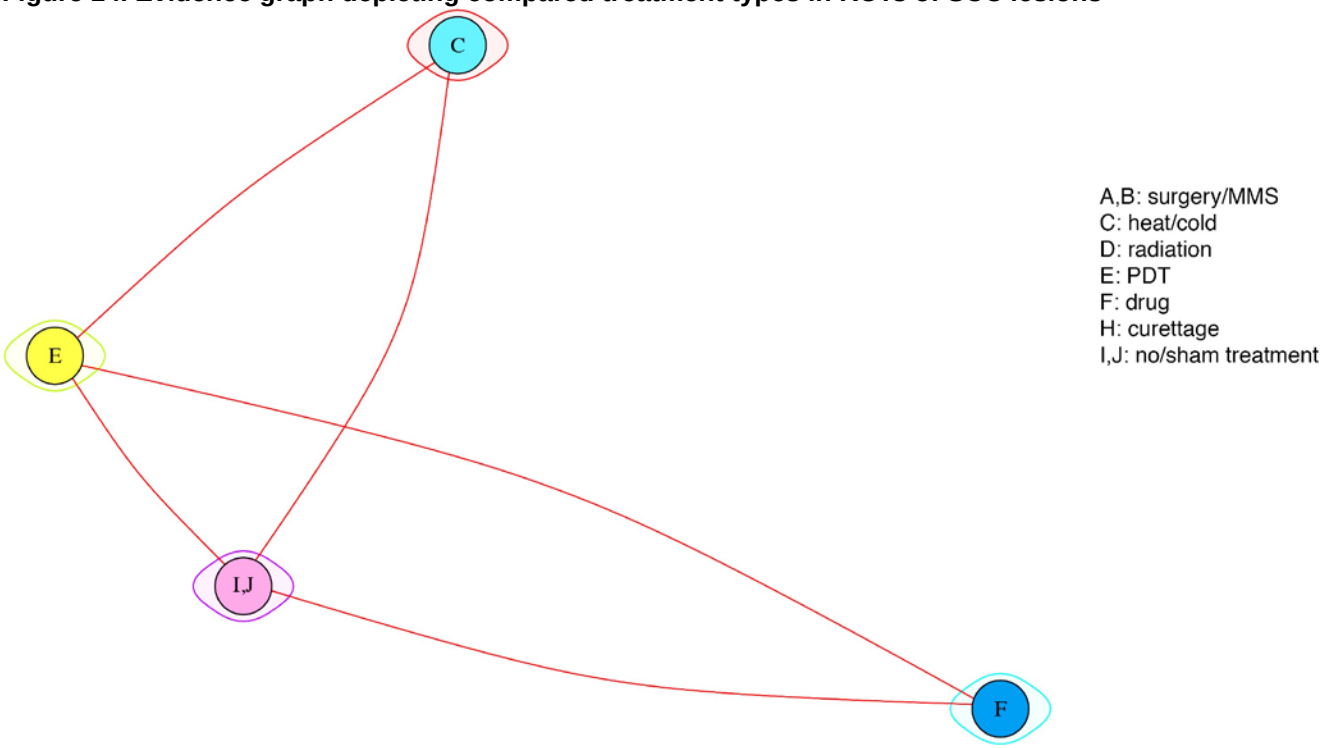
We identified one NRCS comparing curettage (H) versus cryotherapy (C1) in patients with SCC lesions. This study is described separately.[141]

Figure 13. Evidence graph depicting compared treatments in RCTs of SCC lesions



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

Figure 14. Evidence graph depicting compared treatment types in RCTs of SCC lesions



MMS = Mohs micrographic surgery; PDT = photodynamic therapy

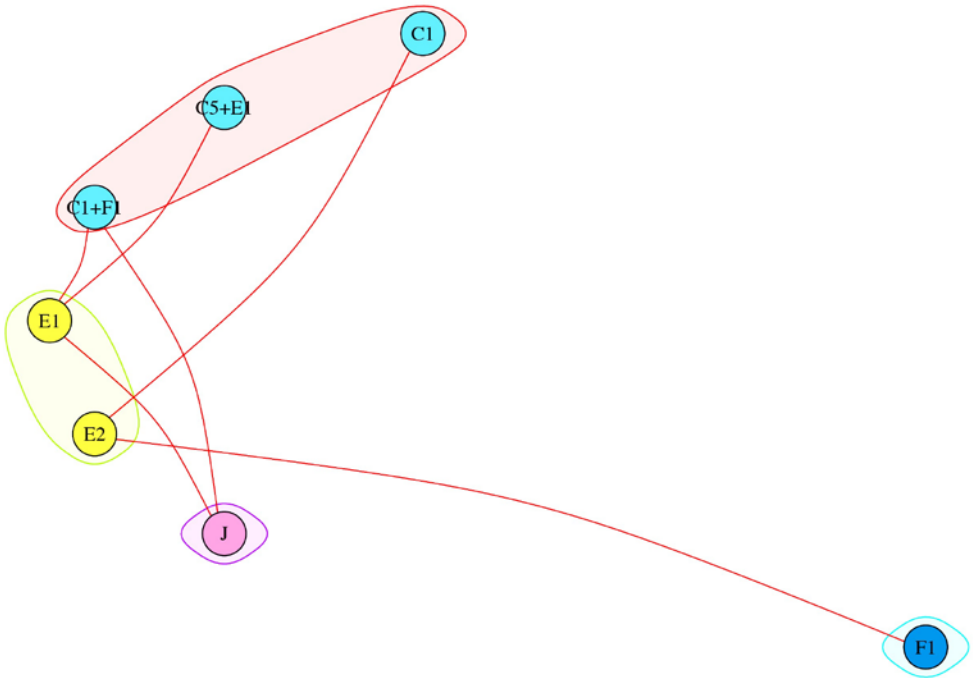
The characteristics of the six included RCTs are summarized in Table 59. All RCTS included only participants with SCC in situ (SCCIS).

Across all trials, the mean or median age of enrollees ranged between 68.9 and 76 (median 74, 25th-75th percentile: 72.4 to 76). The proportion of female patients ranged between 40 and 87.5 percent (median 62.8, 25th-75th percentile: 54 to 80). When reported, the mean or median lesion area was between 82 and 429 mm^2, and the maximum diameter was between 18.9 and 26.2 mm. The majority of RCTs included lesions in various body locations, and only a few reported results stratified by lesion location (discussed separately). Based on this information, the RCTs included patients and lesions are typically encountered in clinical practice. No RCT focused on patients who were immunocompromised or had substantially limited life expectancy.

In terms of design characteristics, five RCTs had two arms and one had three arms. Analyzed sample sizes ranged between 18 and 209 (median=23.5, 25th-75th percentile: 18.25 to 37); sample sizes per RCT arm ranged between 11 and 91. Based on what was reported in the RCTs, we deemed that the allocation sequence was randomized using formal methods in one and successfully concealed in two RCTs, and that patients, providers, and outcome assessors were successfully blinded to the received treatments in one, two, and three RCTs, respectively. Our consensus assessment of the reported baseline characteristics across the compared arms in each RCT was that half of the RCTs (n=3) had arms that were likely balanced at baseline. In four RCTs fewer than 20 percent of patients had missing outcomes for any eligible outcome in any arm.

Figure 15. Evidence graphs for recurrence, histologic clearance, and clinical clearance for RCTs of SCC lesions

(A) Recurrence



A: surgical excision
B: MMS

C1: cryotherapy
C3: curettage + diathermy
C4: curettage + cryotherapy
C5: laser

D1: external radiation
D2: brachytherapy

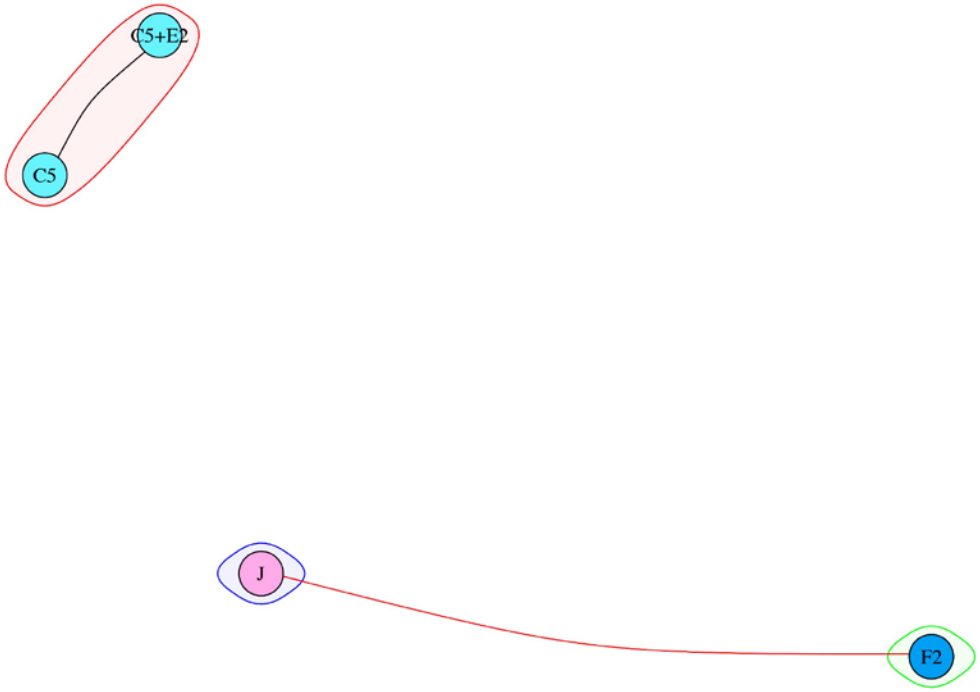
E1: PDT (MAL)
E2: PDT (ALA)

F1: 5–FU
F2: imiquimod
F3: INF
F4: ingenol
F5: other medical

H: curettage

I: no treatment
J: placebo/sham

(B) Lack of histologic clearance



A: surgical excision
B: MMS

C1: cryotherapy
C3: curettage + diathermy
C4: curettage + cryotherapy
C5: laser

D1: external radiation
D2: brachytherapy

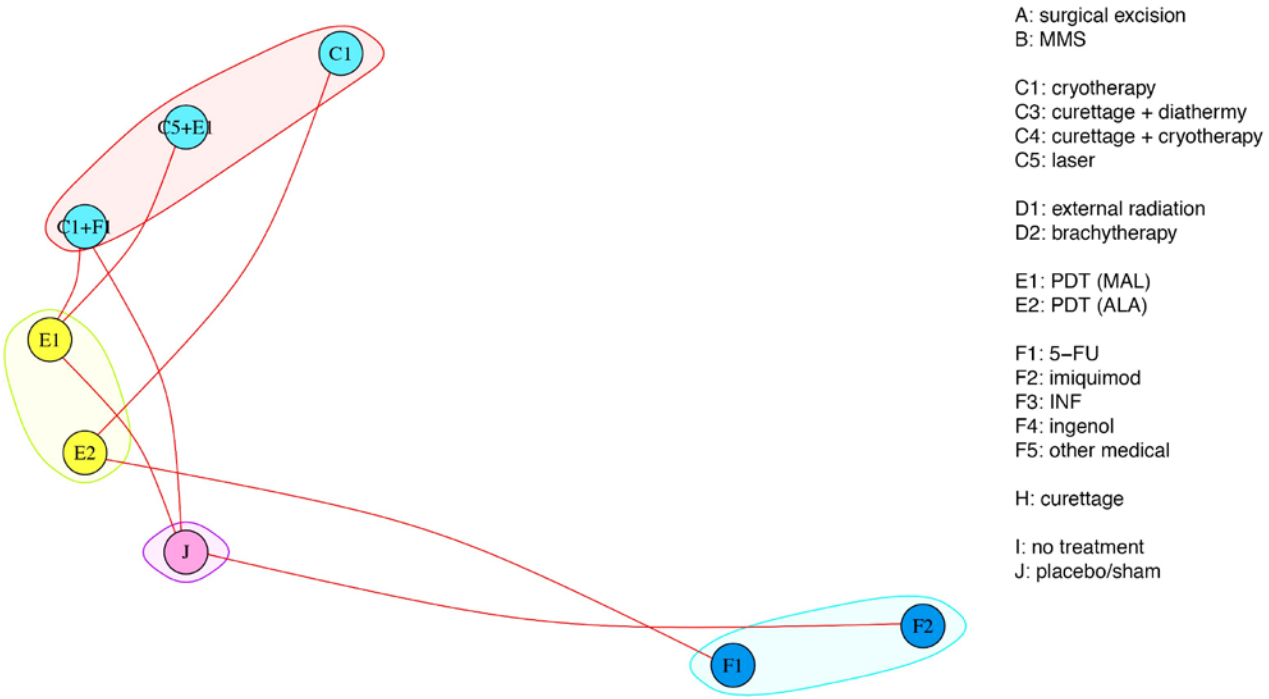
E1: PDT (MAL)
E2: PDT (ALA)

F1: 5–FU
F2: imiquimod
F3: INF
F4: ingenol
F5: other medical

H: curettage

I: no treatment
J: placebo/sham

(C) Lack of clinical clearance



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

Table 59. Characteristics of studies of SCC populations

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
SCCIS												
Cai 2015 25899562	ALA-PDT + CO2 Laser	NR	50	2.62 cm	NR	Unsure	Yes	Yes	Unsure	Yes	Yes	Yes
	CO2 Laser	NR	62.5	2.58 cm	NR							
Ko 2014 24102369	Er:YAG AFL PDT	68.9	52.4	NR	extremities (100)	Unsure	No	Yes	No	Unsure	Yes	Yes
	MAL-PDT	68.9	52.4	NR	extremities (100)							
Morton 1996 8977678	cryotherapy	76	84	82 mm^2	hands (5), face (15), legs (80)	No	No	Yes	No	No	No	No
	ALA-PDT	76	84	150 mm^2	hands (5), face (10), legs (85)							
Morton 2006 16785375	MAL PDT	71.9	62	18.9 mm	face/scalp (23), extremities (65), trunk/neck (12)	No	No	Unsure	No	No	No	Yes
	PDT placebo	73.4	65	19.3 mm	face/scalp (25), extremities (67), trunk/neck (8)							
	Cryotherapy	74	59	19.4 mm	face/scalp (29), extremities (57), trunk/neck (14)							
	Fluorouracil	72.5	63	20.9 mm	face/scalp (19), extremities (69), trunk/neck (11)							
Patel 2006 16713457	imiquimod 5%	74	40	429 mm^2	NR	Yes	Yes	No	Yes	Yes	Yes	No
	vehicle	74	87.5	248 mm^2	NR							
Salim 2003 12653747	PDT	76	80	NR	extremities (100)	No	No	No	No	No	No	Yes
	5-FU	76	80	NR	face (12), extremities (88)							
SCC microinvasive												

Study	Arm	Age, Mean	Female %	Lesion Size, Mean	Lesion Location (%)	1* Adequate Randomiz-ation	2* Allocation Conceal-ment	3* Arms Similar at Baseline	4* Patients Blinded	5* Providers Blinded	6* Outcome Assessors Blinded	7* <20% Loss to Followup
Choi 2017 28199463	MAL-PDT	75.1	54.6	11.8 mm	Face or scalp (75.0), extremities (16.7), trunk/neck (8.3)	Yes	No	Yes	No	No	Yes	Yes
	MAL-PDT + Er:YAG	76.4	71.4	11.5 mm	Face or scalp (76.2), extremities (19.0), trunk/neck (4.8)							

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon; SCC = squamous cell carcinoma; Er:YAG = ablative fractional laser; NR = not reported

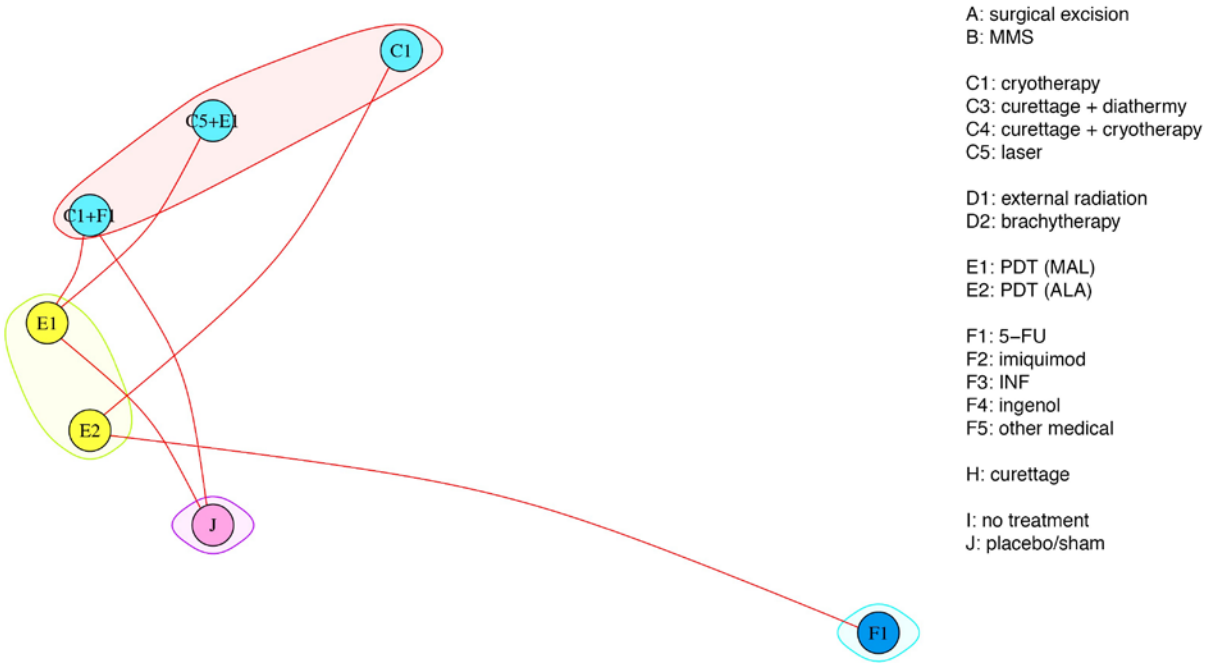
*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm. PDT=photodynamic therapy.

Recurrence, SCCIS Lesions

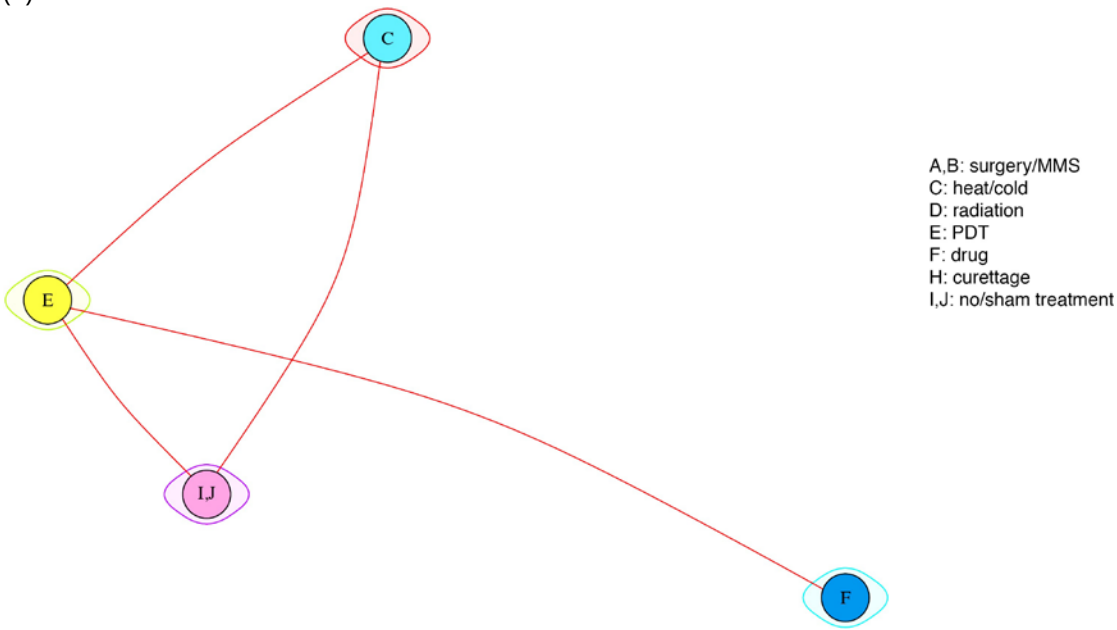
The evidence graph for recurrence with respect to individual treatments is sparse (Figure 15 (A) – reproduced in Figure 16 (A) for ease of reference). Detailed results at the RCT-level are in Appendix I.

Figure 16. Evidence graph of RCTs evaluating recurrence in SCCIS across (A) individual interventions and (B) types of interventions

(A)



(B)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon; SCCIS = squamous cell carcinoma in situ

Comparisons Across Intervention Categories

In total, 4 RCTs (348 lesions) were included in this analysis.[72, 79, 80, 89] Two RCTs were deemed to be at low or moderate risk of bias. The comparisons are described in Table 60.

Table 60. Sample information, recurrence (SCCIS, intervention categories)

Studies (total sample)	4 (348)
Total sample by intervention	(C): 136; (E): 175; (F): 33; (I,J): 4
Total sample by intervention, (min, max)	4, 175
Data by comparison	(C--E): 3 (278); (C--I,J): 1 (101); (E--F): 1 (66); (E--I,J): 1 (107)
Studies by comparison (min, max)	1, 3
Total sample by comparison (min, max)	66, 278
Followup median (min, max)	12 (12, 24) months

A = surgical excision, B = Mohs micrographic surgery; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo; SCCIS = squamous cell carcinoma in situ

Table 61 shows the relative odds ratios for recurrence across intervention categories. Based on direct data, the odds ratio for recurrence is not statistically significantly different between interventions that destroy the lesions with heat or cold (C) and PDT (E); however, the confidence interval does not exclude differences in the odds as large as 50 percent in either direction. Based on direct data, the odds ratio between PDT (E) and drugs (F) is statistically significant, favoring PDT.

In the table, shaded cells correspond to comparisons that have been inferred from the analysis model, but that have not been examined in the included RCTs. For example, comparisons of drugs (F) and interventions that destroy the lesion with heat or cold (E) are indirect, and have very wide confidence intervals. For all comparisons that are empirically observed (all nonshaded cells in the table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 61.

Table 61. Relative odds ratios for recurrence between intervention categories (SCCIS lesions, Figure 16B)

Heat/cold (C)	0.83 (0.33, 2.06)	*0.17 (0.05, 0.55)*	0.18 (0.02, 1.59)
1.21 (0.49, 3.01)	PDT (E)	*0.20 (0.07, 0.62)*	0.22 (0.03, 1.86)
5.96 (1.81, 19.61)	*4.93 (1.6, 15.15)*	Drugs (F)	1.06 (0.11, 10.44)
5.61 (0.63, 50.1)	4.64 (0.54, 39.96)	0.94 (0.1, 9.25)	No/sham treatment (I,J)

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. Results are given as odds ratios (95% confidence intervals).

PDT = photodynamic therapy; SCCIS = squamous cell carcinoma in situ.

Table 62 offers complementary information from the same analysis. For each intervention category, it shows the mean recurrence rate across the included RCTs. Interventions that destroy the lesion with heat or cold (C) and PDT (E) had on average lower recurrence rates (15.1% and 17.7%, respectively) compared to the other treatments. These estimates describe the outcome

rates in the RCT arms, and are based on the relative effects in Table 61 and the observed baseline rates in the RCTs. Of note, the recurrence rate for drugs is 51.5 percent (95% CI 28.9 to 73.5), reflecting the high recurrence rates observed in the single RCT comparing 5-FU with PDT (ALA) in this analysis.

Table 62. Mean recurrence rates by intervention category (SCCIS lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Heat/cold (C)	15.1 (8.1, 26.5)	15.1 (6.3, 32.1)
PDT (E)	17.7 (10.8, 27.8)	17.7 (8.1, 34.4)
Drugs (F)	51.5 (28.9, 73.5)	51.5 (24.7, 77.5)
No/sham treatment (I,J)	50.0 (11.2, 88.8)	50.0 (10.1, 89.9)

PDT = photodynamic therapy; SCCIS = squamous cell carcinoma in situ; CI = confidence interval

Comparisons Across Individual Interventions

As is evident from Figure 16, there are two connected subgraphs for this outcome: a smaller one comprising the comparison among cryotherapy (C1), MAL with ALA (E2), and 5-FU (F1), and a larger one among PDT with MAL with and without laser preparation (E1 and C5+E1), cryotherapy with 5-FU (C1+F1), and placebo. In total, 4 RCTs (348 lesions) were included in these analyses, as summarized in Table 63.

Table 63. Sample information, recurrence (SCCIS, interventions)

	First subgraph[72, 79]	Second subgraph[80, 89]
Studies (total sample)	2 (242)	2 (106)
Total sample by intervention	(C5+E1): 19; (E1): 122; (C1+F1): 97; (J): 4	(C1): 20; (E2): 53; (F1): 33
Total sample by intervention, (min, max)	4, 122	20, 53
Data by comparison	(C5+E1--E1): 1 (38); (E1--C1+F1): 1 (200); (E1--J): 1 (107); (C1+F1--J): 1 (101)	(C1--E2): 1 (40); (E2--F1): 1 (66)
Studies by comparison (min, max)	1, 1	1, 1
Total sample by comparison (min, max)	38, 200	40, 66
Followup (min, max)	(12, 12) months	(12, 24) months

A = surgical excision; B = Mohs micrographic surgery; C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; C5 = laser; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F1 = 5-FU; F2 = Imiquimod; F3 = Interferon; F4 = Ingenol; H = curettage; J = placebo; SCCIS = squamous cell carcinoma in situ

Table 64 shows the relative effects for both subgraphs. Because the comparisons across individual observations are sparse, however, the confidence intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the compared interventions.

Table 65 shows, for each intervention, the mean recurrence rates across all RCTs; estimates for interventions in both subgraphs are listed in the table. It was not possible to compare statistically the estimated recurrence rates between an intervention in the first subgraph (e.g., PDT with MAL [E1]) and the second subgraph (e.g., cryotherapy [C1]), because they come from disjoint analyses.

Table 64. Relative odds ratios for recurrence between individual interventions (SCCIS lesions, Figure 16A)

Cryotherapy + 5-FU (C1+F1)	6.14 (0.48, 77.78)	1.12 (0.31, 3.96)	0.24 (0.02, 2.48)			
0.16 (0.01, 2.06)	**Laser + PDT (MAL) (C5+E1)**	0.18 (0.02, 1.95)	***0.04 (<0.005, 0.94)***			
0.9 (0.25, 3.18)	5.5 (0.51, 58.9)	**PDT (MAL) (E1)**	0.22 (0.02, 2.13)			
4.11 (0.4, 41.76)	***25.2 (1.06, 598.92)***	4.58 (0.47, 44.79)	**Placebo/sham (J)**			
				Cryotherapy (C1)	1.34 (0.06, 28.22)	0.19 (0.01, 5.5)
				0.75 (0.04, 15.75)	**PDT (ALA) (E2)**	0.14 (0.01, 1.55)
				5.27 (0.18, 153)	7.06 (0.65, 77.1)	**5-FU (F1)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. Results are given as odds ratios (95% confidence intervals).

PDT (MAL) = methyl aminolaevulinate photodynamic therapy; PDT (ALA)= aminolevulinic acid photodynamic therapy; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ

Table 65. Mean and forecasted recurrence rates by intervention category (SCCIS lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
First subgraph (Figure 16)		
Cryotherapy + 5-FU (C1+F1)	22.4 (8.0, 48.8)	22.4 (5.3, 60.0)
Laser + PDT (MAL) (C5+E1)	4.5 (0.5, 31.6)	4.5 (0.4, 37.6)
PDT (MAL) (E1)	20.5 (9.0, 40.3)	20.5 (5.5, 53.3)
Placebo/sham (J)	54.2 (11.2, 91.8)	54.2 (8.8, 93.6)
Second subgraph (Figure 16)		
Cryotherapy (C1)	13.0 (1.1, 67.2)	13.0 (0.5, 82.5)
PDT (ALA) (E2)	10.1 (1.5, 45.3)	10.1 (0.5, 69.4)
5-FU (F1)	44.1 (7.5, 88.5)	44.1 (3.1, 95.1)

PDT (MAL) = methyl aminolaevulinate photodynamic therapy; PDT (ALA) = aminolevulinic acid photodynamic therapy; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ; CI = confidence interval

Recurrence, Other Subgroup Analyses (Lesion Location, Lesion Size)

Evidence From RCTS

Table 66 below shows results on subgroup analyses for a four-arm RCT.[77, 79] Neither lesion location nor size were associated with differences in the treatment effect beyond what is expected by chance.

Table 66. Subgroup analyses by lesion location and size: results for recurrence (SCCIS lesions)

Study	Comparison	Timepoint	Subgroup	n/N Arm 1 vs. n/N Arm 2 vs. n/N arm 3	OR (95% CI); P-Value Within	P- Value Between
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs.	12 months	lesion location: extremities	11/60 vs. 11/63 vs. 0/1	1.06 (0.42, 2.67); 0.70 (0.03, 18.23);	p=0.483

Study	Comparison	Timepoint	Subgroup	n/N Arm 1 vs. n/N Arm 2 vs. n/N arm 3	OR (95% CI); P-Value Within	P- Value Between
	MAL-PDT (E1) vs. sham PDT (J)				0.66 (0.03, 17.18); p=1.000	
			lesion location: face/scalp	6/22 vs. 2/27 vs. 1/2	4.69 (0.84, 26.15); 0.38 (0.02, 7.00); 0.08 (0.00, 1.82); p=0.084	
			lesion location: neck/trunk	2/15 vs. 2/13 vs. 1/1	0.85 (0.10, 7.04); 0.06 (0.00, 1.99); 0.07 (0.00, 2.35); p=0.209	
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	12 months	lesion diameter: 5-14 mm	0/27 vs. 4/40 vs. 1/1	0.15 (0.01, 2.86); 0.01 (0.00, 0.43), 0.04 (0.00, 1.17); p=0.018	NA
			lesion diameter: 15-29 mm	15/55 vs. 5/43 vs. 1/3	2.85 (0.94, 8.61); 0.75 (0.06, 8.89); 0.26 (0.02, 3.46); p=0.093	
			lesion diameter: >= 30 mm	3/12 vs. 6/20 vs. 0/0	0.78 (0.15, 3.93); NA; p=1.000	

NA = not significant; PDT (MAL) = methyl aminolaevulinate photodynamic therapy; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ

Evidence From NRCSs

One NRCS reported recurrence for 80 SCCIS lesions in 67 people, treated with either curettage (44 lesions) or cryotherapy (36 lesions). This study was deemed to be of high risk of bias, primarily for lack of reporting (baseline data and dropout numbers were not given by arm), but also for lack of blinding and for a high long-term dropout rate. The mean age was 74 (range: 46 to 89), and the mean lesion area was 336 mm^2 (range 30 to 1890 mm^2). Eighty-two percent were female, and the lesions were located on the extremities (84%), trunk (7.5%), and head/neck (8.5%). The cryotherapy arm had a significantly higher rate of recurrence up to 22 months than the curettage arm (OR 5.65; 95% CI 1.65 to 19.39).[141]

Lack of Histological Clearance, SCCIS Lesions

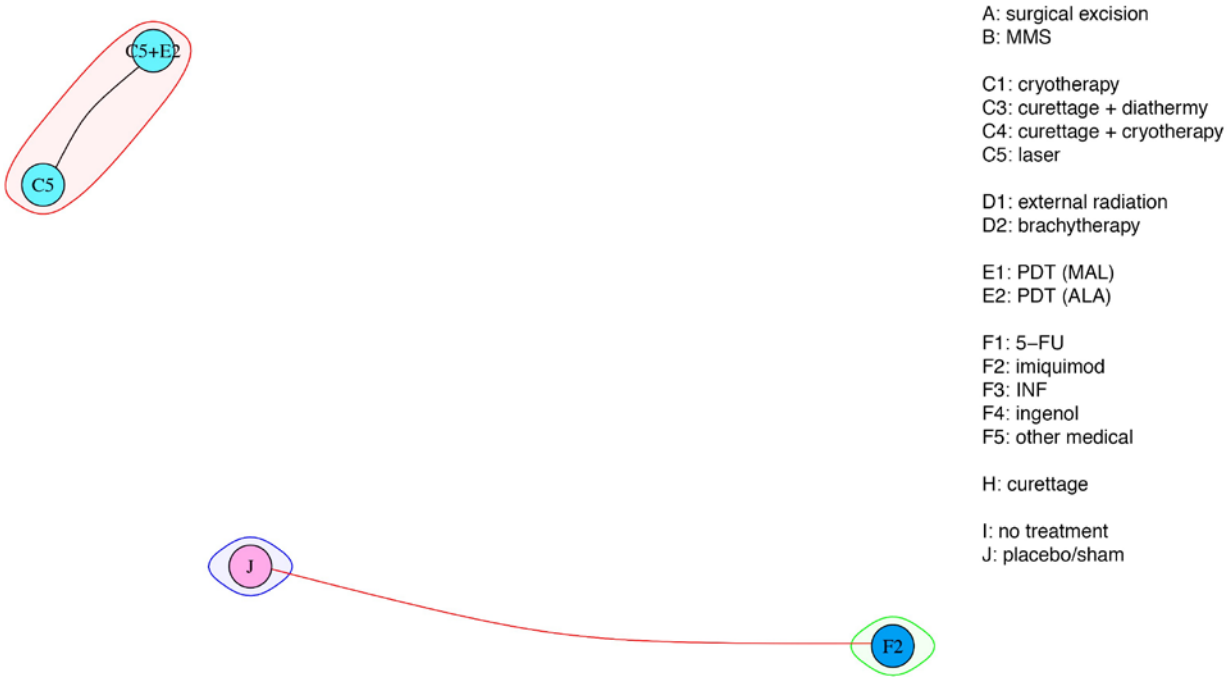
The evidence graph for recurrence with respect to individual treatments is sparse (Figure 15 (B) – reproduced in Figure 17 for ease of reference). For this outcome, one RCT compared between laser ablation (C5) versus a combination of laser ablation and PDT with ALA (C5+E2), and one RCT compared 5-FU (F2) versus placebo (J). An analysis of comparisons between intervention categories is superfluous, in that it would include the same evidence as in the latter comparison of 5-FU (F2) versus placebo (J). The comparisons in the two RCTs (50 lesions) are described in Table 67.

Table 67. Sample information, lack of histological clearance (SCCIS)

	Figure 17, first subgraph[83]	Figure 17, second subgraph[57]
Studies (total sample)	1 (28)	1 (22)
Total sample by intervention	(F2): 12; (J): 16	(C5): 11; (C5+E2): 11
Total sample by intervention, (min, max)	12, 16	11, 11
Data by comparison	(F2--J): 1 (28)	(C5--C5+E2): 1 (22)
Studies by comparison (min, max)	1, 1	1, 1
Total sample by comparison (min, max)	28, 28	22, 22
Followup	7 months	6 months

A = surgical excision; B = Mohs micrographic surgery; C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; C5 = laser; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F1 = 5-FU; F2 = Imiquimod; F3 = Interferon; F4 = Ingenol; H = curettage; J = placebo; SCCIS = squamous cell carcinoma in situ

Figure 17. Evidence graph of RCTs evaluating lack of histological clearance in SCCIS lesions across individual interventions



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon; SCCIS = squamous cell carcinoma in situ

Table 68 shows the relative odds ratios for lack of histological clearance between individual interventions. Because of the very small sample sizes, the confidence intervals are very large. Table 69 has the respective fractions for lack of histological clearance in the two RCTs.

Table 68. Relative odds ratios for lack of histological clearance between individual interventions (SCCIS lesions, Figure 17)

(F1) 5-FU	***0.01 (<0.005, 0.22)***		
99 (4.45, 2202.23)	**(J) placebo**		
		(C5) laser	8.33 (0.78, 89.47)
		0.12 (0.01, 1.29)	**(C5+E2) laser + PDT (ALA)**

Note: Bold-italic indicates that the result is statistically significant; Results are given in odds ratios and 95% confidence intervals.

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ

Table 69. Mean lack of histological clearance (all SCCIS lesions)

Intervention Type	Mean Percent (95% CI)
First comparison	
5-FU (F1)	25.0 (8.3, 55.2)
Placebo (J)	97.1 (66.4, 99.8)
Second comparison	
Laser (C5)	45.5 (20.3, 73.2)
Laser with PDT (ALA) (C5+E2)	9.1 (1.3, 43.9)

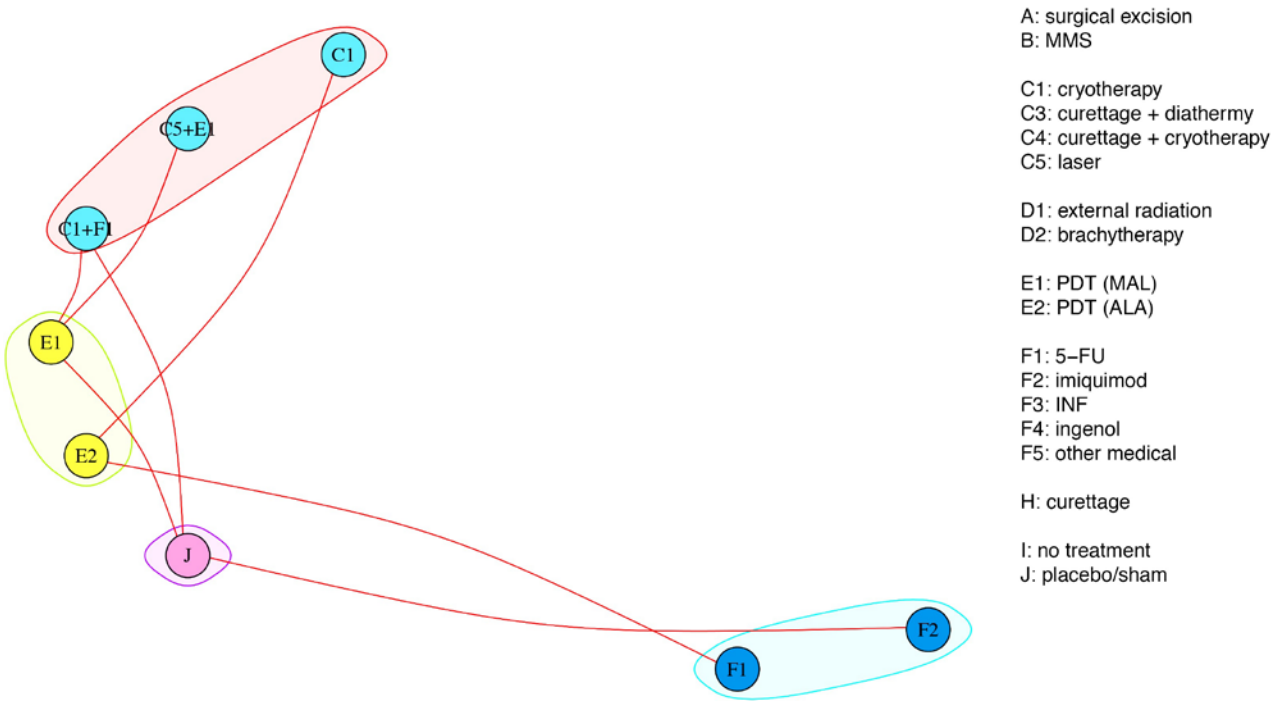
PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ; CI = confidence interval

Lack of Clinical Clearance, SCCIS Lesions

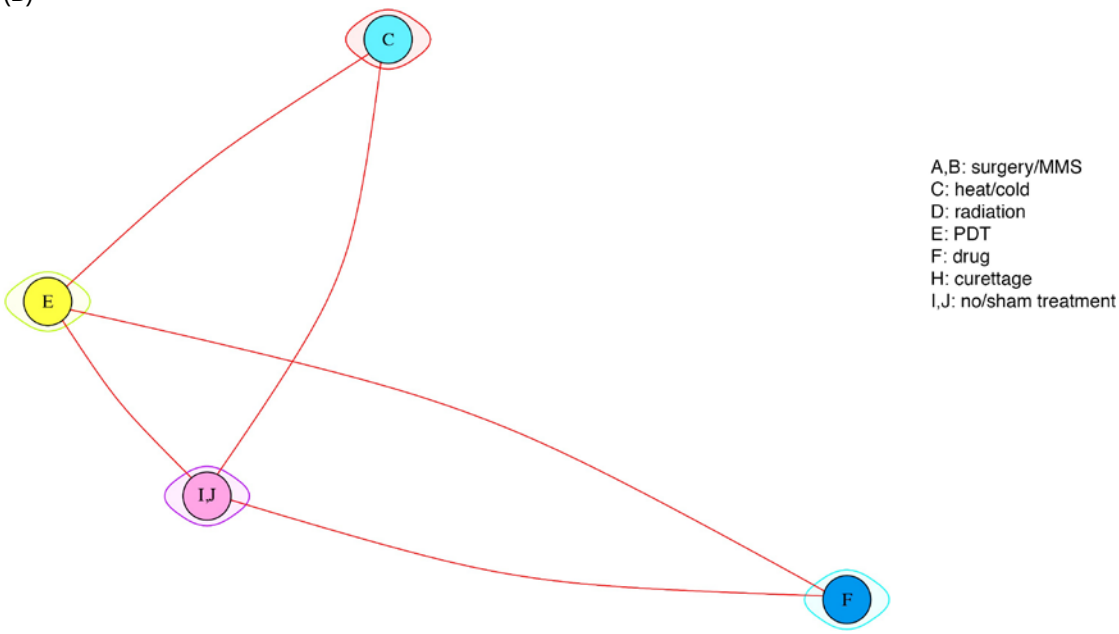
The evidence graph for recurrence with respect to individual treatments is sparse (Figure 15 [C] – reproduced in Figure 18 [A] for ease of reference). Detailed results at the RCT-level are in Appendix I.

Figure 18. Evidence graph of RCTs evaluating lack of clinical clearance in SCCIS lesions across (A) individual interventions and (B) types of interventions

(A)



(B)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL=methyl aminolevulinate; FU = fluorouracil; INF = interferon; SCCIS = squamous cell carcinoma in situ

Comparisons Across Intervention Categories

In total, five RCTs (436 lesions) were included in this analysis.[72, 79, 80, 83, 89] Three RCTs were deemed to be at low or moderate risk of bias. The comparisons are described in Table 70.

Table 70. Sample information, lack of clinical clearance (SCCIS, intervention categories)

Studies (total sample)	5 (436)
Total sample by intervention	(C): 166; (E): 190; (F): 45; (I,J): 35
Total sample by intervention, (min, max)	35, 190
Data by comparison	(C--E): 3 (323); (C--I,J): 1 (133); (E--F): 1 (66); (E--I,J): 1 (130); (F--I,J): 1 (28)
Studies by comparison (min, max)	1, 3
Total sample by comparison (min, max)	28, 323
Followup median (min, max)	3 (2, 12) months

A = surgical excision; B = Mohs micrographic surgery; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo; SCCIS = squamous cell carcinoma in situ

Table 71 shows the relative odds ratios for clinical clearance across intervention categories. There were no statistically significant differences between the active interventions, although the confidence intervals for the odds ratios were wide and could not exclude large differences in the odds of the outcome in either direction. Nevertheless, all active interventions were favored beyond chance versus placebo.

Table 71. Relative odds ratios for lack of clinical clearance between intervention categories (SCCIS lesions, Figure 18B)

Heat/cold (C)	0.69 (0.13, 3.6)	0.29 (0.04, 2.17)	***0.02 (<0.005, 0.15)***
1.45 (0.28, 7.52)	**PDT (E)**	0.42 (0.07, 2.65)	***0.02 (<0.005, 0.19)***
3.42 (0.46, 25.34)	2.37 (0.38, 14.83)	**Drugs (F)**	***0.06 (0.01, 0.58)***
60.64 (6.87, 535.12)	***41.96 (5.22, 337.2)***	***17.73 (1.72, 182.98)***	**No/sham treatment (I,J)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. Results are given as odds ratios (95% confidence intervals).

PDT = photodynamic therapy; SCCIS = squamous cell carcinoma in situ

Table 72 offers complementary information from the same analysis. The fraction of lesions without clinical clearance was between 10.8 and 29.2 percent in the active treatments and 88 percent with placebo. The confidence intervals for each estimate are wide.

Table 72. Mean and forecasted lack of clinical clearance fractions by intervention category (SCCIS lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
Heat/cold (C)	10.8 (3.1, 31.3)	10.8 (1.2, 54.7)
PDT (E)	14.9 (5.4, 34.9)	14.9 (1.9, 61.0)
Drug (F)	29.2 (8.4, 65.1)	29.2 (3.6, 82.2)
No/sham treatment (I,J)	88.0 (54.2, 97.8)	88.0 (34.7, 99.0)

PDT = photodynamic therapy; SCCIS = squamous cell carcinoma in situ

Comparisons Across Individual Interventions

As is evident from Figure 18, there are two connected subgraphs: a smaller one comprising the comparison between cryotherapy (C1), MAL with ALA (E2) and 5-FU (F1), and a larger one between PDT with MAL with and without laser preparation (E1 and C5+E1), cryotherapy with 5-FU (C1+F1), and placebo. In total, five RCTs (436 lesions) were included in these analyses, as summarized in Table 73.

Table 73. Sample information, lack of clinical clearance (SCCIS, interventions)

	First subgraph[72, 79, 83]	Second subgraph[80, 89]
Studies (total sample)	3 (330)	2 (106)
Total sample by intervention	(C5+E1): 32; (E1): 137; (C1+F1): 114; (J): 35; (F2): 12	(C1): 20; (E2): 53; (F1): 33
Total sample by intervention, (min, max)	12, 137	20, 53
Data by comparison	(C5+E1--E1): 1 (58); (E1--C1+F1): 1 (225); (E1--J): 1 (130); (C1+F1--J): 1 (133); (J--F2): 1 (28)	(C1--E2): 1 (40); (E2--F1): 1 (66)
Studies by comparison (min, max)	1, 1	1, 1
Total sample by comparison (min, max)	28, 225	40, 66
Followup median (min, max)	7 (3, 12) months	2.5 (2, 3) months

A = surgical excision; B = Mohs micrographic surgery; C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; C5 = laser; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F1 = 5-FU; F2 = Imiquimod; F3 = Interferon; F4 = Ingenol; H = curettage; J = placebo; SCCIS = squamous cell carcinoma in situ

Table 74 shows the relative effects for both subgraphs, respectively. Because the comparisons across individual observations are sparse, however, the confidence intervals of the odds ratios for most indirect comparisons are broad and cannot exclude very large differences between the compared interventions.

Table 75 shows, for each intervention, the mean recurrence rates across all RCTs; estimates for interventions in both subgraphs are listed in Table 75. One cannot compare statistically the estimated recurrence rates between an intervention in the first subgraph (e.g., PDT with MAL [E1]) and the second subgraph (e.g., cryotherapy [C1]), because they come from disjoint analyses.

Table 74. Relative odds ratios for lack of clinical clearance between individual interventions (SCCIS lesions, Figure 18A)

Cryotherapy + 5-FU (C1+F1)	***13.7 (2.92, 64.25)***	2.11 (0.88, 5.06)	3.04 (0.21, 44.58)	***0.04 (0.01, 0.15)***			
0.07 (0.02, 0.34)	**Laser + PDT (MAL) (C5+E1)**	0.15 (0.04, 0.56)	0.22 (0.01, 4.18)	***<0.005 (<0.005, 0.02)***			
0.47 (0.2, 1.14)	***6.49 (1.79, 23.58)***	**PDT (MAL) (E1)**	1.44 (0.1, 21.22)	***0.02 (0.01, 0.07)***			
0.33 (0.02, 4.81)	4.5 (0.24, 84.77)	0.69 (0.05, 10.21)	**Imiquimod (F2)**	***0.01 (<0.005, 0.19)***			
22.62 (6.89, 74.26)	***310.05 (51.68, 1860.02)***	***47.78 (13.39, 170.52)***	***68.87 (5.18, 915.22)***	**Placebo/sham (J)**			
					Cryotherapy (C1)	0.28 (0.01, 7.38)	0.06 (<0.005, 1.59)
					3.59 (0.14, 95.23)	**PDT (ALA) (E2)**	0.21 (0.04, 1.08)
					16.9 (0.63, 453.4)	4.7 (0.93, 23.88)	**5-FU (F1)**

Note: Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. Results are given as odds ratios (95% confidence intervals).

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ

Table 75. Mean and forecasted lack of clinical clearance fractions by intervention (SCCIS lesions)

Intervention Type	Mean Percent (95% CI)	Forecast Percent (95% CI)
First subgraph		
Cryotherapy + 5-FU (C1+F1)	41.3 (9.4, 82.7)	41.3 (2.3, 95.5)
Laser + PDT (MAL) (C5+E1)	4.9 (0.6, 31.0)	4.9 (0.1, 64.4)
PDT (MAL) (E1)	25.0 (4.9, 68.5)	25.0 (1.1, 90.8)
Imiquimod (F2)	18.8 (1.7, 75.5)	18.8 (0.5, 91.4)
Placebo (J)	94.1 (67.9, 99.2)	94.1 (33.1, 99.8)
Second subgraph		
Cryotherapy (C1)	2.6 (0.1, 35.5)	2.6 (0.1, 40.3)
PDT (ALA) (E2)	8.8 (2.4, 27.6)	8.8 (1.6, 36.4)
5-FU (F1)	31.2 (10.7, 63.2)	31.2 (7.3, 72.3)

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ; CI = confidence interval

Lack of Clinical Clearance, Other Subgroup Analyses (Lesion Location, Lesion Size), SCCIS Lesions

Evidence From RCTS

Table 76 shows results on subgroup analyses for a four-arm RCT.[77, 79] Neither lesion location nor size were associated with differences in the treatment effect beyond what is expected by chance.

Table 76. Subgroup analyses by lesion location and size: results for lack of clinical clearance (SCCIS lesions)

Study	Comparison	Time Point	Subgroup	n/N Arm 1 vs. n/N Arm 2 vs. n/N Arm 3	OR (95% CI); P-Value Within	P- Value Between
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	after first treatment	lesion diameter: 5-14 mm	4/30 vs. 5/42 vs. 6/7	1.14 (0.28, 4.65); 0.03 (0.00, 0.27); 0.02 (0.00, 0.23); p<0.001	p=0.457
			lesion diameter: 15-29 mm	21/65 vs. 11/48 vs. 7/10	1.61 (0.69, 3.76); 0.20 (0.05, 0.87); 0.13 (0.03, 0.58); p=0.016	
			lesion diameter: >= 30 mm	10/18 vs. 7/21 vs. 2/2	2.50 (0.68, 9.16); 0.25 (0.01, 5.87); 0.10 (0.00, 2.44); p=0.102	
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	after last treatment	lesion diameter: 5-14 mm	3/30 vs. 2/42 vs. 6/7	2.22 (0.35, 14.20); 0.02 (0.00, 0.21); 0.01 (0.00, 0.11); p<0.001	p=0.522
			lesion diameter: 15-29 mm	10/65 vs. 5/48 vs. 7/10	1.56 (0.50, 4.91); 0.08 (0.02, 0.35); 0.05 (0.01, 0.26); p<0.001	

Study	Comparison	Time Point	Subgroup	n/N Arm 1 vs. n/N Arm 2 vs. n/N Arm 3	OR (95% CI); P-Value Within	P- Value Between
			lesion diameter: >= 30 mm	4/18 vs. 1/21 vs. 2/2	5.71 (0.58, 56.73); 0.06 (0.00, 1.55); 0.01 (0.00, 0.47); p=0.007	
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	after last treatment	lesion location: extremities	12/72 vs. 6/69 vs. 11/12	2.10 (0.74, 5.95); 0.02 (0.00, 0.15); 0.01 (0.00, 0.08); p<0.001	NA
			lesion location: face/scalp	5/27 vs. 1/28 vs. 3/5	1.56 (0.50, 56.48); 0.15 (0.02, 1.16); 0.02 (0.00, 0.36); p=0.007	
			lesion location: neck/trunk	0/15 vs. 1/14 vs. 1/2	0.29 (0.01, 7.74); 0.03 (0.00, 1.20); 0.08 (0.00, 2.39); p=0.062	

PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; NA = not significant; SCCIS = squamous cell carcinoma in situ

Evidence From NRCSs

One NRCS reported lack of clinical clearance for 80 SCCIS lesions in 67 people, treated with either curettage (44 lesions) or cryotherapy (36 lesions). This study was deemed to be of high risk of bias, primarily for lack of reporting (baseline data and dropout numbers were not given by arm), but also for lack of blinding. The mean age was 74 (range: 46 to 89), and the mean lesion area was 336 mm^2 (range 30 to 1890 mm^2). Eighty-two percent were female, and the lesions were located on the extremities (84%), trunk (7.5%), and head/neck (8.5%). The cryotherapy arm had a higher rate of lack of clinical clearance at 2 weeks (2 of 36 vs. 0 of 44).[141]

Patient-Reported Cosmetic Outcomes, SCCIS Lesions

We did not identify any studies with results for this outcome in this population.

Observer-Reported Cosmetic Outcomes, SCCIS Lesions

In this section, we describe only the results between intervention categories, because data are sparse for the comparison of individual observations. In total, two RCTs (204 lesions) were included in this analysis, both at low to moderate risk of bias for this outcome.[72, 79] The evidence graph in Figure 19 shows the observed comparisons based on RCTs that report observers' (investigators' or providers') assessments of "at least good" cosmetic outcome. The cosmetic outcome was assessed using different scales in each RCT. The evidence graph is sparsely connected. Details about the comparisons are in Table 77.

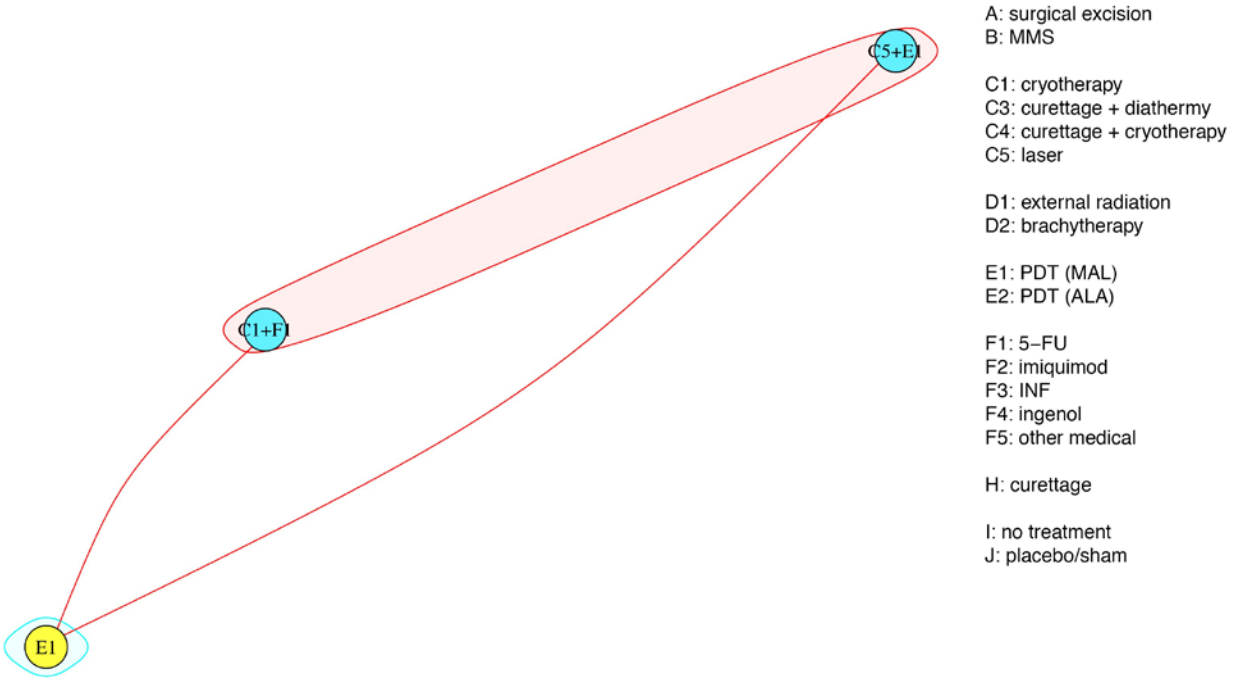
Table 77. Sample information, observer-reported cosmetic outcomes (SCCIS)

Studies (total sample)	2 (204)
Total sample by intervention	(C5+E1): 18; (E1): 100; (C1+F1): 86
Total sample by intervention, (min, max)	18, 100
Data by comparison	(C5+E1--E1): 1 (36); (E1--C1+F1): 1 (168)

Studies by comparison (min, max)	1, 1
Total sample by comparison (min, max)	36, 168
Followup (min, max)	12, 12 months

C1 = cryotherapy; C3 = diathermy and curettage; C4 = cryotherapy and curettage; C5 = laser; D1 = external radiation; E1 = MAL photodynamic therapy; E2 = ALA photodynamic therapy; F1 = 5-FU; F2 = Imiquimod; F3 = Interferon; F4 = Ingenol; H = curettage; J = placebo; SCCIS = squamous cell carcinoma in situ

Figure 19. Evidence graph of RCTs comparing observer-assessed cosmetic outcomes (all SCC lesions)



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

Table 78 has the results of the comparisons between intervention categories based on a network meta-analysis. Based on the odds ratios in Table 78, the combination of cryotherapy and 5-FU (C1+F1) had statistically significantly better observer-assessed cosmetic outcomes than PDT with MAL (E1). The other two comparisons were not statistically significant. However, based on their confidence intervals one could not exclude differences in the odds of the outcome as large as 50 percent in either direction.

Table 78. Relative odds ratios between interventions for at least good cosmetic outcome, as assessed by an observer (SCCIS lesions, Figure 19)

Cryotherapy+5-FU (C1+F1)	0.32 (0.07, 1.51)	***0.09 (0.02, 0.30)***
3.1 (0.66, 14.5)	**Laser + PDT (MAL) (C5+E1)**	0.26 (0.04, 1.71)
11.71 (3.37, 40.66)	3.78 (0.58, 24.48)	**PDT (MAL) (E1)**

PDT = photodynamic therapy; MAL=methyl aminolevulinate, FU= fluorouracil; SCCIS=squamous cell carcinoma in situ. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. Results are given as odds ratios (95% confidence intervals).

Table 79 shows the average percentage of patients with at least good cosmetic outcomes in the RCTs, based on the same network meta-analysis as the Table 78. The average number of lesions with cosmetic outcomes rated as good or excellent ranged between 72.1 and 96.8; however, the confidence intervals for these proportions were wide. Refer to Table 78 for a pairwise comparison between these treatments.

Table 79. Mean fractions of lesions with at least good cosmetic outcome, as assessed by an observer (SCCIS lesions)

Intervention	Mean percent (95% CI)
Cryotherapy + 5-FU (C1+F1)	72.1 (61.7, 80.5)
Laser + PDT (MAL) (C5+E1)	88.9 (64.8, 97.2)
PDT (MAL) (E1)	96.8 (90.5, 99.0)

PDT = photodynamic therapy; MAL = methyl aminolevulinate; FU = fluorouracil; SCCIS = squamous cell carcinoma in situ; CI = confidence interval

Evidence From NRCSs

No NRCS reported the outcome of interest in populations where the majority of lesions were SCCs. Refer to the section on this outcome in the BCC section for a description of an NRCS that included SCCs (29%) and compared a lower dose of radiation (37 Gy) with a higher dose (45 Gy). For observer assessed cosmetic outcomes and among all lesions, the relative risk favored the lower dose, but not statistically significantly so.[151]

Quality of Life, SCCIS Lesions

We did not identify any studies with results for this outcome in this population.

Mental Health, SCCIS Lesions

We did not identify any studies with results for this outcome in this population.

Patient Satisfaction, SCCIS Lesions

We did not identify any studies with results for this outcome in this population.

Mortality, SCCIS Lesions

We did not identify any studies with results for this outcome in this population.

Costs and Resource Use, SCCIS Lesions

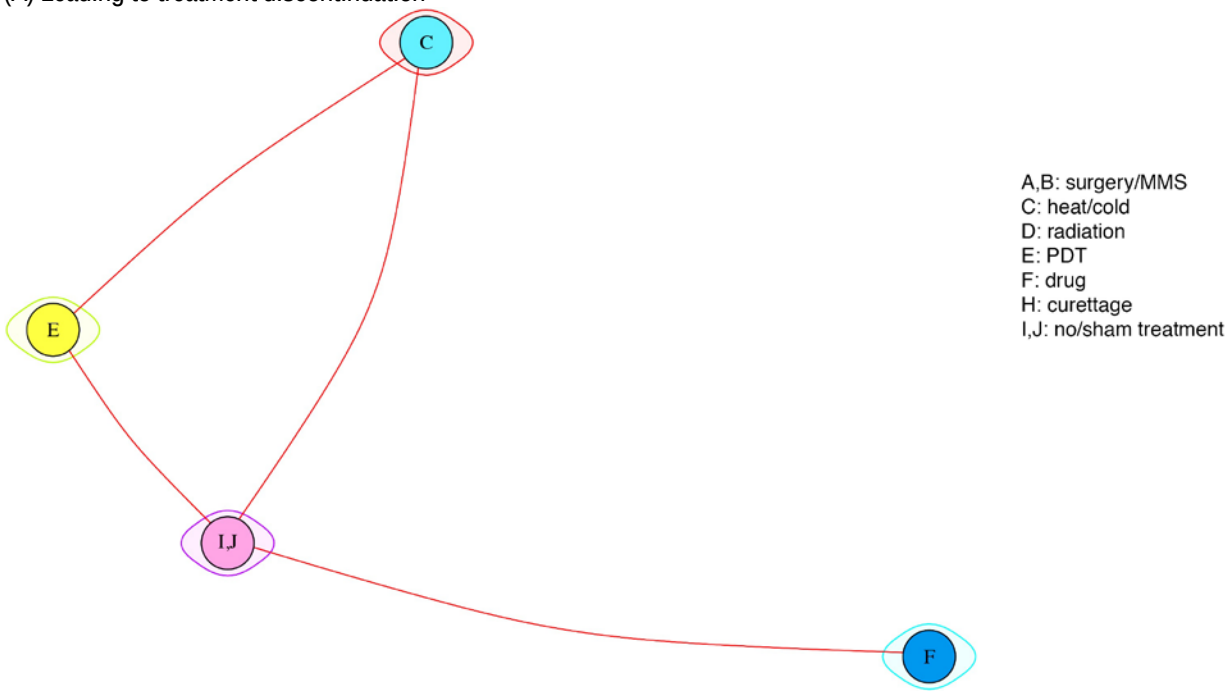
We did not identify any studies with results for this outcome in this population.

Adverse Events, All SCCIS Lesions

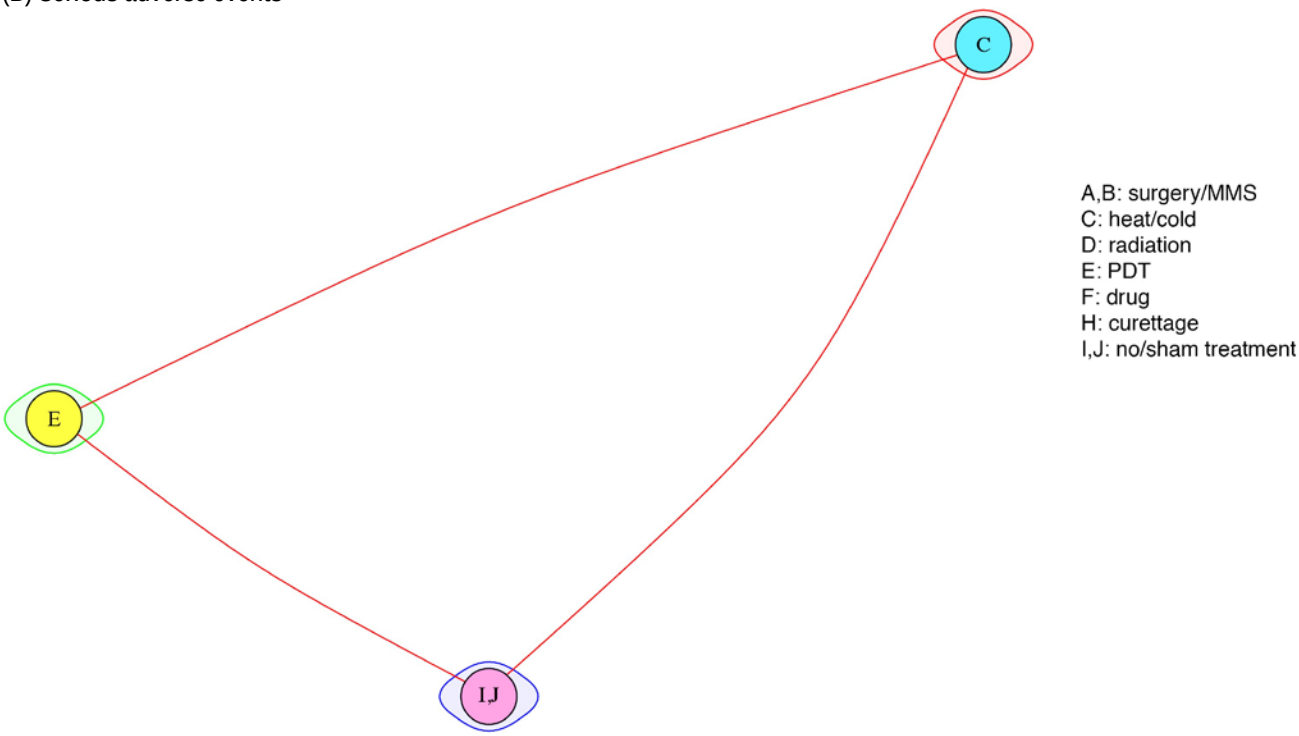
We describe only results between intervention categories, because data are sparse for the comparison of individual observations. Figure 20 shows the evidence graph for the comparison of the frequency of adverse events leading to discontinuation, serious adverse events, pain after treatment completion, and infection of the treated site. Reporting of adverse events was not consistent across RCTs. Appendix I enumerates other types of adverse events that were reported.

Figure 20. Evidence graph of RCTs comparing frequency of adverse events (SCCIS lesions)

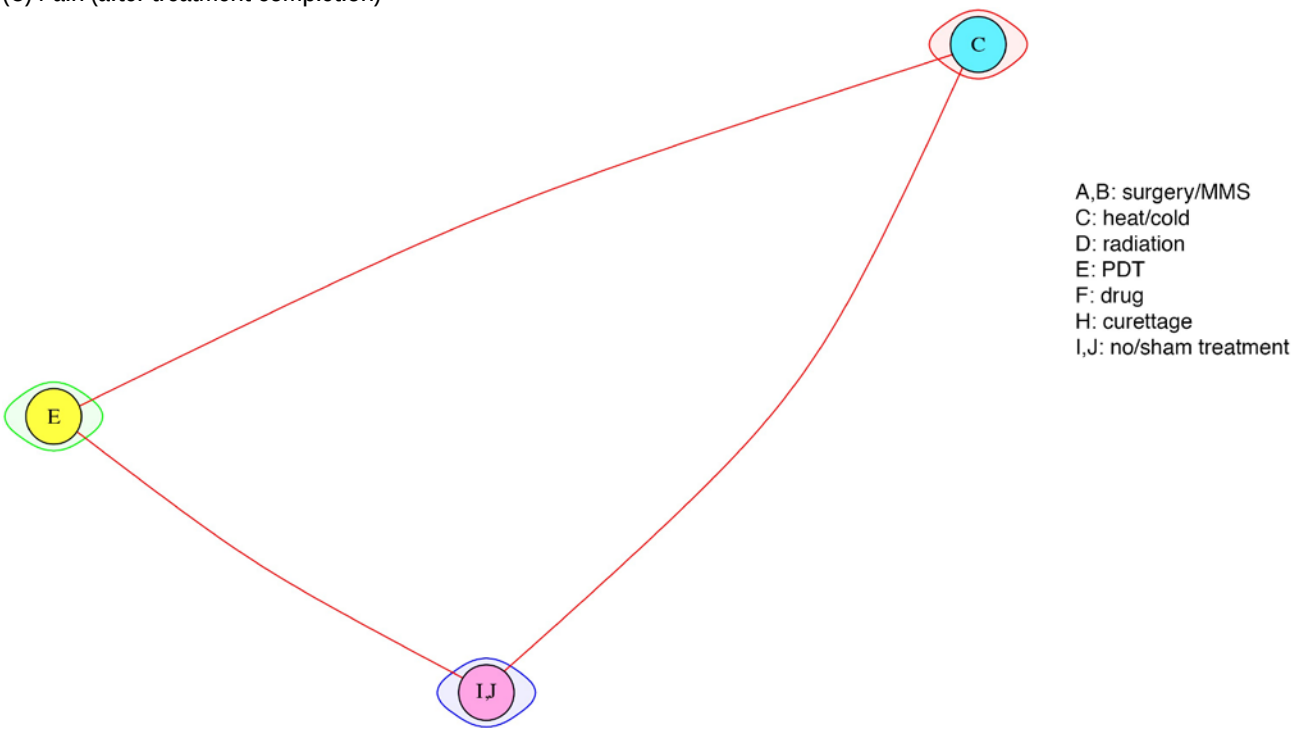
(A) Leading to treatment discontinuation



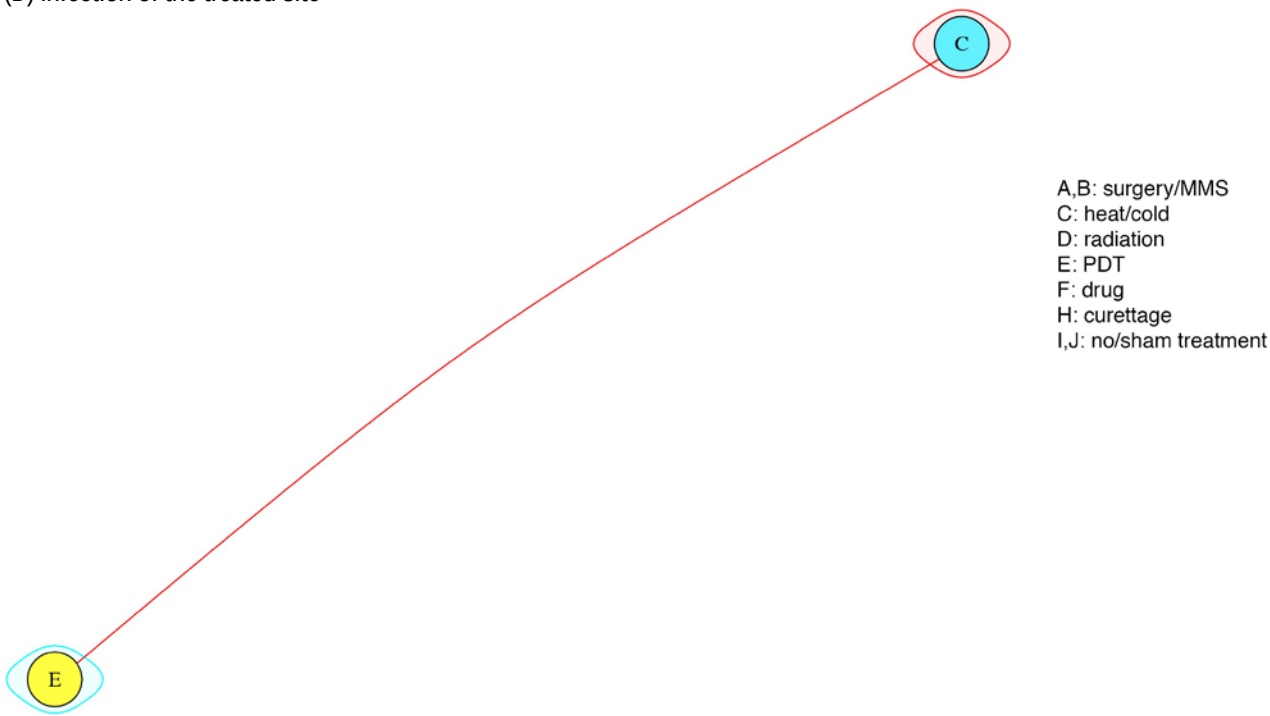
(B) Serious adverse events



(C) Pain (after treatment completion)



(D) Infection of the treated site



MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil; INF = interferon

The evidence graphs in Figure 20 are sparsely connected. For parsimony, we do not report relative effects for comparisons of the frequency of each type of adverse event. Table 80 has details about the comparisons by type of adverse event.

Table 80. Sample information, adverse events (SCCIS)

	Adverse Events Leading to Treatment Discontinuation [72, 79, 83]	Serious Adverse Events[79]	Pain After Treatment[79, 80]	Infection of Treated Site[72]
Studies (total sample)	3 (292)	1 (225)	2 (265)	1 (36)
Total sample by intervention	(C): 130; (E): 114; (I,J): 33; (F): 15	(C): 112; (E): 96; (I,J): 17	(C): 132; (E): 116; (I,J): 17	(C): 18; (E): 18
Total sample by intervention, (min, max)	15, 130	17, 112	17, 132	18, 18
Data by comparison	(C--E): 2 (244); (C--I,J): 1 (129); (E--I,J): 1 (113); (I,J--F): 1 (31)	(C--E): 1 (208); (C--I,J): 1 (129); (E--I,J): 1 (113)	(C--E): 2 (248); (C--I,J): 1 (129); (E--I,J): 1 (113)	(C--E): 1 (36)
Studies by comparison (min, max)	1, 2	1, 1	1, 2	1, 1
Total sample by comparison (min, max)	31, 244	113, 208	113, 248	36, 36
Followup median (min, max)	[during treatment]	3 (3, 3) months	1.5 (0.3, 3) months	1 week

A = surgical excision; B = Mohs micrographic surgery; C = heat/cold; D = radiation; E = photodynamic therapy; F = drugs; H = curettage; I = no treatment; J = placebo

We report rates of adverse events per intervention category, based on a joint analysis of all RCTs reporting the same outcome. Most likely, adverse events were defined differently across studies, but these definitions were often not clearly described. Results for different types of adverse events, as defined by each study, are in Table 81 and come from different analyses.

Drugs had the highest rate of adverse events leading to treatment discontinuation was (13.3%; 95% CI, 3.4 to 40.5); the rate for interventions destroying the lesion with heat or cold was 2.0 percent (C). This outcome was not applicable for PDT, because it is a one-time intervention.

The frequency of adverse events characterized as "serious" by the investigators was smaller than 1 percent for all intervention categories.

Rates of pain after treatment ranged between 23.4 and 34.1 percent (including sham treatments).

The outcome of infection at the treatment site was reported in a single RCT at 0 percent.[68]

Table 81. Mean fractions of adverse events, using each RCT's definitions (SCCIS lesions)

Intervention Type	Leading to Discontinuation (Figure 20 A)		Serious (Figure 20 B)*	Pain After Treatment (Figure 20 C)		Infection of the Treated Site (Figure 20 D)*
	Mean	Forecast	Mean	Mean	Forecast	Mean
Heat/cold (C)	1.9 (0.6, 6.4)	1.9 (0.6, 6.4)	0.9 (0.1, 6.1)	34.1 (20.0, 51.6)	34.1 (14.7, 60.9)	0 (0, 31)
PDT (E)	Not defined**	Not defined**	0.5 (0.0, 7.7)	23.4 (12.4, 39.5)	23.4 (9.0, 48.5)	0 (0, 31)
Drugs (F)	13.3 (3.4, 40.5)	13.3 (3.4, 40.5)	NA	NA	NA	NA
No/sham treatment (I,J)	4.7 (0.9, 20.1)	4.7 (0.9, 20.1)	0 (0, 32.2)	28.4 (9.7, 59.3)	28.4 (7.8, 65.0)	NA

Note: Letters in outcomes refer to Figure 20. Results are given as percent and 95 percent confidence interval.

PDT = photodynamic therapy; NA = not applicable; SCCIS = squamous cell carcinoma in situ; RCT = randomized controlled trial

* No forecasts for these outcomes (fixed effects analyses only).

** PDT is a one-time treatment; discontinuation is not defined, but for parsimony, it was entered as 0 in the analysis.

Evidence From NRCSs

One NRCS reported pain for 80 SCCIS lesions in 67 people, treated with either curettage (44 lesions) or cryotherapy (36 lesions). The mean age was 74 (range: 46 to 89), and the mean lesion area was 336 mm2 (range 30 to 1890 mm2). Eighty-two percent were female, and the lesions were located on the extremities (84%), trunk (7.5%), and head/neck (8.5%). The cryotherapy arm had a significantly higher patient-reported pain during the treatment to 1 day after the procedure (OR 10.4; P-value <0.001).[141]

Microinvasive SCC Lesions

We found one RCT that compared MAL-PDT with laser-primed PDT in 45 people. The mean age was 76 and the majority of lesions were on the face or scalp in both arms (75% in the MAL-PDT arm and 76.2% in the laser-primed PDT arm). The rest of the lesions were on the

extremities (16.7% and 19%, respectively) and trunk/neck (8.3% and 4.8%, respectively). The majority of tumors were moderately differentiated (75% in the MAL-PDT arm and 81% in the laser-primed PDT arm), while the rest were poorly differentiated. Risk of bias for this study was judged to be low (details in Table 59).[43]

Recurrence, Microinvasive SCC Lesions

At 12 months, recurrence rates were significantly lower in the laser-primed PDT arm (2 of 16 patients; 12.5%; 95% CI 0.1%, 29.2%) than in the MAL-PDT arm (7 of 11 patients; 63.6%; 95% CI 33.8%; 93.5%; P between arms 0.006). At 24 months, the difference remained significantly lower in the laser-primed PDT arm (3 of 16 patients; 18.8%; 95% CI 0.1%, 38.5%) than in the MAL-PDT arm (8 of 11 patients; 95% CI 45.1%, 99.9%; P between arms 0.005).[43]

Lack of Histological Clearance, Microinvasive SCC Lesions

Lack of histological clearance was measured at 3, 12, and 24 months. At each time point, lack of histological clearance was lower in the laser-primed arm. At three months, 3 of 19 participants in the laser-primed PDT arm showed a lack of histological clearance (15.8%) compared to 47.6% in the MAL-PDT arm (P=0.03). At 12 months, 5 of 19 participants in the laser-primed PDT arm showed a lack of histological clearance (26.3%) compared to 17 of 21 (80.9%) in the MAL-PDT arm (P=0.001). Finally, at 24 months, 6 of 19 participants in the laser-primed PDT arm showed a lack of histological clearance (31.6%) compared to 18 of 21 (85.7%) in the MAL-PDT arm (P=0.001).[43]

Observer-Reported Cosmetic Outcomes, Microinvasive SCC Lesions

Cosmetic outcomes were only reported for patients who had a complete response at 24 months, so the sample sizes were too small to detect statistical significance. In the laser-primed PDT arm, observer-reported cosmetic outcome were at least good in 10 of 13 people (77%). In the MAL-PDT arm, they were at least good in 2 of 3 (67%).[43]

Adverse Events, Microinvasive SCC Lesions

Everyone in both arms reported at least one adverse event, which included erythema, crusting, hyperpigmentation, pruritus, edema, bullae, and burning sensations. A higher percentage of patients in the laser-primed PDT arm reported each adverse event than in the MAL-PDT arm, but the difference was not statistically significant.

Everyone in both arms also reported experiencing pain during the procedure, with similar mean VAS scores for laser-primed PDT (6.0; SD, 1.7) and MAL-PDT (5.7; SD, 1.7; P = 0.59).[43]

Discussion

Evidence Summary

Tables 82 and 83 summarize our conclusions on comparisons between types of intervention for treating basal cell carcinomas (BCCs) and squamous cell carcinoma in situ (SCCIS).

The conclusions in the Tables are general and do not cover all the analyses we explored. We estimated effects for 213 comparisons between intervention categories and 565 comparisons between individual interventions for the outcomes of interest, not counting information from dose-response analyses (e.g., Table 58) and from nonrandomized studies. Providing conclusions and rating the "strength of the evidence" for each of these hundreds of comparisons is not productive. Consumers of our report who have specific interests should consult the pertinent results.

Within the existing evidence, with respect to BCC recurrence, surgical treatments and radiation therapy appear to be (statistically significantly) better than interventions that destroy lesions with heat or cold, photodynamic therapy (PDT), or curettage. However, PDT was associated with improved cosmetic outcomes. With regards to drugs for the treatment of BCC, recurrence rates with imiquimod were not significantly different than with surgical excision in a single large randomized controlled trial (RCT) (Table 8).

Given that lack of recurrence is, essentially, cure from disease, these results support the use of surgical and radiation treatment for low-risk BCC. For SCCIS, the use of cryotherapy and PDT is supported over topical 5-fluorouracil with regards to recurrence. However, how these treatments perform for SCCIS compared with surgical treatments, which are commonly used in clinical practice, is not ascertainable based on the currently available evidence.

For patients and clinicians, though, cure is not the only important endpoint. Surgery, radiation and each of the other treatments under study are associated with benefits and drawbacks that patients and clinicians consider routinely. For example, while external beam radiation therapy is effective, its remote sequelae, such as skin atrophy and the development of secondary tumors, make it less advisable for younger patients. For patients for whom cosmesis is a primary concern, treatment with PDT may be preferable despite its higher recurrence rates. Despite sparse evidence on their ability to cure BCC and SCCIS, some patients may prefer the convenience provided by topical medical treatments such as 5-fluorouracil and imiquimod which can be applied by the patient at home; this contrasts with the multiple visits to hospitals or specialty clinics required for radiation therapy which are not be practical for some patients. Access to treatments will also impact clinical decisionmaking. Specialty care is not available in all communities; while primary care physicians can perform basic surgical procedures and prescribe topical medications, they do not have access to specialized treatments such as Mohs micrographic surgery (MMS), radiotherapy, and PDT.

We acknowledge that the clinical applicability of some of these results is limited. The analyses cannot adequately account for heterogeneity of the populations in included studies, particularly for low-risk BCCs, because, although the RCTs had comparable populations (see Tables 3-6), many did not stratify their results by histologic subtype (superficial or nodular) or location. Thus, we were unable to incorporate these important factors into the analyses. For example, radiation (because of its expense and poor cosmetic outcomes) is rarely used in routine clinical practice to treat low-risk BCC; its use is generally limited to patients with high risk or recurrent disease or for patients with contraindications to surgery. However, the four RCTs that

included radiation arms did not differ significantly in population from the other studies included in the low-risk BCC network, with the exception that they included a larger percentage of lesions in high-risk (face, eyelids) areas. Conversely, use of topical drugs is generally limited to primary, superficial tumors. Therefore, comparisons of the efficacy of radiation and drugs for the low-risk BCCs included in our study may not be relevant in the clinical decision making for most patients and clinicians. That said, the analysis contains an RCT that looks at the direct comparison of radiation and imiquimod in a high-risk location (eyelids), so it might be that they are more relevant for low-risk lesions in high-risk locations.[67]

Perhaps the most striking observation is the dearth of information that is available comparing interventions for these very common cancers. For example, consider comparisons between interventions for BCC lesion recurrence (Figure 7), a most important outcome from a clinical, public health and cost perspective.

Within the existing evidence, with respect to BCC recurrence, surgical treatments and radiation therapy appear to be (statistically significantly) better than interventions that destroy lesions with heat or cold, PDT, or curettage. A comparison of surgery and imiquimod showed that surgery was not significantly better in terms of recurrence. Only 13 RCTs (n=1664 lesions) examining BCC recurrence were included, of which only 20 were treated with curettage. Further, the amount of evidence in the 10 comparisons with head to head data was limited: the number of RCTs per comparison ranged between 1 and 3, and the cumulative number of lesions ranged between 27 and 355.

For SCCs, data on recurrence are even sparser. First, only one RCT examined invasive SCCs, the subgroup of lesions that are most likely to recur or metastasize, and thus most important to evaluate. In clinical practice, these lesions are routinely treated with surgical excision with or without intraoperative margin evaluation, and in most cases are considered appropriate for Mohs surgery in the American Academy of Dermatology appropriate use criteria.[159] Radiation is also commonly used for invasive SCC. The lack of evidence comparing efficacy among these commonly used treatments is striking.

For SCCISs, only 4 RCTs (348 lesions) compared 4 types of interventions, namely a drug (imiquimod), interventions that destroy lesions with heat or cold, PDT, and sham treatments (Figure 16 (B) and Table 61). Note that surgical interventions, radiation therapy and curettage, therapies commonly used in clinical practice, were not examined.

Table 82. Summary conclusions for BCC lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, all BCC						
(1) Surgical interventions (A,B) and radiation (D) were associated with lower recurrence rates than interventions that destroy lesions with heat or cold (C), and PDT (E) (moderate to high strength of evidence) (2) Curettage (H) may have higher recurrence rates than surgical interventions (A,B) or radiation (D) (3) Imiquimod (F) was associated with recurrence rates that were not significantly different than that of surgical interventions (A,B) (4) [Imprecise data on the comparison on curettage and interventions that destroy lesions with heat or cold (C) or PDT (E)]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) Moderate to High (2) Low (3) Low (4) [Insufficient]	• Surgery/MMS (A,B) had significantly fewer recurrences than heat/cold, PDT, and curettage; not significantly fewer than radiation; and not significantly more than drugs (7 RCTs; 2 NRCSs) • Heat/cold (C) interventions had significantly more recurrences than surgery and radiation; not significantly more than drugs and curettage, and not significantly fewer than PDT (7 RCTs) • Radiation (D) had significantly fewer recurrences than thermal interventions and PDT, not significantly fewer than curettage, and not significantly more than surgery and drugs (3 RCTs) • PDT (E) had significantly more recurrences than radiation and surgery, and not significantly more than heat/cold, drugs, and curettage (6 RCTs, 1 NRCS) • Imiquimod (F) had more recurrences than surgery, but not significantly so (1 RCT) • Curettage (H) had significantly more recurrences than surgery, not significantly more recurrences than drugs and radiation, and not significantly fewer recurrences than PDT and heat/cold (2 RCTs)
Histologic clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better histological clearance outcomes and were statistically significantly better than interventions that destroy lesions with heat or cold (C), PDT (E), drugs (F), and placebo (I,J). (2) Interventions that destroy lesions with heat or cold (C), PDT (E), and drugs (F) have better histological outcomes than placebo (I,J) (3) [imprecise data on the relative comparisons of nonsurgical active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed significantly better than heat/cold, drugs, and placebo, and nonsignificantly better than PDT (2 RCTs) • Thermal interventions (C) performed significantly better than placebo, nonsignificantly better than drugs, nonsignificantly worse than PDT, and significantly worse than surgery (2 RCTs) • PDT (E) performed significantly better than placebo, nonsignificantly better than drugs and heat/cold, and nonsignificantly worse than surgery (7 RCTs, 1 NRCS) • Drugs (F) performed significantly better than placebo, nonsignificantly worse than PDT and heat/cold, and significantly worse than surgery (8 RCTs, 2 (NRCSs)
Clinical clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better clinical clearance outcomes than PDT (E), drugs (F) and placebo (I,J) (2) All active treatments were associated with better clinical clearance outcomes than placebo (3) [Imprecise data on relative comparisons between nonsurgical active treatments]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed statistically significantly better than drugs and placebo, and nonsignificantly better than heat/cold and PDT (4 RCTs); this comparison is less relevant as surgery ought to achieve 100% clinical clearance • Thermal interventions (C)performed statistically significantly better than plecebo, nonsignificantly better than drugs and PDT, and nonsignificantly worse than surgery (3 RCTs) • PDT (E) performed statistically significantly better than placebo, nonsignificantly better than drugs, and nonsignificantly worse than surgery and heat/cold (7 RCTs)

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
						• Drugs (F) performed statistically significantly better than placebo, nonsignificantly worse than PDT and heat/cold, and significantly worse than surgery (5 RCTs)
Patient-reported cosmetic outcomes, all BCC						
(1) PDT is associated with better cosmetic outcomes than other intervention categories (2) [Imprecise data on relative comparisons between nonsurgical active intervention categories]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Low (2) Insufficient	• Surgery(A,B) had significantly better outcomes than heat/cold and radiation, significantly worse outcomes than PDT, and nonsignificantly worse outcomes than drugs (4 RCTs) • Thermal interventions (C)had significantly worse outcomes than surgery and PDT and nonsignificantly worse than radiation and drugs (2 RCTs) • Radiation (D) had nonsignificantly better outcomes than heat/cold, nonsignificantly worse outcomes than drugs, and significantly worse outcomes than PDT and surgery (2 RCTs) • PDT (E) had significantly better outcomes than surgery, heat/cold, and radiation and nonsignificantly better outcomes than drugs (4 RCTs) • Drugs (F) had better outcomes than surgery, heat/cold, and radiation, and nonsignificantly worse outcomes than PDT, but not statistically significantly so (1 RCT)
Observer-reported cosmetic outcomes, all BCC						
(1) PDT is associated with significantly better cosmetic outcomes than surgery (A,B) (2) [PDT may be associated with better cosmetic outcomes compared to nonsurgical active intervention categories] (3) [Imprecise data on relative comparisons between heat/cold (C), radiation, and drugs (D)]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) [Insufficient] (3) [Insufficient]	• Surgery(A,B) had nonsignificantly better outcomes than radiation, significantly worse outcomes than PDT, and nonsignificantly worse outcomes than drugs, heat/cold, and placebo (4 RCTs, 1 NRCS) • Heat/cold interventions (C) had significantly better outcomes than radiation, nonsignificantly better outcomes than surgery, and nonsignificantly worse outcomes than PDT, drugs, and placebo (1 RCT) • Radiation (D) had significantly worse outcomes than heat/cold, PDT, drugs, and placebo, and nonsignificantly worse outcomes than surgery (1 RCT, 2 NRCS) • PDT (E) had significantly better outcomes than surgery and radiation, nonsignificantly better outcomes than drugs and heat/cold, and nonsignificantly worse outcomes than placebo (7 RCTs, 1 NRCS) • Drugs (F) had significantly better outcomes than radiation, nonsignificantly better outcomes than surgery and heat/cold, and nonsignificantly worse outcomes than PDT and placebo (1 RCT)
Adverse effects, all BCC						

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
(1) Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with surgical interventions (A,B), heat or cold (C), PDT (E) and drugs (F) (2) For the interventions above, on average, 1 in 10 to 1 in 5 patients report experiencing pain after treatment	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events have wide 95% CIs	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) Low	• For active interventions, point estimates for percentage of discontinuation of treatment, serious adverse events, and infection of the treatment site range from 0/not defined to 5.5%. Forecast CIs are wide (as high as 29%) • For active interventions, point estimates for the percentage of pain after treatment range between 9.9 and 21.6%. Forecast CIs are wide (as high as 88%)
Other outcomes, all BCC						
[Evidence on quality of life, mental health, patient satisfaction, mortality, cost and resource use is reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

Note: When a summary conclusion cannot be made, the description is given in square brackets.

RoB = risk of bias; BCC = basal cell carcinoma; SCC = squamous cell carcinoma; MMS = Mohs micrographic surgery; PDT = photodynamic therapy; RCT = randomized controlled trial; NRCS = nonrandomized comparative study; CI = confidence interval

Table 83. Summary conclusions for SCCIS lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence-base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, SCCIS						
(1) Interventions that destroy the lesions with heat or cold (C) and PDT (E) were associated with lower recurrence rates than 5 FU (F) (2) [Imprecise data on the relative effect of thermal interventions versus PDT]	Moderate	Possibly consistent (No robust indications of inconsistency)	Moderately precise. Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) Low (2) [Insufficient]	• Thermal interventions (C) had statistically significantly fewer recurrences than drugs, and not significantly fewer than PDT or placebo (2 RCTs) • PDT (E) had statistically significantly fewer recurrences than drugs, but not statistically significantly fewer than placebo or more than heat/cold (4 RCTs) • Drugs (F) had statistically significantly more recurrences than heat/cold and PDT, and not significantly more than placebo (1 RCT)
Histologic clearance, SCCIS						
(1) [Laser (C5) + PDT with ALA (E2) results in better histologic clearance over laser alone] (2) 5-FU (F) results in better histologic clearance than placebo (I,J)	(1) Low (2) High	[Not rated]	(1) Imprecise (2) Precise	(1) Direct (2) Direct	(1) [Insufficient] (2) Low	[2 RCTs, 50 patients.]
Clinical clearance, all SCCIS						
(1) Examined types of active interventions (heat/cold [C], PDT (E), and drugs [5-FU, imiquimod; F]) were associated with better clinical outcomes than placebo (2) [Imprecise data on relative comparisons between types of active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	(1) High (2) [Insufficient]	• Thermal interventions (C) performed significantly better than placebo, and nonsignificantly better than drugs and PDT (4 RCTs) • PDT (E) performed significantly better than placebo, nonsignificantly better than drugs, and nonsignificantly worse than heat/cold (5 RCT) • Drugs (F) (5-FU, imiquimod) performed significantly better than placebo, and nonsignificantly worse than PDT and heat/cold (2 RCT)
Observer-reported cosmetic outcomes, SCCIS						
(1) Cryotherapy plus 5-FU (C1+F1) is associated with better outcomes than PDT (MAL) (E1) (2) [No difference between laser pretreatment of the lesion before PDT versus PDT alone]	Low	Unclear (Consistency cannot be rated)	(1) Precise (2) Imprecise	Mix of direct and indirect data	(1) Moderate (2) [Insufficient]	[2 RCTs, 204 patients.]
Adverse effects, SSCIS						
(1) [Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with heat or cold (C), PDT (E) and drugs (F)] (2) [On average, 1 in 4 and 1 in 3 patients report experiencing pain after treatment with PDT (E) and heat or cold (C), respectively]	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events have wide 95% CIs	Mix of direct and indirect data (most comparisons based on indirect data)	(1) [Insufficient] (2) [Insufficient]	[3 RCTs 292 patients.]

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Other outcomes, SCCIS						
[Evidence on patient-reported cosmetic outcomes, quality of life, mental health, patient satisfaction, mortality, cost and resource use id reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

Note: When a summary conclusion cannot be made, the description is given in square brackets.

RoB = risk of bias; BCC = basal cell carcinoma; SCC = squamous cell carcinoma; MMS = Mohs micrographic surgery; PDT = photodynamic therapy; RCT = randomized controlled trial; NRCS = nonrandomized comparative study; CI = confidence interval

Evidence Limitations

With few exceptions and for most outcomes, individual studies were deemed to have at most moderate risk of confounding, selection, or measurement biases. The risk of bias of individual studies was not a major determinant for the conclusions in Tables 82 and 83 Assessing impact of the risk of bias of individual studies on the conclusions of a network meta-analysis is not straightforward.[160] The comparison effects estimated from a network meta-analysis are a combination of the estimated effects from head-to-head studies and from studies contributing through indirect comparisons. For example, assume that there is a highly-biased study in a network meta-analysis: it would be a concern primarily for the comparison it directly informs on, it may be a smaller (or even negligible) concern for comparisons that it informs indirectly, and it will be no concern for comparisons to which it contributes zero information.[161] In this analysis we deemed qualitatively that risk of bias concerns would not change our conclusions. While qualitative-only assessments are precarious, we opted for high-level conclusions that may be robust.

By far the major concern, however, is that the evidence is sparse when one considers the richness of the clinical questions that can be posed. Comparisons between intervention categories are not as informative as comparisons between individual interventions. We have provided analyses at the individual intervention level, but opt not to draw conclusions based on them, because most are based on indirect data and small numbers. In addition, sample sizes were small leading to concerns about generalization.

A second consequence of the paucity of the evidence base is that one cannot directly address questions that may have important health and cost implications for insurers and patients. For example, there are no studies on the effectiveness of external radiation therapy delivered with portable machines in the office setting versus radiation therapy delivered in specialized facilities or versus other interventions. Empirical data on this radiation therapy modality would be useful because there are only limited data on radiation therapy to extrapolate from. Adjuvant treatment in the case of positive margins post excision or in the case of high-risk features, such as adjuvant radiotherapy and new drugs (including epidermal growth factor receptor inhibitors, such as cetuximab and erlotinib) were not within the scope of this review but also have utility in treating BCC and SCC lesions.

Other large gaps remain in the knowledge base: There is no information on subgroups of patients who have limited life expectancy, are frail, or who are immunocompromised (e.g., have chronic lymphocytic leukemiaand other malignancies, immunodeficiency disorders, or who receive immunomodulating or immunosuppressive treatments). There is limited or no information on high risk BCC lesions, and on invasive SCCs. There is limited data on patient- and lesion-specific modifiers of intervention effects.

The inconsistent reporting of adverse events was a challenge in this report. The specific adverse events reported and their definitions varied greatly among studies and treatment modalities. Because of the large number of individual adverse events reported, we grouped them for analysis. However, this can lead to misclassification, especially given that different treatments have different associated harms.

Finally, outcomes such as histological clearance and clinical clearance are surrogates for lesion recurrence. In particular, clinical clearance may be informative when comparing among PDT, medical, and radiation-based therapies, but is not an informative outcome for surgical

interventions: any surgical treatment, regardless of margin control, removes all clinically visible tumor. Therefore, our conclusion in Table 82 that surgical interventions are better than all other interventions with respect to clinical clearance, while very likely to be true, is almost meaningless.

Future Research Recommendations

We have identified a number of important gaps in the medical literature on the topic of treating BCC and SCC. They are described briefly in the following paragraphs.

More trials are needed comparing commonly used treatment modalities such as simple excision, Mohs surgery, PDT and topical medical therapy. Further, in order to justify routine use of various forms of radiotherapy for these patients, more trials comparing radiotherapy with other modalities are needed. As it stands, the lack of evidence on radiotherapy has led the American Academy of Dermatology to discourage the use of superficial radiotherapy and electronic brachytherapy for keratinocyte carcinomas except in select patients.[162, 163] As these tumors are very common and generally have low morbidity and mortality, recruitment for such trials may not prove to be prohibitively difficult.

All trials for BCC and SCC should, where possible, use recurrent disease as a primary or secondary outcome as it is the most clinically important outcome. Trials should also attempt to incorporate measures of health care resource utilization, which were lacking in our review of the existing evidence save for one RCT and one NRCS.[20, 155] Future trials would also benefit from standardization and consistent definition of all outcomes, particularly adverse events and patient-reported outcomes such as cosmesis. To this end, we encourage the development of a core outcome set as is being done for other skin diseases such as psoriasis (The International Dermatology Outcome Measures)[164] and atopic dermatitis (Harmonising Outcome Measures for Eczema).

While more evidence is needed overall, future research should also focus on specific subgroups that have minimal evidence to date. Aggressive histologic subtypes of BCC, including infiltrative and sclerosing patterns, account for very little of the evidence found in our review. While their increased likelihood of recurrence has led to their inclusion as appropriate indications for Mohs surgery (except for lesions ≤0.5 cm on the trunk and extremities, whose appropriateness is rated as "uncertain"), there is scant evidence to support this.[159] With regards to SCC, only one included RCT in this report concerns invasive SCC with the rest concerning in situ disease. Given that invasive SCC is responsible for mortality in 3900-8800 people in the United States each year,[6] in addition to morbidity and health care costs, there is a clear need for comparative effectiveness research for invasive SCC treatments. No comparative evidence was found on keratinocyte carcinoma in high-risk groups such as organ transplant recipients and patients with other altered immune states such as HIV and Chronic Lymphocytic Leukemia (CLL). Patients with limited life-expectancy are another subgroup of interest who warrant study.

Given how common these tumors are and their burden on the health care system, research funding directed to determine the most effective and cost-effective measures for these tumors is needed. It is incumbent on funding agencies and health care payers to fund research examining important questions in this field. Patients, clinicians, payers, and research funders would benefit from a decision analysis of the management of BCC and SCC lesions.

Finally, better monitoring of population trends in BCCs and SCCs can help focus research on most consequential subtypes. Such monitoring can be performed by SEER (which currently

ignores these cancers), the CDC, or large health organizations taking advantage of advances in health information technology. While the volume of these tumors makes surveillance logistically difficult and costly, advances in health information technology and big data analytic techniques should make it more feasible.[165]

Conclusions

Based on sparse evidence, surgical, radiation and some topical drug treatments have lower recurrence rates than other modalities for the treatment of low-risk BCC, and PDT appears to have superior cosmetic outcomes. Large gaps remain in the literature regarding the comparison of individual interventions, and very little or no information on immunocompromised patients, patients with limited life expectancy, and on patients with specific lesion categories, including high risk BCCs and invasive SCCs. In order for clinicians, patients and payers to make informed decisions regarding the treatment of these lesions, new RCT or high-quality NRCS evidence is needed.

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Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin: BCC Addendum

An updated search, using the same search strategy from the original report but limited to basal cell carcinoma (BCC), was conducted in May 2018. The methods used for this addendum were the same as those used in the original report. The updates are for individual interventions only.

Summary of Studies

The updated search yielded three new studies[1-3] and a paper with 5-year results from a fourth.[4] Study characteristics for the three new studies are summarized in Table 1. Two compared photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) compared to PDT with methyl aminolevulinate (MAL).[2, 3] The third compared surgery, cryotherapy, and laser diathermy.[1]

Table 1. Characteristics of eligible randomized trials

Study	Arm	N people	Age, Mean	Female %	Lesion A[rea] (mm^2), D[iameter] (mm), or T[hickness] (mm)	Head and neck location (%)	Max FU (mo)	1* RNG	2* AC	3* Bal	4* Bl-Pt	5* Bl-Dr	6* Bl-As	7* <20% attrition	ROB summary (across all outcomes)
Kessels 2018 28886209[2]	PDT (MAL), E1	80	64	56	D=11	1	12	Yes	No	Yes	No	Yes	No	Yes	Low
	PDT (ALA), E2	82	66	51	D=11	8									
Morton 2018 29432644[3]	PDT (MAL), E1	133	67	50	T=0.46	>= 17**	12	Yes	Unsure	No	Yes	Yes	Yes	No	Low
	PDT (ALA), E2	129	67	37	T=0.41	>= 17**									
Zane 2017 28291062[1]	Surgical excision, A	80	68	45	NR	0	3	Yes	Yes	Yes	No	No	No	Yes	Low
	Cryotherapy, C1	80	69	41	NR	0									
	Laser diathermy, C5	80	68	40	NR	0									

*Design items: 1: RNG = Adequate generation of a randomized sequence reported; 2: AC=Adequate allocation concealment reported; 3: Bal=Group similarity at baseline; 4: Bl Pt = Adequate blinding of patients reported; 5: Bl Dr = Adequate blinding of providers reported; 6: Bl As = Adequate blinding of outcome assessors reported; 7: Less than 20% of sample size missing for any eligible outcome in any arm.

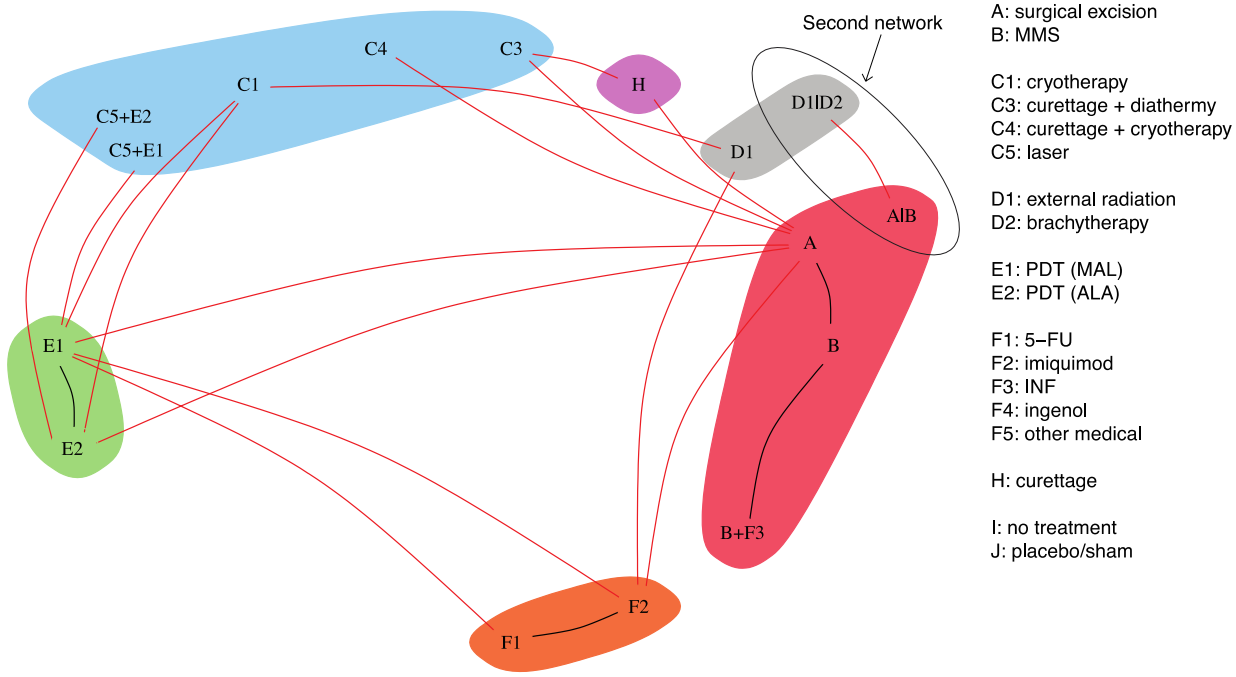
** Neck lesions are counted with torso/extremities.

Abbreviations: PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon; NR=not reported.

Recurrence

The updated evidence graph for recurrence with respect to individual treatments is shown in Figure 1. It replaces the graph shown in Figure 7 of the report.

Figure 1. Evidence graph of RCTs evaluating recurrence in BCCs across individual interventions



Abbreviations: MMS=Mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon. Layout as in Figure 1. This evidence graph comprises three connected networks. The first is the largest group of nodes and is not labeled explicitly. The second and third connected networks are labeled explicitly.

Table 2 replaces Table 11 from the original report, giving the relative effects for the larger subgraph. The results from the smaller network, given in Table 12 of the original report, were unaffected by this update. The new data changed the direction of the comparison for MAL- versus ALA-PDT from an odds ratio of 0.65 (95% CI 0.25, 1.73) to an odds ratio of 1.07 (95% CI 0.34, 3.35). Nevertheless, the comparison remains nonsignificant, with wide confidence intervals. Similarly, surgery went from being better than Mohs surgery (MMS) (OR 1.04, 95% CI 0.21, 5.23) to worse (OR 0.86; 95% CI 0.13, 5.76), again with wide confidence intervals. MMS is no longer statistically significantly better than cryotherapy or PDT, with or without laser therapy. Other comparisons changed in magnitude, but not in direction or statistical significance.

Table 2. Relative odds ratios for recurrence in the larger network in Figure 1

Sur-gery	0.86 (0.13, 5.76)	0.70 (0.02, 21.26)	***0.13 (0.03, 0.48)***	0.53 (0.06, 4.83)	***0.16 (0.03, 0.96)***	0.25 (0.03, 2.18)	***0.10 (0.01, 0.78)***	1.02 (0.14, 7.39)	***0.16 (0.05, 0.5)***	***0.17 (0.05, 0.6)***	***0.10 (0.02, 0.56)***	***0.20 (0.05, 0.76)***	0.19 (0.03, 1.36)
	MMS	0.82 (0.02, 30.59)	0.15 (0.02, 1.13)	0.62 (0.04, 9.79)	0.19 (0.02, 2.2)	0.29 (0.02, 4.13)	0.11 (0.01, 1.5)	1.19 (0.1, 14.54)	0.18 (0.03, 1.26)	0.19 (0.03, 1.45)	0.12 (0.01, 1.19)	0.24 (0.03, 1.88)	0.22 (0.02, 2.89)
		MMS + INF	0.18 (0.01, 5.58)	0.76 (0.01, 38.1)	0.23 (0.01, 9.48)	0.35 (0.01, 16.35)	0.14 (<0.005, 6.06)	1.45 (0.03, 60.47)	0.22 (0.01, 6.5)	0.24 (0.01, 7.24)	0.15 (<0.005, 5.33)	0.29 (0.01, 9.21)	0.26 (0.01, 11.82)
			Cryotherapy	4.19 (0.4, 43.92)	1.29 (0.18, 9.3)	1.95 (0.22, 17.33)	0.76 (0.09, 6.24)	***8.04 (1.28, 50.51)***	1.23 (0.39, 3.83)	1.31 (0.38, 4.56)	0.81 (0.14, 4.53)	1.61 (0.39, 6.66)	1.46 (0.17, 12.54)
				Curettage and Diathermy	0.31 (0.02, 4.58)	0.47 (0.03, 8.55)	0.18 (0.01, 3.12)	1.92 (0.12, 30.51)	0.29 (0.03, 2.82)	0.31 (0.03, 3.21)	0.19 (0.01, 2.55)	0.38 (0.04, 4.12)	0.35 (0.03, 3.94)
					Curettage and Cryo-therapy	1.51 (0.11, 20.74)	0.59 (0.05, 7.51)	6.24 (0.53, 72.8)	0.95 (0.15, 6.21)	1.01 (0.14, 7.16)	0.63 (0.07, 5.91)	1.25 (0.17, 9.21)	1.13 (0.09, 14.22)
						Laser + PDT (MAL)	0.39 (0.03, 5.96)	4.12 (0.29, 57.8)	0.63 (0.08, 4.68)	0.67 (0.08, 5.93)	0.42 (0.04, 4.64)	0.83 (0.09, 7.59)	0.75 (0.05, 11.74)
							Laser + PDT (ALA)	10.59 (0.81, 138.59)	1.62 (0.21, 12.24)	1.72 (0.23, 12.82)	1.07 (0.1, 11.47)	2.12 (0.24, 18.39)	1.92 (0.13, 28.17)
								External Radiotherap y	0.15 (0.02, 1.01)	0.16 (0.02, 1.17)	***0.10 (0.01, 0.97)***	0.20 (0.03, 1.52)	0.18 (0.01, 2.44)
									PDT (MAL)	1.07 (0.34, 3.35)	0.66 (0.15, 2.89)	1.31 (0.4, 4.28)	1.19 (0.15, 9.32)
										PDT (ALA)	0.62 (0.11, 3.44)	1.23 (0.3, 5.02)	1.11 (0.13, 9.41)
											5-FU	1.99 (0.43, 9.21)	1.8 (0.16, 19.87)
												Imiquimod	0.91 (0.1, 7.99)
													Curettage

MMS=Mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, 5-FU= 5-fluorouracil, INF=interferon, BCC=basal cell carcinoma. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

Table 3 replaces tables 13 and 27 from the main report. There is no change in the overall findings for recurrence, though the mean percentages changed some in magnitude.

Table 3. Mean outcome rates for specific interventions for basal cell carcinoma

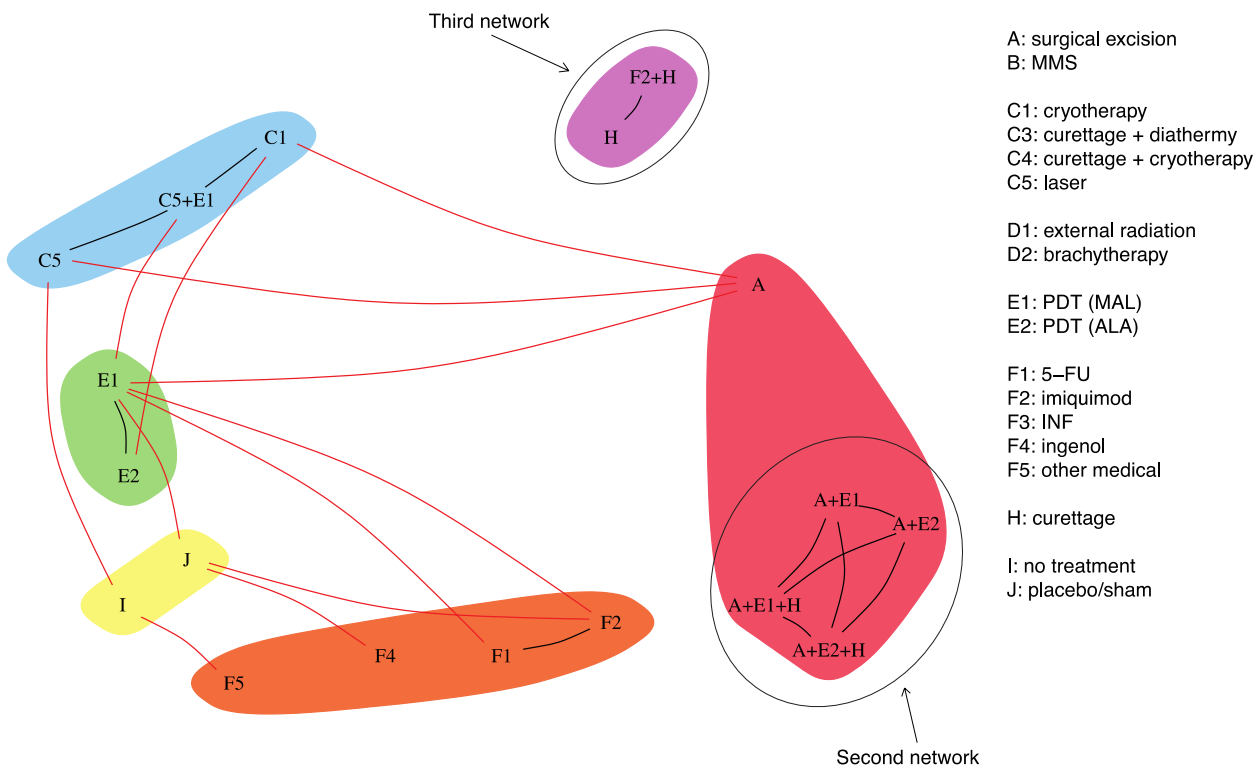
Intervention	Recurrence Mean Percent (95% CI)
First network in Figure 1	
Surgical excision (A)	3.3 (1.3, 7.8)
MMS (B)	3.8 (0.7, 18.9)
MMS+INF (B+F3)	4.6 (0.2, 56.2)
Cryotherapy (C1)	21.0 (9.0, 41.4)
Diathermy+curettage (C3)	5.9 (0.7, 34.9)
Cryotherapy+curettage (C4)	17.1 (3.6, 53.4)
Laser+PDT (MAL) (C5+E1)	12.0 (1.8, 49.6)
Laser+PDT (ALA)	25.9 (5.1, 69.6)
External radiation (D1)	3.2 (0.6, 16.1)
PDT (MAL) (E1)	17.8 (9.1, 31.8)
PDT (ALA) (E2)	16.9 (7.3, 34.4)
5-fluorouracil (F1)	24.7 (7.1, 58.4)
Imiquimod (F2)	14.1 (5.4, 32.4)
Curettage (H)	15.4 (2.6, 55.3)
Second network in Figure 1	
Surgical excision or Mohs (A|B)	0.6 (0.1, 4.0)
External radiation or brachytherapy (D1|D2)	4.6 (2.3, 9.0)

Intervention	Lack of Histological Clearance Mean Percent (95% CI)
First network in Figure 2	
Surgical excision (A)	1.7 (0.3, 9.9)
Cryotherapy (C1)	11.7 (3.1, 35.3)
Laser (C5)	33.7 (10.9, 67.9)
Laser + PDT (MAL) (C5+E1)	37.5 (4.7, 87.9)
PDT (MAL) (E1)	14.5 (5.4, 33.6)
PDT (ALA) (E2)	11.0 (2.1, 41.4)
5-FU (F1)	5.5 (0.5, 38.8)
Imiquimod (F2)	28.6 (14.6, 48.6)
Ingenol (F4)	77.1 (23.7, 97.3)
Other medical (F5)	78.1 (23.9, 97.6)
No treatment (I)	81.8 (48.3, 95.6)
Placebo (J)	86.3 (72.1, 93.9)
Second network in Figure 2	
Surgery + PDT (MAL) (A+E1)	36.4 (14.3, 66.1)
Surgery + PDT (MAL) + curettage (A+E1+H)	20.0 (5.0, 54.1)
Surgery + PDT (ALA) (A+E2)	36.4 (14.3, 66.1)
Surgery + PDT (ALA) + curettage (A+E2+H)	18.2 (4.6, 50.7)
Third network in Figure 2	
Imiquimod + curettage (F2+H)	10.0 (1.4, 46.7)
Curettage (H)	40.0 (15.8, 70.3)

Lack of Histologic Clearance

The evidence graph for lack of histologic clearance with respect to individual treatments in Figure 2 replaces the one in Figure 8 of the main report

Figure 2. Evidence graph for lack of BCC histological clearance



Abbreviations: MMS=Mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon. Layout as in Figure 1. This evidence graph comprises three connected networks. The first is the largest group of nodes and is not labeled explicitly. The second and third connected networks are labeled explicitly.

Table 4 replaces Table 24 of the main report. Tables 25 and 26 remain unchanged. Similar to what was seen in recurrence, MAL-PDT changed from performing non-significantly worse than ALA-PDT (OR 0.67; 95% CI 0.30, 15.3) to non-significantly better (OR 1.37; 95% CI 0.17, 10.74), with wide confidence intervals. Surgery's superiority over MAL-PDT with or without Laser, and Ingenol went from nonsignificant to significant. Ingenol performed statistically significantly worse than PDT and 5-FU. Other comparisons changed in magnitude, but not in direction or statistical significance. Table 3 replaces Table 27 from the report, but as was the case with recurrence, there are no changes, except in magnitude and precision.

Table 4. Relative odds ratios for lack of histological clearance between individual interventions (large network in Figure 2)

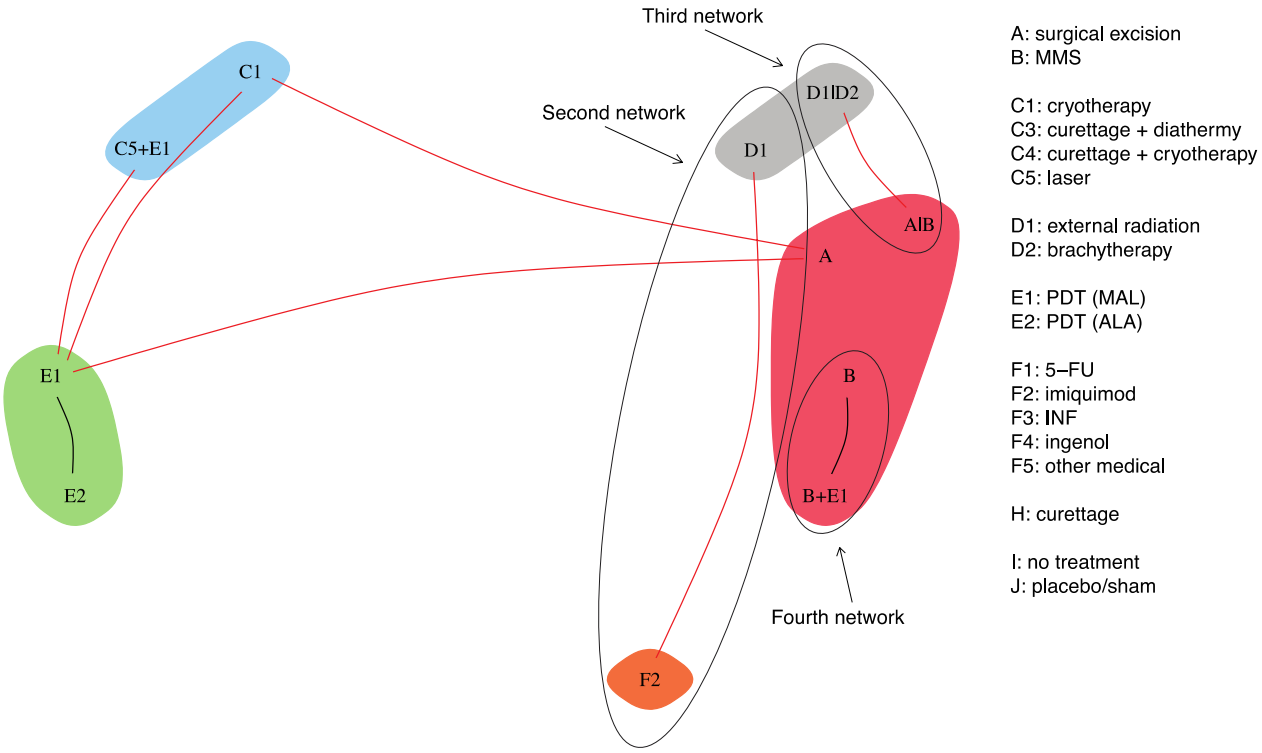
Sur-gery	0.13 (0.01, 1.33)	***0.03 (<0.005, 0.35)***	***0.03 (<0.005, 0.64)***	***0.1 (0.01, 0.87)***	0.14 (0.01, 1.77)	0.3 (0.01, 6.11)	***0.04 (0.01, 0.33)***	***0.01 (<0.005, 0.1)***	***<0.005 (<0.005, 0.1)***	***<0.005 (<0.005, 0.04)***	***<0.005 (<0.005, 0.02)***
	Cryothera py	0.26 (0.03, 1.94)	0.22 (0.01, 3.9)	0.78 (0.13, 4.68)	1.07 (0.11, 10.12)	2.29 (0.14, 36.81)	0.33 (0.06, 1.73)	***0.04 (<0.005, 0.63)***	***0.04 (<0.005, 0.62)***	***0.03 (<0.005, 0.24)***	***0.02 (<0.005, 0.11)***
		Laser	0.85 (0.05, 15.04)	3 (0.5, 18.11)	4.11 (0.43, 39.1)	8.78 (0.54, 142.06)	1.27 (0.24, 6.69)	0.15 (0.01, 2.42)	0.14 (0.01, 2.39)	***0.11 (0.01, 0.94)***	***0.08 (0.02, 0.43)***
			Laser + PDT (MAL)	3.54 (0.23, 54.09)	4.85 (0.23, 101.95)	10.35 (0.33, 328.52)	1.5 (0.11, 20.96)	0.18 (0.01, 5.62)	0.17 (0.01, 5.48)	0.13 (0.01, 2.55)	0.1 (0.01, 1.35)
				PDT (MAL)	1.37 (0.17, 10.74)	2.92 (0.21, 40.58)	0.42 (0.11, 1.7)	***0.05 (<0.005, 0.69)***	***0.05 (<0.005, 0.68)***	***0.04 (0.01, 0.26)***	***0.03 (0.01, 0.11)***
					PDT (ALA)	2.13 (0.11, 41.16)	0.31 (0.04, 2.15)	***0.04 (<0.005, 0.7)***	***0.03 (<0.005, 0.69)***	***0.03 (<0.005, 0.29)***	***0.02 (<0.005, 0.14)***
						5-FU	0.14 (0.01, 1.83)	***0.02 (<0.005, 0.5)***	***0.02 (<0.005, 0.49)***	***0.01 (<0.005, 0.23)***	***0.01 (<0.005, 0.12)***
							Imiquimod	0.12 (0.01, 1.5)	0.11 (0.01, 1.48)	***0.09 (0.01, 0.53)***	***0.06 (0.02, 0.22)***
								Ingenol	0.94 (0.03, 28.3)	0.75 (0.04, 12.94)	0.53 (0.04, 6.78)
									Other medical	0.79 (0.04, 14.35)	0.57 (0.04, 7.56)
										No treatment	0.71 (0.12, 4.34)
											Placebo/ sham

PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, BCC=basal cell carcinoma, MMS = Mohs micrographic surgery. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

Patient- and Observer-Reported Cosmetic Outcomes

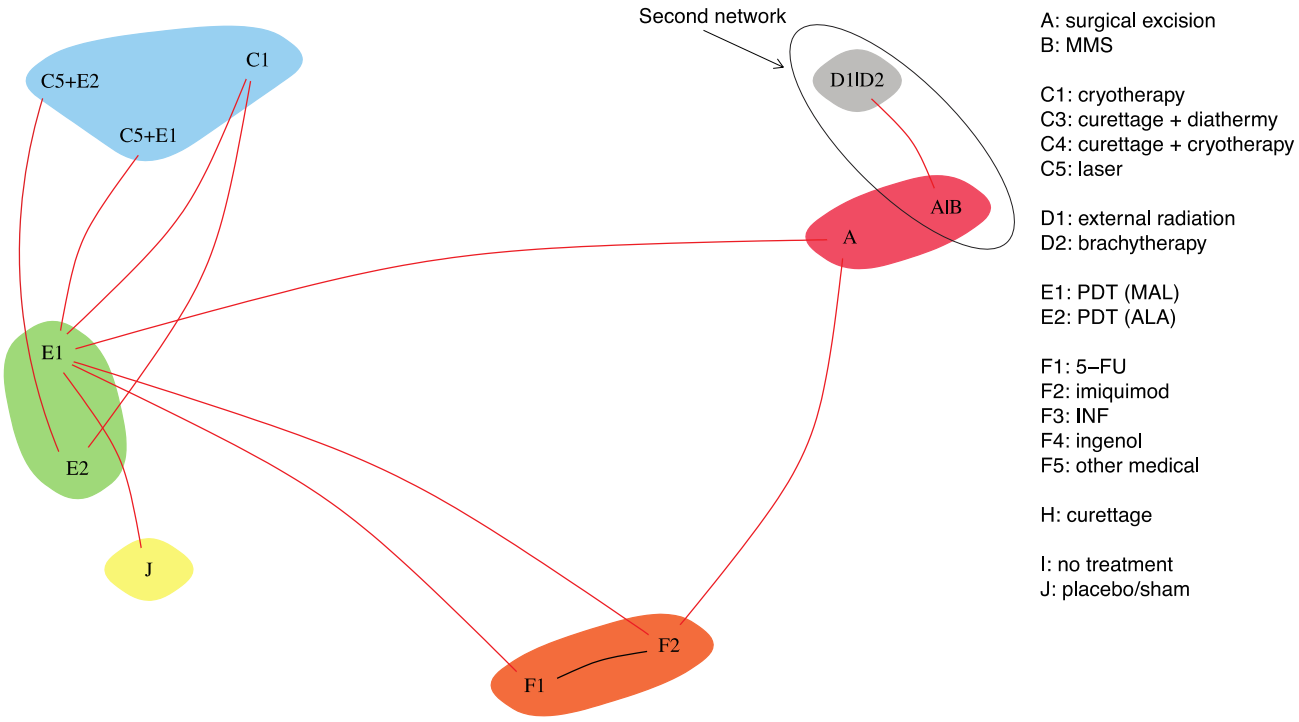
The report only gives results for intervention categories for these outcomes, so this data is additional. Figure 3 gives the evidence graph for patient-reported cosmetic outcomes, while Figure 4 gives the evidence graph for observer-reported cosmetic outcomes.

Figure 3. Evidence graph for patient-reported cosmetic outcomes of BCC treatment



Abbreviations: MMS=Mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon. Layout and naming of connected networks as in Figure 1.

Figure 4. Evidence graph for observer-reported cosmetic outcomes of BCC treatments



Abbreviations: MMS=Mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon. Layout and naming of connected networks as in Figure 1.

As shown in Figure 3, patient-reported cosmetic outcomes comparisons in RCTs were sparse and involved four treatment networks. Table 5 gives the analysis of the largest network of 7 trials comparing 5 treatments (739 total lesions, range 23 to 169). Each of the other three networks comprised a single RCT. In one, an RCT (n=27) did not find a difference between external radiation and imiquimod (OR 0.81, 95% CI 0.01, 43.6). Another RCT favored surgical excision or Mohs micrographic surgery over external radiation/brachytherapy (n=244; OR 2.15, 95% CI 1.2, 3.86). In the last RCT, 7/7 patients rated their outcome as good or better after methyl-aminolevulinic acid PDT followed by Mohs micrographic surgery and 10/10 after Mohs surgery alone.

Table 6 gives outcome rates for each intervention subgraph. In general, patients rated their cosmetic outcomes as good or better significantly more often with PDT using methyl-aminolevulinic acid (93.8%, 95% CI 79.2, 98.3) or aminolevulinic acid (95.8%, 95% CI 84.2, 99.0) compared with standard excision (77.8%, 95% CI 44.8, 93.8), cryotherapy (51.1%, 95% CI 15.8, 85.4) or PDT combined with laser preparation of the lesion (20%, 95% CI 1.9, 76.6). All other comparisons were statistically not significant and had wide confidence intervals.

Table 5. Relative odds ratios for patient-reported cosmetic outcome

Surgery	3.35 (0.58, 19.5)	14.01 (0.97, 201.93)	**0.23 (0.08, 0.65)**	***0.16 (0.05, 0.49)***
	Cryotherapy	4.18 (0.23, 77.64)	**0.07 (0.01, 0.39)**	***0.05 (0.01, 0.28)***
		Laser + PDT (MAL)	**0.02 (<0.005, 0.21)**	***0.01 (<0.005, 0.15)***
			PDT (MAL)	0.67 (0.38, 1.15)
				PDT (ALA)

PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

Table 6. Mean outcome rates by specific intervention (all BCC lesions)

Intervention	Patient-reported good or better cosmetic outcome Mean Percent (95% CI)	Intervention	Observer-reported good or better cosmetic outcome Mean Percent (95% CI)
First network in Figure 3		*First network in Figure 4*	
Surgical excision (A)	77.8 (44.8, 93.8)	Surgical excision (A)	46.7 (19.4, 76.1)
Cryotherapy (C1)	51.1 (15.8, 85.4)	Cryotherapy (C1)	60.1 (23.1, 88.3)
Laser+PDT (MAL) (C5+E1)	20.0 (1.9, 76.6)	Laser+PDT (MAL) (C5+E1)	93.5 (63.5, 99.2)
PDT (MAL) (E1)	93.8 (79.2, 98.3)	Laser+PDT (ALA) (C5+E2)	5.9 (0.5, 45.9)
PDT (ALA) (E2)	95.8 (84.2, 99.0)	PDT (MAL) (E1)	87.9 (73.3, 95.1)
Second network in Figure 3		PDT (ALA) (E2)	53.4 (15.9, 87.4)
External radiation (D1)	96.2 (59.7, 99.8)	5-fluorouracil	57.5 (13.0, 92.4)
Imiquimod (F2)	96.9 (65.0, 99.8)	Imiquimod	61.0 (24.8, 88.1)
Third network in Figure 3		Placebo/sham	93.3 (41.5, 99.6)
Surgical excision or Mohs (A|B)	80.9 (73.3, 86.8)	*Second network in Figure 4*	
External radiation or brachytherapy (D1|D2)	66.4 (57.2, 74.5)	Surgical excision or Mohs (A|B)	78.6 (70.8, 84.8)
Fourth network in Figure 3		External radiation or brachytherapy (D1|D2)	39.8 (31.2, 49.1)
MMS (B)	95.5 (55.2, 99.7)		
MMS +PDT (MAL) (B+E1)	93.8 (46.1, 99.6)		

MMS=Mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon; BCC=basal cell carcinoma; CI=confidence interval

Observer-reported cosmetic outcomes were evaluated in 11 RCTs and 1 NRCS. The larger network in Figure 4 consists of 10 RCTs that compare 9 treatments (3,505 total lesions, samples ranging from 23 to 563). As can be seen on Tables 6 and 7, good or better cosmetic outcomes were estimated to be more common for MAL-PDT than for ALA-PDT, surgical excision, cryotherapy, topical 5-fluorouracil, and imiquimod. The smaller network in Figure 4 was a single RCT that favored surgical excision or Mohs micrographic surgery over external radiation/brachytherapy (n=244; odds ratio 5.56 (3.17, 9.76]).

Table 7. Relative odds ratios for observer-reported good or better cosmetic outcome

Sur-gery	0.58 (0.07, 4.58)	***0.06 (0.01, 0.73)***	14.02 (0.76, 257.68)	***0.12 (0.02, 0.61)***	0.76 (0.08, 7)	0.65 (0.05, 8.31)	0.56 (0.07, 4.24)	0.06 (<0.005, 1.61)
	Cryotherapy	0.11 (0.01, 1.49)	***24.1 (1.12, 517.07)***	0.21 (0.03, 1.36)	1.31 (0.12, 14.7)	1.11 (0.07, 17.02)	0.96 (0.1, 9.05)	0.11 (<0.005, 3.18)
		Laser + PDT (MAL)	***228.74 (7.99, 6544.69)***	1.96 (0.19, 20.04)	12.48 (0.78, 199.23)	10.56 (0.5, 222.5)	9.14 (0.66, 125.66)	1.02 (0.03, 39.29)
			Laser + PDT (ALA)	***0.01 (<0.005, 0.14)***	0.05 (<0.005, 1.3)	0.05 (<0.005, 1.4)	***0.04 (<0.005, 0.83)***	<0.005 (<0.005, 0.23)
				PDT (MAL)	6.35 (0.82, 49.22)	5.38 (0.48, 59.82)	4.65 (0.74, 29.3)	0.52 (0.02, 11.97)
					PDT (ALA)	0.85 (0.05, 14.54)	0.73 (0.07, 7.92)	0.08 (<0.005, 2.66)
						5-FU	0.87 (0.06, 12.85)	0.1 (<0.005, 3.93)
							Imiquimod	0.11 (<0.005, 3.23)
								Placebo/ sham

PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, BCC=basal cell carcinoma, MMS = Mohs micrographic surgery. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic numbers indicate statistical significance. Results are given as odds ratios (95% confidence intervals).

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Appendix A. Search Strategy

PubMed (3/8/17)

(("Bowen's Disease"[Mesh] OR bowen's Or "basal cell carcinoma" or "basal cell carcinomas" or "Carcinoma, Basal Cell"[Mesh] or BCC Or "squamous cell carcinoma" or "squamous cell carcinomas" OR "Carcinoma, Squamous Cell"[Mesh] or SCC OR ((keratinocyte* or "Keratinocytes"[Mesh]) and (carcinoma* or "Carcinoma"[Mesh])) OR "non-melanoma" OR "non melanoma" OR "nonmelanoma") NOT (Oropharynx OR Oropharyngeal neoplasms or "Oropharyngeal Neoplasms"[Mesh] OR Pharynx OR Pharyngeal neoplasms OR "Pharyngeal Neoplasms"[Mesh] or "Lung Neoplasms"[Mesh] or "Urinary Bladder Neoplasms"[Mesh] or "Uterine Cervical Neoplasms"[Mesh] or "Esophageal Neoplasms"[Mesh] or "Laryngeal Neoplasms"[Mesh]))

AND

(((Surger* or surgic*) and (excision or removal)) Or "shave removal" Or "external beam radiation" Or "external-beam radiation" Or brachytherap* or "Brachytherapy"[Mesh] Or chemotherap* OR Sensus OR X-ray OR "X-Ray Therapy"[Mesh] OR radiotherapy OR "Radiotherapy"[Mesh] Or (topical and (medications or chemotherap*)) Or observation Or "watchful waiting" Or ((Mohs or micrographic*) and surgery) Or "Mohs Surgery"[Mesh] Or Curett* or "Curettage"[Mesh] Or diathermy or "Diathermy"[Mesh] Or cauterization or "Cautery"[Mesh] Or Cryotherapy or "Cryotherapy"[Mesh] Or electrodesiccation Or ((CO2 or "carbon dioxide") and laser and therapy) Or "Laser Therapy"[Mesh] Or plesiotherapy Or "Methyl 5-aminolevulinate" or "methyl 5-aminolevulinate" [Supplementary Concept] OR MALA Or "5-aminolevulinic acid" or "Aminolevulinic Acid"[Mesh] Or ALA Or Photodynamic or "Photochemotherapy"[Mesh] or Photochemotherap* Or 5-fluorouracil Or 5-FU Or Methotrexate Or "Methotrexate"[Mesh] Or Bleomycin or "Bleomycin"[Mesh] Or imiquimod or "imiquimod" [Supplementary Concept] Or BEC-5 Or diclofenac or "Diclofenac"[Mesh] Or interferon or IFN Or "Ingenol mebutate" or "3-ingenyl angelate" [Supplementary Concept] or PEP005 or PEP-005 or "PEP 005" Or Vismodegib Or Erivedge or "HhAntag691" [Supplementary Concept] or NSC747691 or NSC-747691 or "NSC 747691" or R-3616 or R3616 or "R 3616" or RG-3616 or RG3616 or "RG 3616" or GDC-0449 or GDC0449 or "GDC 0449" Or Sonidegib or Odomzo or "LDE225" [Supplementary Concept] or NVP-LDE225 Or Itraconazole or "Itraconazole"[Mesh] or Sporanox or Orungal or R51211 or R-51211 or "R 51211")

AND

("Cohort Studies"[Mesh] OR cohort OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR (follow-up or followup) OR longitudinal OR "Placebos"[Mesh] OR placebo* OR "Research Design"[Mesh] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Comparative Study" [Publication Type] OR ((comparative OR Intervention) AND study) OR pretest* OR pre test* OR posttest* OR post test* OR prepost* OR pre post* OR "before and after" OR interrupted time* OR time serie* OR intervention* OR ((quasi-experiment* OR quasiexperiment* OR quasi experiment*) and (method or study or trial or design*)) OR "Case-Control Studies"[Mesh] OR (case and control) OR Clinical Studies OR "Clinical Studies as Topic"[Mesh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random* OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Placebos"[Mesh] OR placebo OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or

mask*)) OR rct OR "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR randomized)
NOT
("addresses"[pt] or "autobiography"[pt] or "bibliography"[pt] or "biography"[pt] or "case reports"[pt] or "comment"[pt] or "congresses"[pt] or "dictionary"[pt] or "directory"[pt] or "editorial"[pt] or "festschrift"[pt] or "government publications"[pt] or "historical article"[pt] or "interview"[pt] or "lectures"[pt] or "legal cases"[pt] or "legislation"[pt] or "letter"[pt] or "news"[pt] or "newspaper article"[pt] or "patient education handout"[pt] or "periodical index"[pt] or "comment on" or "review"[pt] or "systematic"[sb] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murinae)

Cochrane (3/8/17)
((bowen's Or bowens OR basal cell carcinoma or BCC Or squamous cell carcinoma or SCC OR keratinocyte* and carcinoma* OR "non-melanoma" OR "non melanoma" OR "nonmelanoma") NOT (Oropharynx OR Oropharyngeal neoplasms OR Pharynx OR Pharyngeal neoplasms))
AND
(((Surger* or surgic*) and (excision or removal)) Or "shave removal" Or "external beam radiation" Or "external-beam radiation" Or brachytherap* Or chemotherap* OR Sensus OR X-ray OR radiotherapy Or (topical and (medications or chemotherap*)) Or observation Or "watchful waiting" Or ((Mohs or micrographic*) and surgery) Or Curett* Or diathermy or cauterization Or Cryotherapy Or electrodesiccation Or ((CO2 or "carbon dioxide") and laser and therapy) Or plesiotherapy Or "Methyl 5-aminolevulinate" or "methyl 5-aminolevulinate" or MALA Or "5-aminolevulinic acid" or ALA Or Photodynamic or Photochemotherap* Or 5-fluorouracil Or 5-FU Or Methotrexate Or Bleomycin Or imiquimod Or BEC-5 Or diclofenac Or interferon or IFN Or "Ingenol mebutate" or "3-ingenyl angelate" or PEP005 or PEP-005 or "PEP 005" Or Vismodegib Or Erivedge or NSC747691 or NSC-747691 or "NSC 747691" or R-3616 or R3616 or "R 3616" or RG-3616 or RG3616 or "RG 3616" or GDC-0449 or GDC0449 or "GDC 0449" Or Sonidegib or Odomzo or NVP-LDE225 Or Itraconazole or Sporanox or Orungal or R51211 or R-51211 or "R 51211")

EMBASE (3/8/17)
(bowen* OR basal cell carcinoma or BCC Or squamous cell carcinoma or SCC OR keratinocyte* and carcinoma* OR non-melanoma OR non melanoma OR nonmelanoma) NOT (Oropharynx OR Oropharyngeal neoplasms OR Pharynx OR Pharyngeal neoplasms)
AND
(((Surger* or surgic*) and (excision or removal)) Or "shave removal" Or "external beam radiation" Or "external-beam radiation" Or brachytherap* Or chemotherap* OR Sensus OR X-ray OR radiotherapy Or (topical and (medications or chemotherap*)) Or observation Or "watchful waiting" Or ((Mohs or micrographic*) and surgery) Or Curett* Or diathermy or cauterization Or Cryotherapy Or electrodesiccation Or ((CO2 or "carbon dioxide") and laser and therapy) Or plesiotherapy Or "Methyl 5-aminolevulinate" or "methyl 5-aminolevulinate" or MALA Or "5-aminolevulinic acid" or ALA Or Photodynamic or Photochemotherap* Or 5-fluorouracil Or 5-FU Or Methotrexate Or Bleomycin Or imiquimod Or BEC-5 Or diclofenac Or interferon or IFN Or "Ingenol mebutate" or "3-ingenyl angelate" or PEP005 or PEP-005 or "PEP 005" Or Vismodegib Or Erivedge or NSC747691 or NSC-747691 or "NSC 747691" or R-

3616 or R3616 or “R 3616” or RG-3616 or RG3616 or “RG 3616” or GDC-0449 or GDC0449 or “GDC 0449” Or Sonidegib or Odomzo or NVP-LDE225 Or Itraconazole or Sporanox or Orungal or R51211 or R-51211 or “R 51211”)
AND
(Clinical trial/ OR Randomized controlled trial/ OR Randomization/ OR Single blind procedure/ OR Double blind procedure/ OR Crossover procedure/ OR Placebo/ OR Randomi?ed controlled trial$.tw. OR Rct.tw. OR Random allocation.tw. OR Randomly allocated.tw. OR Allocated randomly.tw. OR (allocated adj2 random).tw. OR Single blind$.tw. OR Double blind$.tw. OR ((treble or triple) adj blind$).tw. OR Placebo$.tw. OR Prospective study/ OR Clinical study/ OR Case control study OR Family study/ OR Longitudinal study/ OR Retrospective study/ OR Prospective study/ OR Randomized controlled trials/ OR Cohort analysis/ OR (Cohort adj (study or studies)).mp. OR (Case control adj (study or studies)).tw. OR (follow up adj (study or studies)).tw. OR (observational adj (study or studies)).tw. OR (epidemiologic$ adj (study or studies)).tw. OR (cross sectional adj (study or studies)).tw.)

Limits: (human and english language and (adult <18 to 64 years> or aged <65+ years>))

ClinicalTrials.gov (8/25/16) 376 records
(bowen’s disease OR basal cell carcinoma OR BCC OR squamous cell carcinoma OR SCC OR keratinocyte carcinoma OR “non-melanoma”)
AND (skin OR dermatology OR dermatological OR derma)

ICTRP (8/25/16) 601 records
bowen’s disease OR basal cell carcinoma OR BCC OR squamous cell carcinoma AND skin OR SCC AND skin OR keratinocyte carcinoma OR non-melanoma AND skin

Appendix B. Excluded Studies

Table B-1. Excluded studies

UID	First Author	Title	Journal	Reason for Exclusion
4455059	Abad Iglesias, R.	[Topical treatment of basocellular epitheliomas with 5-fluorouracil and vinblastine. Radiobiologic evaluation and comparison with its status with radiotherapy]	Actas Dermosifiliogr	Not English (Spanish)
24669636	Afridi, R. A.	Demographics of basal cell carcinoma and its surgical management	J Ayub Med Coll Abbottabad	not comparative between treatment nodes
CN-00450646	Ahmed, I.	Comparison of cryotherapy versus curettage in the treatment of Bowen's disease. Abstract	British journal of dermatology	duplicate/conference abstract and we have full publication
CN-00400052	Almenar, D. F. E.	Comparative study of CDDP + 5-FU vs CDDP + Ftorafur in advanced head and neck squamous-cell carcinoma	Libro de ResÃºmenes. I Congreso Iberoamericano de OncologÃ-a	not treatment of skin cancer or <80% SCC or BCC
8708151	Alpsoy, 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	duplicate/conference abstract and we have full publication
16374471	Angell-Petersen, E.	Porphyrin formation in actinic keratosis and basal cell carcinoma after topical application of methyl 5-aminolevulinate	J Invest Dermatol	not comparative between treatment nodes
19863513	Apalla, Z.	Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study	Br J Dermatol	not treatment of skin cancer or <80% SCC or BCC
26489922	Arenas, M.	Hypofractionated high-dose-rate plesiotherapy in nonmelanoma skin cancer treatment	Brachytherapy	not comparative between treatment nodes
24749843	Arits, A. H.	Cost-effectiveness of topical imiquimod and fluorouracil vs. photodynamic therapy for treatment of superficial basal-cell carcinoma	Br J Dermatol	no outcomes of interest
CN-00789999	Arits, Ahmm	Three non-invasive treatment options for superficial basal cell carcinoma: photodynamic therapy versus imiquimod versus 5-fluorouracil. TTOP-sBCC trial	Melanoma research	duplicate/conference abstract and we have full publication
23930247	Asilian, A.	Comparison between examination with naked eye, curretage and dermoscopy in determining tumor extension before Mohs micrographic surgery	Adv Biomed Res	not comparative between treatment nodes
5450847	Aurora, A. L.	Reappraisal of basal cell carcinoma of the eyelids	Am J Ophthalmol	>20% recurrent or % recurrent not given
7917206	Austin, J. R.	Squamous cell carcinoma of the external auditory canal. Therapeutic prognosis based on a proposed staging system	Arch Otolaryngol Head Neck Surg	not treatment of skin cancer or <80% SCC or BCC
CN-00465907	Avril, M.	Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomised study Abstract W12-6 The 7th Congress of the European Academy of Dermatology and Venereology, Nice, 7-11 Ocober 1998	Journal of the European Academy of Dermatolo	duplicate/conference abstract and we have full publication

UID	First Author	Title	Journal	Reason for Exclusion
			gy and Venereology : JEADV	
11453910	Baas, P.	Photodynamic therapy with meta-tetrahydroxyphenylchlorin for basal cell carcinoma: a phase I/II study	Br J Dermatol	not comparative between treatment nodes
4782176	Babaiants, R. S.	[Clinical characteristics of skin cancer and comparative characteristics of different methods of its treatment at remote periods]	Vestn Dermatol Venerol	Not English (Russian)
8985019	Bachaud, J. M.	Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial	Int J Radiat Oncol Biol Phys	not treatment of skin cancer or <80% SCC or BCC
15933497	Backous, D. D.	Craniofacial resection for nonmelanoma skin cancer of the head and neck	Laryngoscope	not comparative between treatment nodes
23648439	Balamucki, C. J.	Impact of radiographic findings on for prognosis skin cancer with perineural invasion	Am J Clin Oncol	No analysis by population of interest
26985197	Ballester-Sanchez, R.	Electronic brachytherapy for superficial and nodular basal cell carcinoma: a report of two prospective pilot trials using different doses	J Contemp Brachytherapy	duplicate/conference abstract and we have full publication
16836497	Baptista, J.	Our PDT experience in the treatment of non-melanoma skin cancer over the last 7 years	J Eur Acad Dermatol Venereol	not comparative between treatment nodes
CN-00094532	Bar-Am, A.	High- and low-power CO2 lasers. Comparison of results for three clinical indications	The Journal of reproductive medicine	not treatment of skin cancer or <80% SCC or BCC
CN-00478464	Basset-Seguin Net	Photodynamic therapy using methyl aminolaevulinate is as efficacious as cryotherapy in basal cell carcinoma, with better cosmetic results. British Association of Dermatologists 83rd Annual Meeting. Abstract P-66	British journal of dermatology	duplicate/conference abstract and we have full publication
CN-00616027	Basset-Seguin Net, al	MAL-PDT Versus Cryotherapy for Treatment of Primary Superficial Basal Cell Carcinoma: Results of a Five Years Prospective Randomized Trial Abstract PO7. 3rd Meeting of the European Association of Dermato-Oncology, Rome 23-25 June 2006	Journal of investigative dermatology	duplicate/conference abstract and we have full publication
NA	Basset-Seguin, N., et al.	Methyl aminolaevulinate photodynamic therapy vs. cryotherapy in primary superficial basal cell carcinoma: results of a 36-month follow-up.	British Journal of Dermatology 153.1 (2005): 29-29.	duplicate/conference abstract and we have full publication
CN-00550836	Basset-Sequin, N.	Methyl aminolaevulinate photodynamic therapy vs.cryotherapy in primary superficial basal cell carcinoma: results of a 36-month follow-up (Abstract P-30). The 85th BAD Annual Meeting 5-8th July 2005, Glasgow, UK	British journal of dermatology	duplicate/conference abstract and we have full publication
21664850	Ben Salah, H.	[Radiotherapy for cutaneous cancers with xeroderma pigmentosum]	Cancer Radiother	not treatment of skin cancer or <80% SCC or BCC
17657178	Bernard, P.	[Therapeutic modalities and economic assessment in the treatment of superficial basal	Ann Dermatol	not treatment of skin cancer or <80% SCC or

UID	First Author	Title	Journal	Reason for Exclusion
		cell carcinomas and multiple actinic keratoses by French dermatologists]	Venereol	BCC
9448970	Berridge, J. K.	A comparison of late cosmetic results following two different radiotherapy techniques for treating basal cell carcinoma	Clin Oncol (R Coll Radiol)	>20% recurrent or % recurrent not given
CN-00610206 (17573890)	Berroeta, L.	A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma	The British journal of dermatology	duplicate/conference abstract and we have full publication
CN-00550829	Berroeta, L.	Surgery versus debulking curettage plus topical photodynamic therapy for low-risk nodular basal cell carcinomas. Abstract DS-16 The 85th BAD Annual Meeting 5-8th July 2005, Glasgow, UK	British journal of dermatology	duplicate/conference abstract and we have full publication
18563776	Betz, C. S.	Optimization of treatment parameters for Foscan-PDT of basal cell carcinomas	Lasers Surg Med	not comparative between treatment nodes
15210467	Bialy, T. L.	Mohs micrographic surgery vs traditional surgical excision: a cost comparison analysis	Arch Dermatol	not comparative between treatment nodes
5676901	Binder, S. C.	Epidermoid carcinoma of the skin of the nose	Am J Surg	not comparative between treatment nodes
17598036	Bogelund, F. S.	Factors affecting the recurrence rate of basal cell carcinoma	Acta Derm Venereol	data not extractable
25410443	Borghi, A.	Basal cell carcinoma incompletely excised: a case-control study on recurrence	G Ital Dermatol Venereol	not comparative between treatment nodes
3802321	Brasseur, G.	[Treatment of epithelioma of the eyelid by interstitial radiotherapy. Long-term results. Limitation of the method]	Bull Soc Ophtalmol Fr	not comparative between treatment nodes
9243982	Breuninger, H.	Micrographic surgery of malignant skin tumors: a comparison of the frozen technique with paraffin sectioning	Facial Plast Surg	not comparative between treatment nodes
17513803	Brewster, A. M.	Randomized trial of adjuvant 13-cis-retinoic acid and interferon alfa for patients with aggressive skin squamous cell carcinoma	J Clin Oncol	>20% recurrent or % recurrent not given
CN-01056929	Brinkhuizen, T.	Topical Diclofenac and Vitamin D as treatment for (micro)nodular and superficial basal cell carcinoma	Nederlands Tijdschrift voor Dermatologie en Venereologie	duplicate/conference abstract and we have full publication
16103328	Brown, V. L.	Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: randomized, double-blind, placebo-controlled trial	Arch Dermatol	not treatment of skin cancer or <80% SCC or BCC
2217841	Brzezinska-Wcislo, L.	[Evaluation of the methods of treatment of epithelioma basocellulare at the I Dermatology Clinic, Silesian Medical Academy, in Katowice]	Przegl Dermatol	Not English (Polish)
1875617	Budiak, V. A.	[Effectiveness of some methods in the treatment of primary squamous cell cancer of the skin]	Klin Khir	Not English (Russian)
2013106063	Caddick, J.	Psychological outcomes following surgical excision of facial skin cancers	European Journal of Plastic Surgery	not comparative between treatment nodes
1791498	Calzavara, F.	Photodynamic therapy: clinical experience at the Department of Radiotherapy at Padova General Hospital	J Photochem Photobiol	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
			B	
18197827	Campbell, S. M.	A clinical investigation to determine the effect of pressure injection on the penetration of topical methyl aminolevulinate into nodular basal cell carcinoma of the skin	J Environ Pathol Toxicol Oncol	not comparative between treatment nodes
18544077	Campbell, S. M.	Clinical investigation of the novel iron-chelating agent, CP94, to enhance topical photodynamic therapy of nodular basal cell carcinoma	Br J Dermatol	not comparative between treatment nodes
12410674	Campolmi, P.	Superpulsed CO2 laser treatment of basal cell carcinoma with intraoperatory histopathologic and cytologic examination	Dermatol Surg	not comparative between treatment nodes
21324035	Carducci, M.	Margin detection using digital dermatoscopy improves the performance of traditional surgical excision of basal cell carcinomas of the head and neck	Dermatol Surg	not comparative between treatment nodes
CN-00478488	Caro, I.	Efficacy and safety of imiquimod 5% cream in the treatment of superficial basal cell carcinoma. Abstract P5-20 The 12th Congress of the European Academy of Dermatology and Venereology. Barcelona, Spain 15-18th October 2003	Journal of the European Academy of Dermatology and Venereology : JEADV	duplicate/conference abstract and we have full publication
19418331	Castineiras, I.	Actinic cheilitis: evolution to squamous cell carcinoma after carbon dioxide laser vaporization. A study of 43 cases	J Dermatolog Treat	not comparative between treatment nodes
15752124	Chan, A. L.	Pharmacokinetics and clinical effects of mono-L-aspartyl chlorin e6 (NPe6) photodynamic therapy in adult patients with primary or secondary cancer of the skin and mucosal surfaces	Photodermatol Photoimmunol Photomed	not comparative between treatment nodes
2012242601	Chan, D. V.	Radiation therapy in the management of unilesional primary cutaneous T-cell lymphomas	British Journal of Dermatology	not treatment of skin cancer or <80% SCC or BCC
19027512	Chang, C. H.	Treatments and outcomes of malignant tumors of external auditory canal	Am J Otolaryngol	No analysis by population of interest
7712447	Chao, C. K.	Reirradiation of recurrent skin cancer of the face. A successful salvage modality	Cancer	>20% recurrent or % recurrent not given
0	Cheraghi, N.	Retrospective study of punch scoring versus freehand approach for first stage mohs micrographic surgery	Journal of Clinical and Aesthetic Dermatology	not comparative between treatment nodes
8171136	Childers, B. J.	Long-term results of irradiation for basal cell carcinoma of the skin of the nose	Plast Reconstr Surg	not comparative between treatment nodes
11074693	Chiller, K.	Efficacy of curettage before excision in clearing surgical margins of nonmelanoma skin cancer	Arch Dermatol	no outcomes of interest
10487003	Cho, S.	Clinical and histopathological characteristics of basal cell carcinoma in Korean patients	J Dermatol	not treatment of skin cancer or <80% SCC or BCC
CN-01055091	Choi, S. H.	Efficacy of ablative fractional laser-assisted photodynamic therapy for nodular basal cell carcinoma: A prospective, randomized study	Journal of dermatology	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
		with 12-month follow-up		
18728281	Christian, J. B.	Association of ACE inhibitors and angiotensin receptor blockers with keratinocyte cancer prevention in the randomized VATTC trial	J Natl Cancer Inst	not treatment of skin cancer or <80% SCC or BCC
26207539	Christopoulos, G.	Surgical Treatment and Recurrence of Cutaneous Nasal Malignancies: A 26-Year Retrospective Review of 1795 Patients	Ann Plast Surg	not comparative between treatment nodes
12914598	Clark, C.	Topical 5-aminolaevulinic acid photodynamic therapy for cutaneous lesions: outcome and comparison of light sources	Photodermatol Photoimmunol Photomed	not comparative between treatment nodes
CN-00452483	Clavel, M.	Randomized trial of cisplatin (C), methotrexate (A), bleomycin (B) and vincristine (O) vs ABO in advanced squamous cell carcinoma of the head and neck	American Society of Clinical Oncology 19th Annual Meeting (ASCO) . San Diego, CA, 22-24 May, 1983	not treatment of skin cancer or <80% SCC or BCC
16436340	Clayton, T. H.	Photodynamic therapy for superficial basal cell carcinoma and Bowen's disease	Eur J Dermatol	not comparative between treatment nodes
2012167915	Codazzi, D.	A single-center retrospective study on 3,957 consecutive excisions of basal cell carcinomas. BCC behavior patterns: Retrospective statistical analysis	European Journal of Plastic Surgery	not comparative between treatment nodes
CN-00500580	Cognetti, F.	Randomized trial of sequential versus simultaneous chemo and radiotherapy (CT-xRT) in patients (PTS) with locally advanced unresectable squamous cell carcinoma of the head and neck (LAU-SCCHN). [abstract no: 826]	European journal of cancer	not treatment of skin cancer or <80% SCC or BCC
CN-00715090	Cognetti, F.	Preliminary results of a randomized trial of sequential versus simultaneous chemo and radiotherapy in patients with locally advanced unresectable squamous cell carcinoma of the head and neck [abstract]	Proceedings of the American Society of Clinical Oncology	not treatment of skin cancer or <80% SCC or BCC
2013060222	Comez, A. T.	Primary malignant tumors of the eyelids	Turk Oftalmoloji Dergisi	not comparative between treatment nodes
19182572	Connelly, T.	Delineating curettage as an adjunct to excision of Basal cell carcinoma: results in 334 cases	Plast Reconstr Surg	not comparative between treatment nodes
10201597	Cook, B. E., Jr.	Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota	Ophthalmology	>20% metastatic/nodal involvement
1994271944	Dailey, J. R.	Squamous cell carcinoma of the eyelid	Ophthalmic Plastic and Reconstructive Surgery	No analysis by population of interest

UID	First Author	Title	Journal	Reason for Exclusion
10678347	Daum-Sontrop, A.	Treatment modalities for primary basal cell carcinomas	J Fam Pract	no primary data
20729963	David, P.	Using a Hydroquinone/Tretinoin-based Skin Care System Before and After Electrodesiccation and Curettage of Superficial Truncal Basal Cell Carcinoma: A Multicenter, Randomized, Investigator-blind, Controlled Study of Short-term Healing	J Clin Aesthet Dermatol	not comparative between treatment nodes
16841035	de Haas, E. R.	Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy	J Invest Dermatol	not comparative between treatment nodes
17310011	de Haas, Ellen RM, et al.	"Response of Bowen disease to ALA-PDT using a single and a 2-fold illumination scheme."	Archives of dermatology 143.2 (2007): 264-276.	not comparative between treatment nodes
22964973	de Vijlder, H. C.	Light fractionation significantly improves the response of superficial basal cell carcinoma to aminolaevulinic acid photodynamic therapy: five-year follow-up of a randomized, prospective trial	Acta Derm Venereol	not comparative between treatment nodes
2014322909	Demirseren, D. D.	Basal cell carcinoma of the head and neck region: A retrospective analysis of completely excised 331 cases	Journal of Skin Cancer	not comparative between treatment nodes
8007618	Denisov, L. E.	[Treatment of epitheliomas]	Khirurgiia (Mosk)	Not English (Russian)
2013198782	Dirschka, T.	Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolaevulinate for the treatment of actinic keratosis	British Journal of Dermatology	not comparative between treatment nodes
327370	Dizon, R. V.	Basal cell carcinoma recurrence: early diagnosis and surgical treatment	Ophthalmic Surg	>20% recurrent or % recurrent not given
18818091	Dognitz, N.	Comparison of ALA- and ALA hexyl-ester-induced PpIX depth distribution in human skin carcinoma	J Photochem Photobiol B	no outcomes of interest
CN-00693262	Domenge, C.	Randomized phase II study of all-trans retinoic acid (ATRA) Â± a-interferon (IFN) in squamous cell carcinoma (SCC) [abstract]	Proceedings of the American Society of Clinical Oncology	>20% metastatic/nodal involvement
CN-00305485	Domenge, C.	All-trans retinoic acid (ATRA) +/- alfa interferon (IFN) in squamous cell carci noma (SCC): A randomized phase II study	Ann-Oncol	>20% metastatic/nodal involvement
CN-00691279	Domenge, C.	Randomized phase II study of ALL-trans retinoic acid (ATRA) +/- alpha-interferon (IFN) in squamous cell carcinoma [abstract]	Proceedings of the American Society of Clinical Oncology	duplicate/conference abstract and we have full publication
16334861	Donohue, K. G.	Safety and efficacy of a bilayered skin construct in full-thickness surgical wounds	J Dermatol	not treatment of skin cancer or <80% SCC or BCC
28188086	Dreno, B.	Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas	Lancet Oncol	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
		(MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial		
0	Dreno, B.	Health-Related Quality of Life (HRQoL) analysis by skindex-16 in MIKIE, a randomized phase 2 study to assess the efficacy and safety of two intermittent Vismodegib (VISMO) regimens in patients (pts) with multiple basal cell Carcinomas (BCCs)	Melanoma Research	not comparative between treatment nodes
21472887	Ebrahimi, A.	Metastatic head and neck cutaneous squamous cell carcinoma: defining a low-risk patient	Head Neck	>20% metastatic/nodal involvement
6630599	Edens, B. L., et al.	"Effectiveness of curettage and electrodesiccation in the removal of basal cell carcinoma."	Journal of the American Academy of Dermatology 9.3 (1983): 383-388.	not comparative between treatment nodes
CN-00726909	Eigentler, T. K.	[A randomised, open therapy study to evaluate the efficacy and safety of Imiquimod 5%-cream, topically applied 3 times per week over an 8 or 12 week period to treat solid basal cell carcinoma - an analysis of 28 patients]	Aktuelle Dermatologie	duplicate/conference abstract and we have full publication
27127144	Espeli, V.	Weekly Multi-agent Chemotherapy (CMF-b) for Advanced Non-melanoma Skin Cancer	Anticancer Res	>20% recurrent or % recurrent not given
17894707	Essers, B.	Perceptions of facial aesthetics in surgical patients with basal cell carcinoma	J Eur Acad Dermatol Venereol	>20% recurrent or % recurrent not given
CN-00493501	Essers, B.	Cost-effectiveness of Mohs' micrographic surgery versus surgical excision for facial basal cell carcinoma: results of a randomised clinical trial [abstract]	Proceedings of the First Annual Meeting of the Health Technology Assessment International (HTAi); 2004 May 30 - June 2	duplicate/conference abstract and we have full publication
20387912	Essers, B. A.	Does the inclusion of a cost attribute result in different preferences for the surgical treatment of primary basal cell carcinoma?: a comparison of two discrete-choice experiments	Pharmacoeconomics	not treatment of skin cancer or <80% SCC or BCC
27283245	Estall, V.	Outcomes following management of squamous cell carcinoma of the scalp: A retrospective series of 235 patients treated at the Peter MacCallum Cancer Centre	Australas J Dermatol	results not extractable
CN-01013219	Euctr, G. B.	An Open-label, International, Multi-Center, Phase I/II, Dose-escalation Trial Investigating the Safety of Zalutumumab, a Human Monoclonal Epidermal Growth Factor Receptor Antibody in Combination with Radiotherapy, in Patients with Stage III, IVa or IVb Locally	EUCTR [www.clinicaltrialsregister.eu]	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
		Advanced Squamous Cell Carcinoma of the Head and Neck Ineligible for Platinum based Chemotherapy - Zalutumumab in combination with radiotherapy in SCCHN patients ineligible for platinum based chemoth		
17917935	Ezughah, F. I.	A randomized parallel study to assess the safety and efficacy of two different dosing regimens of 5% imiquimod in the treatment of superficial basal cell carcinoma	J Dermatolo g Treat	not comparative between treatment nodes
CN-00602233	Ezughah, FIet al	A randomized observer blinded study to assess the safety and ef .cacy of two different dosing regimens of 5% imiquimod cream in the treatment of superficial basal cell carcinoma. Abstract DS-13. British Association of Dermatologists 86th Annual Meeting	British journal of dermatolo gy	duplicate/conference abstract and we have full publication
25809617	Fargnoli, M. C., et al.	"Conventional vs. daylight methyl aminolevulinate photodynamic therapy for actinic keratosis of the face and scalp: an intra-patient, prospective, comparison study in Italy."	Journal of the European Academy of Dermatolo gy and Venereolo gy 29.10 (2015): 1926-1932.	not comparative between treatment nodes
11382109	Federspil, P. A.	[Squamous epithelial carcinomas of the external ear]	Hno	not treatment of skin cancer or <80% SCC or BCC
23209908	Fernandez-Guarino, M.	Pulsed dye laser does not seem as effective as red light in Basal cell carcinoma mal-pdt: a small pilot study	J Skin Cancer	not comparative between treatment nodes
17062045	Fernandez-Jorge, B.	Outpatient dermatology major surgery: a 1-year experience in a Spanish tertiary hospital	J Eur Acad Dermatol Venereol	not comparative between treatment nodes
22881585	Ferrandiz, L.	Assessing physicians' preferences on skin cancer treatment in Europe	Br J Dermatol	no outcomes of interest
12004850	Finizio, L.	What is the current role of radiation therapy in the treatment of skin carcinomas?	Tumori	not comparative between treatment nodes
23120649	Fleiner, F.	Cancer of the external auditory canal-diagnostic and treatment	Indian J Otolaryng ol Head Neck Surg	not treatment of skin cancer or <80% SCC or BCC
CN-00478536	Foley, P.	A phase III randomized study comparing photodynamic therapy (PDT) using methyl aminolevulinate or placebo cream in nodular basal cell carcinoma (NBCC). Abstract P9-14 The 12th Congress of the European Academy of Dermatology and Venereology. Barcelona, Spain 15-18th October 2003	Journal of the European Academy of Dermatolo gy and Venereolo gy : JEADV	duplicate/conference abstract and we have full publication
1583171	Frankel, D. H.	New primary nonmelanoma skin cancer in patients with a history of squamous cell carcinoma of the skin. Implications and recommendations for follow-up	J Am Acad Dermatol	not treatment of skin cancer or <80% SCC or BCC

UID	First Author	Title	Journal	Reason for Exclusion
8191597	Gabriele, P.	Carcinoma of the external auditory meatus and middle ear. Results of the treatment of 28 cases	Tumori	not treatment of skin cancer or <80% SCC or BCC
21926038	Gaitanis, G.	Cryosurgery is more effective in the treatment of primary, non-superficial basal cell carcinomas when applied during and not prior to a five week imiquimod course: a randomized, prospective, open-label study	Eur J Dermatol	not comparative between treatment nodes
424625	Gajewska, B.	[Comparative study of the results of surgical and radiotherapy treatment of basal cell epitheliomas and prickle cell carcinomas]	Przegl Dermatol	Not English (Polish)
15693020	Galloway, T. J.	Impact of radiographic findings on prognosis for skin carcinoma with clinical perineural invasion	Cancer	not comparative between treatment nodes
26165629	Gandhi, A. K.	Treatment of squamous cell carcinoma of external auditory canal: A tertiary cancer centre experience	Auris Nasus Larynx	not treatment of skin cancer or <80% SCC or BCC
14648861	Garcia-Serra, A.	Carcinoma of the skin with perineural invasion	Head Neck	not comparative between treatment nodes
CN-00452584	Garden, A. S.	Preliminary results of RTOG 9703 - a phase II randomized trial of concurrent radiation (RT) and chemotherapy for advanced squamous cell carcinomas (SCC) of the head and neck	Proceedings of the American Society of Clinical Oncology (ASCO)	not treatment of skin cancer or <80% SCC or BCC
11404627	Gayl Schweitzer, V.	Photofrin-mediated photodynamic therapy for treatment of aggressive head and neck nonmelanomatous skin tumors in elderly patients	Laryngoscope	>20% recurrent or % recurrent not given
CN-00469536 (15097956)	Geisse, J.	Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies	Journal of the American Academy of Dermatology	duplicate/conference abstract and we have full publication
CN-00520431	Geisse, J. K.	Imiquimod 5% cream for 12 weeks treating superficial BCC [Abstract]	8th World Congress on Cancer of the Skin. Zurich, Switzerland. July 18-21, 2001	duplicate/conference abstract and we have full publication
CN-01013542	Ghosh-Laskar, S.	Phase II Study of 3-Dimensional Conformal Radiotherapy (3D-CRT) vs Intensity Modulated Radiotherapy (IMRT) for Squamous Cell Carcinoma of the Head and Neck (HNSCC)	Clinicaltrials.gov [www.clinicaltrials.gov]	not treatment of skin cancer or <80% SCC or BCC
CN-00857249	Giglio, R.	No recurrences beyond the second year of follow up in inoperable stage III and IV squamous cell carcinoma of the head and neck patients (IOHN). Final report of a randomized trial of alternating chemotherapy (CT) + hyperfractionated radiotherapy (RT) vs RT alone	Proceedings of the 35th Annual Meeting of the American Society of Clinical	not treatment of skin cancer or <80% SCC or BCC

UID	First Author	Title	Journal	Reason for Exclusion
			Oncology; 1999, May 15-18; Atlanta, Georgia, USA	
7961010	Glicksman, A. S.	Concurrent cis-platinum and radiation with or without surgery for advanced head and neck cancer	Int J Radiat Oncol Biol Phys	not treatment of skin cancer or <80% SCC or BCC
18938044	Gluck, I.	Skin cancer of the head and neck with perineural invasion: defining the clinical target volumes based on the pattern of failure	Int J Radiat Oncol Biol Phys	not comparative between treatment nodes
15747068	Graham, B. D.	Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach	Dis Colon Rectum	not treatment of skin cancer or <80% SCC or BCC
7635774	Griep, C.	Electron beam therapy is not inferior to superficial x-ray therapy in the treatment of skin carcinoma	Int J Radiat Oncol Biol Phys	>20% recurrent or % recurrent not given
4701240	Griffith, B. H.	An appraisal of the treatment of basal cell carcinoma of the skin	Plast Reconstr Surg	not comparative between treatment nodes
20666811	Guardiano, R. A.	A direct comparison of visual inspection, curettage, and epiluminescence microscopy in determining tumor extent before the initial margins are determined for Mohs micrographic surgery	Dermatol Surg	not comparative between treatment nodes
7691784	Haffty, B. G.	Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: results from two randomized clinical trials	Int J Radiat Oncol Biol Phys	not treatment of skin cancer or <80% SCC or BCC
8996152	Haffty, B. G.	Chemotherapy as an adjunct to radiation in the treatment of squamous cell carcinoma of the head and neck: results of the Yale Mitomycin Randomized Trials	J Clin Oncol	not treatment of skin cancer or <80% SCC or BCC
15629602	Haffty, B. G.	Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: final results of a randomized clinical trial	Int J Radiat Oncol Biol Phys	not treatment of skin cancer or <80% SCC or BCC
3676083	Harrison, P. V.	Therapy of basal cell carcinoma--treatment in 1980-81 compared with 1985-86 and advantages of shave excision for smaller tumours	Br J Dermatol	duplicate/conference abstract and we have full publication
10927141	Hashi, N.	The role of radiotherapy in treating squamous cell carcinoma of the external auditory canal, especially in early stages of disease	Radiother Oncol	not treatment of skin cancer or <80% SCC or BCC
15534663	Helsing, P.	[Surgical treatment of basal cell carcinoma]	Tidsskr Nor Laegeforen	Not English (Norwegian)
CN-00451395	Heyden, H. W.	Chemotherapy (CT) of advanced squamous cell carcinoma of the head and neck. A randomized cross-over trial between cis-dichlorodiammine-platinum (II) (CIS-DDP) and bleomycin (BLSM vs. methotrexate (MTX) and vindesine (VDS)	Journal of cancer research and clinical oncology	not treatment of skin cancer or <80% SCC or BCC
113627	Hintz, B.	Randomized study of control of the primary	J Surg	not treatment of skin

UID	First Author	Title	Journal	Reason for Exclusion
		tumor and survival using preoperative radiation, radiation alone, or surgery alone in head and neck carcinomas	Oncol	cancer or <80% SCC or BCC
23241791	Hoefkens, M. F.	Does loupe magnification reduce the gap between the macroscopic and microscopic border of a Basal cell carcinoma?: a prospective clinical study	Ann Plast Surg	not comparative between treatment nodes
25654948	Hosokawa, S.	Carcinoma of the external auditory canal: histological and treatment groups	B-Ent	not treatment of skin cancer or <80% SCC or BCC
2015376689	Hsu, M. C.	Secondary neoplasms arising from nevus sebaceus: A retrospective study of 450 cases in Taiwan	Journal of Dermatology	not treatment of skin cancer or <80% SCC or BCC
15389195	Huang, C. C.	Randomized, controlled surgical trial of preoperative tumor curettage of basal cell carcinoma in Mohs micrographic surgery	J Am Acad Dermatol	not comparative between treatment nodes
27109055	Hussain, A. A.	Adjunct use of optical coherence tomography increases the detection of recurrent basal cell carcinoma over clinical and dermoscopic examination alone	Photodiagnosis Photodyn Ther	not comparative between treatment nodes
1955231	Ikic, D.	Basal cell carcinoma treated with interferon	Int J Dermatol	not comparative between treatment nodes
1937994	Ikic, D.	Interferon therapy for basal cell carcinoma and squamous cell carcinoma	Int J Clin Pharmacol Ther Toxicol	not comparative between treatment nodes
5618951	Jackson, R.	The team approach to the management of skin cancer	Med Serv J Can	No analysis by population of interest
4750192	Jakobsson, P. A.	Fractionation scheme with low individual tumour dose and high total dose	Acta Radiol Ther Phys Biol	not comparative between treatment nodes
24879468	Jarkowski, A., 3rd	Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma (CSCC): The Roswell Park Experience and a Review of the Literature	Am J Clin Oncol	not comparative between treatment nodes
24299572	Jeon, S. Y.	Efficacy of photodynamic diagnosis-guided Mohs micrographic surgery in primary squamous cell carcinoma	Dermatol Surg	not comparative between treatment nodes
10735893	Jeremic, B.	Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial	J Clin Oncol	not comparative between treatment nodes
CN-00742337	Julian, C.	A comparative study of the effects of disposable and Volkmann spoon curettes in the treatment of basal cell carcinoma	The British journal of dermatology	>20% recurrent or % recurrent not given
26362616	Kadouch, D. J.	Treatment of Basal Cell Carcinoma Using a One-Stop-Shop With Reflectance Confocal Microscopy: Study Design and Protocol of a Randomized Controlled Multicenter Trial	JMIR Res Protoc	no outcomes of interest
23352886	Khan, A. A.	Guidelines for the excision of cutaneous squamous cell cancers in the United Kingdom: the best cut is the deepest	J Plast Reconstr Aesthet Surg	not comparative between treatment nodes
1999353368	Khan, N. A.	Role of elective irradiation to drainage sites in squamous cell carcinoma of the skin trunk and extremities	JK Practitioner	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
25675868	Khtibari, Z.	[Squamous cell carcinoma of the eyelids. Review of 7 years of experience of the adult ophthalmology service of the Casablanca university medical center]	J Fr Ophtalmol	Not English (French)
28027517	Kim, S. A	18F-FDG PET/CT surveillance for the detection of recurrence in patients with head and neck cancer	Eur J Cancer	not treatment of skin cancer or <80% SCC or BCC
7037180	Kish, J.	Clinical trial of cisplatin and 5-FU infusion as initial treatment for advanced squamous cell carcinoma of the head and neck	Cancer Treat Rep	not treatment of skin cancer or <80% SCC or BCC
4764924	Klein, E.	Proceedings: Chemotherapy and immunotherapy for cancer involving the skin	Proc Natl Cancer Conf	no primary data
14290308	Klein, E.	TUMORS OF THE SKIN. IV. DOUBLE-BLIND STUDY ON EFFECTS OF LOCAL ADMINISTRATION OF ANTI-TUMOR AGENTS IN BASAL CELL CARCINOMA	J Invest Dermatol	not comparative between treatment nodes
5321314	Klein, E.	Tumors of the skin. V. Local administration of anti-tumor agents to multiple superficial basal cell carcinomas	J Invest Dermatol	not comparative between treatment nodes
5387158	Kleine-Natrop, H. E.	[Clinical aspects and therapy of basal cell epitheliomas and squamous cell carcinomas. A 10-year analysis]	Dermatol Monatsschr	>20% recurrent or % recurrent not given
4850042	Kleine-Natrop, H. E.	[Treatment of recurrent basalioma (author's transl)]	Arch Geschwulstforsch	>20% recurrent or % recurrent not given
9002265	Koderhold, G.	Experiences of photodynamic therapy in dermatology	J Photochem Photobiol B	not comparative between treatment nodes
15611900	Kollert, M.	[Carcinoma of the external auditory canal and middle ear: therapeutic strategy and follow up]	Laryngorhinootologie	No analysis by population of interest
23532618	Krema, H.	Orthovoltage radiotherapy in the management of medial canthal basal cell carcinoma	Br J Ophthalmol	not comparative between treatment nodes
1145348	Krenar, J.	[Surgery or irradiation of skin neoplasms?]	Rozhl Chir	Not English (Czech)
23415573	Kropp, L.	Mohs resection and postoperative radiotherapy for head and neck cancers with incidental perineural invasion	Am J Otolaryngol	>20% recurrent or % recurrent not given
CN-01060149	Kunstfeld, R.	MIKIE: A randomized, double-blind, regimen-controlled, phase II, multicenter study to assess the efficacy and safety of two different vismodegib regimens in patients with multiple basal cell carcinomas	Journal of clinical oncology	no primary data
0	Kunstfeld, R.	Analysis of patients (pts) with and without basal cell carcinoma nevus syndrome (BCCNS) in MIKIE, a randomized phase 2 study to assess the efficacy and safety of two intermittent Vismodegib (VISMO) regimens in pts with multiple Basal Cell Carcinomas (BCCs)	Melanoma Research	not comparative between treatment nodes
20338745	Kyrgidis, A.	Cutaneous squamous cell carcinoma (SCC) of the head and neck: risk factors of overall and recurrence-free survival	Eur J Cancer	>20% metastatic/nodal involvement
7857115	Landthaler, M.	Late irradiation damage to the skin caused by soft X-ray radiation therapy of cutaneous tumors	Arch Dermatol	not comparative between treatment nodes
CN-00194309	Landthaler, M.	TDF factors in soft X-ray therapy. <ORIGINAL> ANWENDUNG DES TDF-FAKTORS IN DER	Der Hautarzt;	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
		RONTGENWEICHSTRAHLENTHERAPIE	Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete	
15275715	Langendijk, J. A.	Radiotherapy of squamous cell carcinoma of the nasal vestibule	Int J Radiat Oncol Biol Phys	not treatment of skin cancer or <80% SCC or BCC
CN-00888049	Lansbury, L.	Interventions for non-metastatic squamous cell carcinoma of the skin: A summarised Cochrane review	Clinical and Experimental Dermatology	no primary data
19210500	Lawrence, C. M.	Formalin-fixed tissue Mohs surgery (slow Mohs) for basal cell carcinoma: 5-year follow-up data	Br J Dermatol	not comparative between treatment nodes
0	Lear, J.	Sonidegib safety in patients with locally advanced Basal Cell Carcinoma and efficacy based on tumor aggressiveness	Melanoma Research	not comparative between treatment nodes
24332515	Lear, J. T.	Evidence-based treatment for low-risk basal cell carcinoma	Lancet Oncol	no primary data
25581584	Lecluse LL	Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial: a critical appraisal.	Br J Dermatol.	no primary data
CN-01039974	Lecluse, L. L. A.	Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: A single blind, non-inferiority, randomised controlled trial: A critical appraisal	British journal of dermatology	no primary data
20840493	Lee, C. Y.	The efficacy of photodynamic diagnosis in defining the lateral border between a tumor and a tumor-free area during Mohs micrographic surgery	Dermatol Surg	not comparative between treatment nodes
16710578	Lindelof, B.	Mortality and clinicopathological features of cutaneous squamous cell carcinoma in organ transplant recipients: a study of the Swedish cohort	Acta Derm Venereol	not comparative between treatment nodes
23699934	Linos, E.	Treatment of nonfatal conditions at the end of life: nonmelanoma skin cancer	JAMA Intern Med	not comparative between treatment nodes
4574777	Littlewood, M.	A clinical trial of the use of 5-fluouracil in the treatment of some cutaneous malignancies	Br J Plast Surg	not comparative between treatment nodes
5091318	Litwin, M. S.	Treatment of basal and squamous cancers of the nose and ear with 5-fluorouracil cream	Laryngoscope	not comparative between treatment nodes
5110339	Litwin, M. S.	Topical chemotherapy of advanced cutaneous malignancy with 5-Fluorouracil creme	J Surg Oncol	not comparative between treatment nodes
11360406	Liu, C. H.	The clinical features and surgical results of malignant eyelid tumors	Chang Gung Med J	not comparative between treatment nodes
1899855	Liu, F. F.	A management approach to incompletely excised basal cell carcinomas of skin	Int J Radiat Oncol Biol Phys	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
11697321	Locke, J.	Radiotherapy for epithelial skin cancer	Int J Radiat Oncol Biol Phys	>20% recurrent or % recurrent not given
1994344416	Long, C. C.	Curettage of small basal cell papillomas with the disposable ring curette is superior to conventional treatment [1]	British Journal of Dermatology	not comparative between treatment nodes
4939510	Lopes, C. F.	[Therapeutic trial with 5-fluorouracil ointment]	Hospital (Rio J)	not treatment of skin cancer or <80% SCC or BCC
21300762	LoRusso, Patricia M., et al.	"Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors."	Clinical Cancer Research 17.8 (2011): 2502-2511.	not comparative between treatment nodes
26353121	Lu, S. M.	Concurrent Radiotherapy With Cetuximab or Platinum-based Chemotherapy for Locally Advanced Cutaneous Squamous Cell Carcinoma of the Head and Neck	Am J Clin Oncol	>20% recurrent or % recurrent not given
14732656	Lui, H.	Photodynamic therapy of multiple nonmelanoma skin cancers with verteporfin and red light-emitting diodes: two-year results evaluating tumor response and cosmetic outcomes	Arch Dermatol	not comparative between treatment nodes
18704969	Madsen, A. R.	Cancer of the external auditory canal and middle ear in Denmark from 1992 to 2001	Head Neck	not comparative between treatment nodes
17764086	Maghami, E. G.	Craniofacial surgery for nonmelanoma skin malignancy: report of an international collaborative study	Head Neck	not comparative between treatment nodes
7569812	Mak, A. S.	Audit of basal cell carcinoma in Princess Margaret Hospital, Hong Kong: usefulness of frozen section examination in surgical treatment	Scand J Plast Reconstr Surg Hand Surg	no outcomes of interest
924616(8)	Mallon E, Dawbor E.	Cryosurgery in the treatment of basal cell carcinoma: assessment of one or two freeze-thaw cycle schedules.	Dermatol Surg 1996;22:854–8.	not comparative between treatment nodes
9246168	Mallon, E.	Cryosurgery in the treatment of basal cell carcinoma. Assessment of one and two freeze-thaw cycle schedules	Dermatol Surg	not comparative between treatment nodes
7096764	Marchac, D.	Curative and aesthetic results of surgical treatment of 138 basal-cell carcinomas	J Dermatol Surg Oncol	not comparative between treatment nodes
CN-00454540	Marks, R.	Optimal dosing duration and dosing regimen for treatment of nodular BCC with imiquimod 5% cream	Annales de Dermatologie Et de Venereologie	Not English (French)
0	Martin, I	Patient preferences for treatment of basal cell carcinoma: Importance of cure and cosmetic outcome	Acta Dermato-Venereologica	not treatment of skin cancer or <80% SCC or BCC
21742301	Martorell-	[Intralesional infusion of methotrexate as	Actas	No analysis by

UID	First Author	Title	Journal	Reason for Exclusion
	Calatayud, A.	neoadjuvant therapy improves the cosmetic and functional results of surgery to treat keratoacanthoma: results of a randomized trial]	Dermosifiliogr	population of interest
21843177	Matthiesen, C.	The role of radiotherapy for T4 non-melanoma skin carcinoma	J Med Imaging Radiat Oncol	>20% recurrent or % recurrent not given
24843224	Mazzoni, A.	Primary squamous cell carcinoma of the external auditory canal: surgical treatment and long-term outcomes	Acta Otorhinolaryngol Ital	No analysis by population of interest
10078643	McCord, M. W.	Skin cancer of the head and neck with incidental microscopic perineural invasion	Int J Radiat Oncol Biol Phys	>20% recurrent or % recurrent not given
24927655	McKechnie, A. J.	See-and-treat surgery for facial skin cancer	Br J Oral Maxillofac Surg	not comparative between treatment nodes
2753698	Mendenhall, W. M.	Carcinoma of the skin of the head and neck with perineural invasion	Head Neck	>20% recurrent or % recurrent not given
1826208	Mendenhall, W. M.	Brachytherapy in head and neck cancer: selection criteria and results at the University of Florida	Oncology (Williston Park)	no primary data
3597161	Mendenhall, W. M.	T2-T4 carcinoma of the skin of the head and neck treated with radical irradiation	Int J Radiat Oncol Biol Phys	not comparative between treatment nodes
15825160	Mendenhall, W. M.	Retromolar trigone squamous cell carcinoma treated with radiotherapy alone or combined with surgery	Cancer	not treatment of skin cancer or <80% SCC or BCC
5555851	Menn, H.	The recurrent basal cell epithelioma. A study of 100 cases of recurrent, re-treated basal cell epitheliomas	Arch Dermatol	>20% recurrent or % recurrent not given
CN-00695148	Merlano, M.	Alternating chemotherapy and radiotherapy (RT) vs RT in advanced inoperable SCC-HN: a cooperative randomized trial [abstract]	Proceedings of the American Society of Clinical Oncology	not treatment of skin cancer or <80% SCC or BCC
CN-00353346	Merlano, M.	Alternating chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck. A randomized trial	Proceedings of the American Society of Clinical Oncology (ASCO)	not treatment of skin cancer or <80% SCC or BCC
CN-00715205	Mickiewicz, R.	No recurrences beyond the second year of follow up in inoperable stage III and IV squamous cell carcinoma of the head and neck patients (IOHN). Final report of a randomized trial of alternating chemotherapy (CT) + hyperfractionated radiotherapy (RT) vs RT alone [abstract]	Proceedings of the American Society of Clinical Oncology: 35th Annual Meeting of the American Society of Clinical Oncology;	not treatment of skin cancer or <80% SCC or BCC

UID	First Author	Title	Journal	Reason for Exclusion
			15-18 May 1999; Atlanta, Georgia, USA	
CN-01088953	Migden, M.	Inhibition of the hedgehog pathway with sonidegib (LDE225) in advanced basal cell carcinoma	Journal of the American Academy of Dermatology	duplicate/conference abstract and we have full publication
CN-01088952	Migden, M.	Quality of life in patients with advanced basal cell carcinoma treated with sonidegib (LDE225)	Journal of the American Academy of Dermatology	duplicate/conference abstract and we have full publication
CN-01088955	Migden, M.	A 12-month update of BOLT, a phase 2, randomized, double-blind study of sonidegib (LDE225) in patients with locally advanced or metastatic basal cell carcinoma	Journal of the American Academy of Dermatology	duplicate/conference abstract and we have full publication
17509254	Miller, S. J.	Basal cell and squamous cell skin cancers	J Natl Compr Canc Netw	no primary data
22548396	Mizutani, K.	Comparison of the efficacy of ALA-PDT using an excimer-dye laser (630 nm) and a metal-halide lamp (600 to 740 nm) for treatment of Bowen's disease	Photodermatol Photoimmunol Photomed	not comparative between treatment nodes
CN-00789893 (20402949)	Moehrle, M.	Imiquimod 5% cream as adjunctive therapy for primary, solitary, nodular basal cell carcinomas before mohs micrographic surgery: A randomized, double-blind, vehicle-controlled study	Dermatologic surgery	no primary data
26442118	Morley, G. L.	A Comparative Study Examining the Management of Bowen's Disease in the United Kingdom and Australia	Dermatol Res Pract	no outcomes of interest
CN-00487882	Morton, C. A.	A placebo-controlled multicentre study comparing photodynamic therapy using methyl aminolaevulinate with cryotherapy and 5-fluorouracil in BowenÂ's disease. Abstract O-4 The 84th BAD Annual Meeting 6-9th July 2004, Belfast,UK	British journal of dermatology	duplicate/conference abstract and we have full publication
CN-00318682	Morton, C. A.	Photodynamic therapy vs cryotherapy in the treatment of Bowen's disease. (Abstract)	Clinical and experimental dermatology	duplicate/conference abstract and we have full publication
CN-00416313	Morton, C. A.	Topical photodynamic therapy for Bowen's disease and basal cell carcinoma- an effective therapy? Abstract	British journal of dermatology	duplicate/conference abstract and we have full publication

UID	First Author	Title	Journal	Reason for Exclusion
15859302	Morton, C. A.	Topical photodynamic therapy for Bowen's disease	Australas J Dermatol	no primary data
11255332	Morton, C. A.	Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma	Arch Dermatol	not comparative between treatment nodes
11069454	Morton, C. A.	Comparison of red and green light in the treatment of Bowen's disease by photodynamic therapy	Br J Dermatol	not comparative between treatment nodes
CN-00616044	Morton, CA	A Randomised, Placebo-Controlled, European Study Comparing MALPDT with Cryotherapy and 5-Fluorouracil in Subjects with BowenÂ's Disease Abstract 13. 3rd Meeting of the European Association of Dermato-Oncology, Rome 23-25 June 2006	Journal of investigative dermatology	duplicate/conference abstract and we have full publication
20497756	Moscarelli, L.	Keratinocyte cancer prevention with ACE inhibitors, angiotensin receptor blockers or their combination in renal transplant recipients	Clin Nephrol	not treatment of skin cancer or <80% SCC or BCC
21056940	Moskalik, K.	Powerful neodymium laser radiation for the treatment of facial carcinoma: 5 year follow-up data	Eur J Dermatol	not comparative between treatment nodes
6419432	Moskalik, K. G.	[Late results and economic aspects of the treatment of skin cancer with impulse laser irradiation]	Vestn Khir Im I I Grek	>20% recurrent or % recurrent not given
7189810	Moskalik, K. G.	[Comparative evaluation of treatment of skin cancer by impulse laser irradiation, radiotherapy or surgery]	Med Radiol (Mosk)	Not English (Russian)
CN-00753875	Mosterd, K.	Mohs micrographic surgery for basal cell carcinoma of the face: A randomized, controlled trial. [Dutch]	Nederlands tijdschrift voor geneeskunde	duplicate/conference abstract and we have full publication
CN-00616039	Muller, F. M.	A randomized study comparing tissue conservation in conventional vs.Mohs' surgery of basal cell carcinoma. Abstract DS-3. The 87th BAD Annual Meeting 10-13 July 2007, Birmingham,UK	British journal of dermatology	duplicate/conference abstract and we have full publication
19500127	Muller, F. M.	Randomized comparison of Mohs micrographic surgery and surgical excision for small nodular basal cell carcinoma: tissue-sparing outcome	Dermatol Surg	no outcomes of interest
12705745	Nagore, E.	Positive margins in basal cell carcinoma: relationship to clinical features and recurrence risk. A retrospective study of 248 patients	J Eur Acad Dermatol Venereol	not comparative between treatment nodes
24411578	Nanji, A. A.	Surgical versus medical treatment of ocular surface squamous neoplasia: a comparison of recurrences and complications	Ophthalmology	No analysis by population of interest
CN-00602168	Nasset-Seguin	Photodynamic therapy using topical methyl aminolaevulinate versus cryotherapy for treatment of primary superficial basal cell carcinoma: results of a five-year prospective randomized trial. Abstract P-80. British Association of Dermatologists 86th Annual Meeting	British journal of dermatology	duplicate/conference abstract and we have full publication
CN-01011816	Naumann, P.	Prophylaxis of acute radiation dermatitis with topical R1 and R2: Interim results of a multicenter, randomized, controlled trial (CREAM-1)	Supportive care in cancer	not treatment of skin cancer or <80% SCC or BCC
25109244	Neittaanmäki-	"Daylight photodynamic therapy for actinic	British	not treatment of skin

UID	First Author	Title	Journal	Reason for Exclusion
	Perttu, N., et al.	keratoses: a randomized double-blinded nonsponsored prospective study comparing 5-aminolaevulinic acid nanoemulsion (BF-200) with methyl-5-aminolaevulinate."	Journal of Dermatology 171.5 (2014): 1172-1180.	cancer or <80% SCC or BCC
26011755	Neittaanmäki-Perttu, N., et al.	"Hexyl-5-aminolaevulinate 0· 2% vs. methyl-5-aminolaevulinate 16% daylight photodynamic therapy for treatment of actinic keratoses: results of a randomized double-blinded pilot trial."	British Journal of Dermatology (2015).	not treatment of skin cancer or <80% SCC or BCC
16876511	Nemet AY, Deckel Y, Martin PA, Kourt G, Chilov M, Sharma V, et al.	Management of periocular basal and squamous cell carcinoma: a series of 485 cases.	Am J Ophthalmol2006;142:293-7	not comparative between treatment nodes
4439437	Nemeth, G.	[Experiences in the treatment of eyelid carcinomas]	Strahlentherapie	not comparative between treatment nodes
11774405	Newman, L. A.	Swallowing and speech ability after treatment for head and neck cancer with targeted intraarterial versus intravenous chemoradiation	Head Neck	not treatment of skin cancer or <80% SCC or BCC
25687314	Nguyen, B. T.	Treatment of superficial basal cell carcinoma and squamous cell carcinoma in situ on the trunk and extremities with ablative fractional laser-assisted delivery of topical fluorouracil	J Am Acad Dermatol	not comparative between treatment nodes
25256352	Nguyen, N. P.	Effectiveness of radiotherapy for elderly patients with non-melanoma skin cancer of the head	Geriatr Gerontol Int	not comparative between treatment nodes
2013665813	Nicoletti, G.	Study to determine whether intraoperative frozen section biopsy improves surgical treatment of non-melanoma skin cancer	Molecular and Clinical Oncology	>20% recurrent or % recurrent not given
288576	Niemczyk, H. M.	[Comparative study of surgical and radiological treatment of basal cell carcinoma in head and neck region]	Dtsch Zahnarztl Z	Not English (German)
16398319	Nikkels, A. F.	Photodynamic therapy and imiquimod immunotherapy for basal cell carcinomas	Acta Clin Belg	not comparative between treatment nodes
10233225	Nordin, P.	Curettage-cryosurgery for non-melanoma skin cancer of the external ear: excellent 5-year results	Br J Dermatol	not comparative between treatment nodes
23871719	O'Bryan, K.	An evolving paradigm for the workup and management of high-risk cutaneous squamous cell carcinoma	J Am Acad Dermatol	>20% recurrent or % recurrent not given
17446002	Ogawa, K.	Treatment and prognosis of squamous cell carcinoma of the external auditory canal and middle ear: a multi-institutional retrospective review of 87 patients	Int J Radiat Oncol Biol Phys	not treatment of skin cancer or <80% SCC or BCC
CN-00622606	Oosten, E. J.	Different pain sensations in photodynamic therapy of nodular basal cell carcinoma: Results from a prospective trial and a review of the literature	Photodiagnosis and photodynamic therapy	duplicate/conference abstract and we have full publication
16788928	Oseroff, A. R.	A dose ranging study of photodynamic therapy with porfimer sodium (Photofrin) for treatment of basal cell carcinoma	Lasers Surg Med	>20% recurrent or % recurrent not given
22293891	Osiecka, B.	The application of Levulan-based photodynamic therapy with imiquimod in the treatment of	Med Sci Monit	>20% recurrent or % recurrent not given

UID	First Author	Title	Journal	Reason for Exclusion
		recurrent basal cell carcinoma		
CN-00452810	Overgaard, J.	The Danish Head and Neck Cancer Study Group DAHANCA 6 & 7 randomized trial of 5 versus 6 fractions per week of conventional radiotherapy of squamous cell carcinoma of the head and neck	Proceedings of the American Society of Clinical Oncology (ASCO) . Chicago, Illinois, 31 May-3 June, 2003	not comparative between treatment nodes
20409337	Ozolins, M.	The SINS trial: a randomised controlled trial of excisional surgery versus imiquimod 5% cream for nodular and superficial basal cell carcinoma	Trials	no primary data
8538187	Palo, G.	Controlled clinical trials with fenretinide in breast cancer, basal cell carcinoma and oral leukoplakia	Journal of cellular biochemistry. Supplement	not treatment of skin cancer or <80% SCC or BCC
12828747	Palsson, S.	Kinetics of the superficial perfusion and temperature in connection with photodynamic therapy of basal cell carcinomas using esterified and non-esterified 5-aminolaevulinic acid	Br J Dermatol	not comparative between treatment nodes
26589877	Pampena, R.	Orthovoltage radiotherapy for nonmelanoma skin cancer (NMSC): Comparison between 2 different schedules	J Am Acad Dermatol	duplicate/conference abstract and we have full publication
2010372046	Pariser, D.	Using a hydroquinone/tretinoin-based skin care system before and after electrodesiccation and curettage of superficial truncal basal cell carcinoma	Journal of Clinical and Aesthetic Dermatology	not comparative between treatment nodes
CN-00130587	Parsons, J. T.	Re: Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck	Journal of the National Cancer Institute	no primary data
2420153	Parvinen, L. M.	Combined bleomycin treatment and radiation therapy in squamous cell carcinoma of the head and neck region	Acta Radiol Oncol	not treatment of skin cancer or <80% SCC or BCC
10496562	Paterson, C. A.	Basal cell carcinoma of the perianal region: 20-year experience	Dis Colon Rectum	not treatment of skin cancer or <80% SCC or BCC
21668511	Pauwels, C.	Topical methyl aminolevulinate photodynamic therapy for management of basal cell carcinomas in patients with basal cell nevus syndrome improves patient's satisfaction and reduces the need for surgical procedures	J Eur Acad Dermatol Venereol	not comparative between treatment nodes
22748679	Pazdrowski, J.	[The recurrence of facial basal cell carcinoma in patients treated at the Head and Neck Surgery Ward and Laryngological Oncology Clinic of the Greater Poland Cancer Centre in the years 2007-2010]	Otolaryngol Pol	Not English (Polish)
19625138	Penagaricano, J. A.	Evaluation of spatially fractionated radiotherapy (GRID) and definitive chemoradiotherapy with curative intent for locally advanced squamous	Int J Radiat Oncol Biol	not treatment of skin cancer or <80% SCC or BCC

UID	First Author	Title	Journal	Reason for Exclusion
		cell carcinoma of the head and neck: initial response rates and toxicity	Phys	
11566277	Peng, Q.	Selective distribution of porphyrins in skin thick basal cell carcinoma after topical application of methyl 5-aminolevulinate	J Photochem Photobiol B	not comparative between treatment nodes
6182982	Pennacchio, J. L.	Combination of cis-platinum and bleomycin prior to surgery and/or radiotherapy compared with radiotherapy alone for the treatment of advanced squamous cell carcinoma of the head and neck	Cancer	not treatment of skin cancer or <80% SCC or BCC
1908427	Perez, C. A.	Electron beam and x-rays in the treatment of epithelial skin cancer: dosimetric considerations and clinical results	Front Radiat Ther Oncol	>20% recurrent or % recurrent not given
1903023	Perez, C. A.	Randomized phase III study comparing irradiation and hyperthermia with irradiation alone in superficial measurable tumors. Final report by the Radiation Therapy Oncology Group	Am J Clin Oncol	No analysis by population of interest
15923570	Perkins, J. L.	Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study	J Clin Oncol	no primary data
17223873	Perrett, C. M.	Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy	Br J Dermatol	not treatment of skin cancer or <80% SCC or BCC
CN-00602171	Perrett, C. M.	A comparative study of topical 5-fluorouracil and topical photodynamic therapy using methylaminolevulinate for actinic keratosis and BowenÂ's disease in organ transplant recipients (Abstract P26) American Academy of Dermatology 64th Annual Meeting March 3-7, 2006	Journal of the American Academy of Dermatology	not treatment of skin cancer or <80% SCC or BCC
12271300	Persaud, A. N.	Clinical effect of imiquimod 5% cream in the treatment of actinic keratosis	J Am Acad Dermatol	not treatment of skin cancer or <80% SCC or BCC
12395436	Pesic, Z.	[Ultrasonography and surgical treatment of facial skin neoplasms]	Srp Arh Celok Lek	not treatment of skin cancer or <80% SCC or BCC
15125510	Pichardo-Velazquez, P.	Surgical option for nonmelanoma skin cancer	Int J Dermatol	not comparative between treatment nodes
6665189	Placek, W.	[Comparative evaluation of 2 methods of fractionated soft X-ray therapy of basal cell carcinoma of the skin]	Przegl Dermatol	Not English (Polish)
4012422	Pletnev, S. D.	[Treatment of recurrent basal-cell skin cancer with laser irradiation]	Sov Med	>20% recurrent or % recurrent not given
24666361	Pomerantz, H.	Predictors of local adverse effects caused by topical tretinoin cream 0.1% in the Veterans Affairs Topical Tretinoin Chemoprevention trial	Br J Dermatol	not treatment of skin cancer or <80% SCC or BCC
1223143	Popkin, G. L.	Excision versus curettage and electrodesiccation as dermatologic office procedures for the treatment of basal-cell carcinomas	J Dermatol Surg	no primary data
10901965	Poulsen, M.	Acute toxicity and cost analysis of a phase III randomized trial of accelerated and conventional radiotherapy for squamous carcinoma of the head and neck: a Trans-	Australas Radiol	not treatment of skin cancer or <80% SCC or BCC

UID	First Author	Title	Journal	Reason for Exclusion
		Tasman Radiation Oncology Group study		
19398900	Prabhu, R.	Squamous cell carcinoma of the external auditory canal: long-term clinical outcomes using surgery and external-beam radiotherapy	Am J Clin Oncol	not comparative between treatment nodes
19138010	Puizina-Ivic, N.	Fractionated illumination improves the outcome in the treatment of precancerous lesions with photodynamic therapy	Coll Antropol	not treatment of skin cancer or <80% SCC or BCC
18173610	Punjabi, S.	Solasodine glycoalkaloids: a novel topical therapy for basal cell carcinoma. A double-blind, randomized, placebo-controlled, parallel group, multicenter study	Int J Dermatol	not treatment of interest (Solasodine glycoalkaloids)
17034468	Quirk, Chris, et al.	"Two-year interim results from a 5-year study evaluating clinical recurrence of superficial basal cell carcinoma after treatment with imiquimod 5% cream daily for 6 weeks."	Australasian journal of dermatology47.4 (2006): 258-265.	not comparative between treatment nodes
12828745	Ramrakha-Jones, V. S.	Treating Bowen's disease: a cost-minimization study	Br J Dermatol	no primary data
25704233	Reigneau, M.	Efficacy of neoadjuvant cetuximab alone or with platinum salt for the treatment of unresectable advanced nonmetastatic cutaneous squamous cell carcinomas	Br J Dermatol	>20% recurrent or % recurrent not given
4919323	Reymann, F.	Treatment of basal cell carcinoma with 5-fluorouracil (5-FU) ointment	Dermatologica	not comparative between treatment nodes
5555850	Reymann, F.	Treatment of basal cell carcinoma of the skin with curettage	Arch Dermatol	not comparative between treatment nodes
6515862	Reymann, F.	[Treatment of basal cell carcinoma of the skin]	Ugeskr Laeger	not comparative between treatment nodes
CN-00454623	Rhodes Let, al	A randomized comparison of excision surgery and PDT using methyl aminolevulinate in nodular BCC Abstract	Annales de dermatologie et de venereologie	duplicate/conference abstract and we have full publication
CN-00478736	Rhodes Let, al	A randomized comparison of excision surgery and photodynamic therapy using methyl aminolaevulinate in nodular basal cell carcinoma. British Association of Dermatologists 83rd Annual Meeting. Abstract P-68	British journal of dermatology	duplicate/conference abstract and we have full publication
CN-00602507	Rhodes, L.	A randomized European comparison of excision surgery and MAL-PDT in nodular basal cell carcinoma: results from a 36-month follow-up. Abstract P08.69. The 14th Congress of the European Academy of Dermatology and Venereology, London,UK. 12-15th October 2005	Journal of the European Academy of Dermatology and Venereology : JEADV	duplicate/conference abstract and we have full publication
CN-00612111 (17875873)	Rhodes, L. E.	Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma	Archives of dermatology	duplicate/conference abstract and we have full publication
CN-00527223	Rhodes, L. E.	A randomized European comparison of MAL-PDT and excision surgery in nodular basal cell carcinoma. Abstract P-29 The 85th BAD Annual	British journal of dermatolo	duplicate/conference abstract and we have full publication

UID	First Author	Title	Journal	Reason for Exclusion
		Meeting 5-8th July 2005, Glasgow, UK	gy	
CN-00602236	Rhodes, L. E.	A randomized european comparison of mal-pdt and excision surgery in nodular basal cell carcinoma	7th Asian Congress of Dermatology Incorporating the 5th Regional Conference of Paediatric Dermatology Kuala Lumpur, Malaysia 28th September -1st October, 2005	duplicate/conference abstract and we have full publication
CN-00616002	Rhodes, LE	A Randomized European Comparison of MAL-PDT and Excision Surgery in Nodular Basal Cell Carcinoma: Results From a 60 Month Follow-Up Study. Abstract PO6. 3rd Meeting of the European Association of Dermato-Oncology, Rome 23-25 June 2006	Journal of investigative dermatology	duplicate/conference abstract and we have full publication
15927410	Rio, E.	Interstitial brachytherapy of periorificial skin carcinomas of the face: a retrospective study of 97 cases	Int J Radiat Oncol Biol Phys	not comparative between treatment nodes
16529964	Rio, E.	[Interstitial brachytherapy of peri-orificial skin carcinomas on the face]	Cancer Radiother	not comparative between treatment nodes
15625362	Rischin, D.	Tirapazamine, Cisplatin, and Radiation versus Fluorouracil, Cisplatin, and Radiation in patients with locally advanced head and neck cancer: a randomized phase II trial of the Trans-Tasman Radiation Oncology Group (TROG 98.02)	J Clin Oncol	not treatment of skin cancer or <80% SCC or BCC
CN-00775868	Rischin, D.	Preliminary results of TROG 98.02 - a randomized phase II study of 5-fluorouracil, cisplatin and radiation versus tirapazamine, cisplatin and radiation for advanced squamous cell carcinoma of the head and neck	Proceedings of the American Society of Clinical Oncology	not treatment of skin cancer or <80% SCC or BCC
CN-00478739	Robinson, J. K.	Imiquimod 5% cream for 12 weeks treating nodular BCC [Abstract]	8th World Congress on Cancer of the Skin. Zurich, Switzerland. July 18-21, 2001	duplicate/conference abstract and we have full publication
21576573	Robinson, J. K.	Evidence-based choice of treatment of NMSC	Arch Dermatol	no primary data
CN-00641211	Rocher, C.	Imiquimod 5% in the treatment of basal cell carcinoma: Assessment of efficacy and tolerability. [Spanish]	Dermatologia Revista Mexicana	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
15605806	Rodrigo, J. P.	[Efficacy of postoperative radiation therapy for squamous cell carcinoma of the head and neck: results of a prospective randomised clinical trial]	Acta Otorrinolaringol Esp	not treatment of skin cancer or <80% SCC or BCC
2894839	Rodriguez-Sains, R. S.	Radiotherapy of periocular basal cell carcinomas: recurrence rates and treatment with special attention to the medical canthus	Br J Ophthalmol	>20% recurrent or % recurrent not given
17190625	Rodriguez-Vigil, T.	Recurrence rates of primary basal cell carcinoma in facial risk areas treated with curettage and electrodesiccation	J Am Acad Dermatol	not comparative between treatment nodes
1390484	Rodriguez, J. M.	The treatment of periocular basal cell carcinomas by radiotherapy	Br J Ophthalmol	not comparative between treatment nodes
CN-00193051	Rogozinski, T. T.	Intralesional treatment with recombinant interferon beta is an effective alternative for the treatment of basal cell carcinoma. Double-blind, placebo-controlled study. <ORIGINAL> DOOGNISKOWE PODAWANIE REKOMBINANTOWEGO INTERFERONU BETA. SKUTECZNA ALTERNATYWA W LECZENIU BASALIOMA (WYNIKI PODWOJNIE SLEPEJ PROBY)	Przeglad dermatologiczny	not comparative between treatment nodes
10759821	Romagosa, Ricardo, et al.	"A Pilot Study to Evaluate the Treatment of Basal Cell Carcinoma with 5-Fluorouracil Using Phosphatidyl Choline as a Transepidermal Carrier."	Dermatologic surgery 26.4 (2000): 338-340.	not comparative between treatment nodes
0	Romanko, Yu S.	Efficacy of photodynamic therapy for basal cell carcinoma using photosensitizers of different classes	Voprosy Onkologii	not comparative between treatment nodes
25935596	Roozeboom, M. H.	Tumor thickness and adnexal extension of superficial basal cell carcinoma (sBCC) as determinants of treatment failure for methylaminolevulinate (MAL)-photodynamic therapy (PDT), imiquimod, and 5-fluorouracil (FU)	J Am Acad Dermatol	no outcomes of interest
26376042	Rotunno, R.	Electrochemotherapy in non-melanoma head and neck skin cancers: a three centers experience and literature review	G Ital Dermatol Venereol	not comparative between treatment nodes
24861492	Rubel, D. M., et al.	"Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial."	British Journal of Dermatology171.5 (2014): 1164-1171.	not treatment of skin cancer or <80% SCC or BCC
4848330	Rubisz-Brzezinska, J.	[Comparative appraisal of results of treatment of basal cell epithelioma with various methods]	Przegl Dermatol	Not English (Polish)
424458	Sakura, C. Y.	Comparison of treatment modalities for recurrent basal cell carcinoma	Plast Reconstr Surg	>20% recurrent or % recurrent not given
CN-00429205	Salim, A.	Comparison of photodynamic therapy with topical 5-8uorouracil in Bowen's disease Abstract	British journal of dermatology	duplicate/conference abstract and we have full publication
25354233	Samain, A.	Cryosurgery and curettage-cryosurgery for basal cell carcinomas of the mid-face	J Eur Acad Dermatol Venereol	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
25136458	Samstein, R. M.	Locally advanced and unresectable cutaneous squamous cell carcinoma: outcomes of concurrent cetuximab and radiotherapy	J Skin Cancer	not treatment of skin cancer or <80% SCC or BCC
25030404	Samy, N. A.	Effect of methylene blue-mediated photodynamic therapy for treatment of basal cell carcinoma	Lasers Med Sci	not comparative between treatment nodes
8720817	Scholten, A. N.	[Electron beam irradiation is effective in the treatment of skin carcinomas; a comparison with superficial roentgen therapy]	Ned Tijdschr Geneeskd	No analysis by population of interest
16310060	Schulte, K. W.	Soft x-ray therapy for cutaneous basal cell and squamous cell carcinomas	J Am Acad Dermatol	not comparative between treatment nodes
26449347	Schulze, B.	Hedgehog pathway inhibitor in combination with radiation therapy for basal cell carcinomas of the head and neck : First clinical experience with vismodegib for locally advanced disease	Strahlenther Onkol	not comparative between treatment nodes
11383121	Schwager, K.	[Carcinoma of the external ear canal and middle ear as interdisciplinary challenge for ear surgery and radiotherapy]	Laryngorhinootologie	No analysis by population of interest
27110895	Sebaratnam, D. F.	Direct Cost-Analysis of Mohs Micrographic Surgery and Traditional Excision for Basal Cell Carcinoma at Initial Margin Clearance	Dermatol Surg	No analysis by population of interest
20946582	Segura, S.	Non-invasive management of non-melanoma skin cancer in patients with cancer predisposition genodermatosis: a role for confocal microscopy and photodynamic therapy	J Eur Acad Dermatol Venereol	>20% recurrent or % recurrent not given
19737291	Seidler, A. M.	Mohs versus traditional surgical excision for facial and auricular nonmelanoma skin cancer: an analysis of cost-effectiveness	Dermatol Surg	not comparative between treatment nodes
22670903	Sekulic, Aleksandar, et al.	"Efficacy and safety of vismodegib in advanced basal-cell carcinoma."	New England Journal of Medicine 366.23 (2012): 2171-2179.	not comparative between treatment nodes
11786562	Shin, D. M.	Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer	J Clin Oncol	>20% recurrent or % recurrent not given
CN-00261581	Shuttleworth, D.	A comparison of the effects of intralesional interferon alpha-2b and topical 5% 5-fluorouracil cream in the treatment of solar keratoses and Bowen's disease	Journal of dermatological treatment	not treatment of skin cancer or <80% SCC or BCC
10802373	Silva, J. J.	Results of radiotherapy for epithelial skin cancer of the pinna: the Princess Margaret Hospital experience, 1982-1993	Int J Radiat Oncol Biol Phys	No analysis by population of interest
1890243	Silverman, M. K.	Recurrence rates of treated basal cell carcinomas. Part 1: Overview	J Dermatol Surg Oncol	not comparative between treatment nodes
1624628	Silverman, M. K.	Recurrence rates of treated basal cell carcinomas. Part 4: X-ray therapy	J Dermatol Surg Oncol	not comparative between treatment nodes
18306163	Smucler, R.	Combination of Er:YAG laser and photodynamic therapy in the treatment of nodular basal cell carcinoma	Lasers Surg Med	>20% recurrent or % recurrent not given

UID	First Author	Title	Journal	Reason for Exclusion
1622958	Smyth, A. G.	A prospective study of 134 consecutive patients requiring diagnosis, excision and repair of a facial cutaneous lesion	Br J Oral Maxillofac Surg	not comparative between treatment nodes
11093368	Soler, A. M.	Photodynamic therapy of residual or recurrent basal cell carcinoma after radiotherapy using topical 5-aminolevulinic acid or methylester aminolevulinic acid	Acta Oncol	>20% recurrent or % recurrent not given
10857368	Soler, A. M.	Photodynamic therapy of superficial basal cell carcinoma with 5-aminolevulinic acid with dimethylsulfoxide and ethylendiaminetetraacetic acid: a comparison of two light sources	Photochem Photobiol	not comparative between treatment nodes
11531838	Soler, A. M.	A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage	Br J Dermatol	not comparative between treatment nodes
16230937	Soriano, E.	[Course and prognosis of basaloid squamous cell carcinoma: case-control study of 49 patients]	Ann Otolaryngol Chir Cervicofac	not comparative between treatment nodes
24754529	Sotiriou, E.	Photodynamic therapy vs. imiquimod 5% cream as skin cancer preventive strategies in patients with field changes: a randomized intraindividual comparison study	J Eur Acad Dermatol Venereol	No analysis by population of interest
17020898	Soysal, H. G.	Invasive squamous cell carcinoma of the eyelids and periorbital region	Br J Ophthalmol	>20% recurrent or % recurrent not given
18520835	Soysal, H. G.	Basal cell carcinoma of the eyelids and periorbital region in a Turkish population	Ophthal Plast Reconstr Surg	>20% recurrent or % recurrent not given
CN-01059263	Spelman, L.	Ingenol mebutate 0.05% gel with full occlusion effectively treats sBCC	JDDG - Journal of the German Society of Dermatology	not comparative between treatment nodes
19839887	Stafanous, S.	Five-year cycle of basal cell carcinoma management re-audit	Orbit	>20% recurrent or % recurrent not given
19639112	Steinbauer, J. M.	Topical photodynamic therapy with porphyrin precursors--assessment of treatment-associated pain in a retrospective study	Photochem Photobiol Sci	not treatment of skin cancer or <80% SCC or BCC
6709010	Stern, R. S.	Cutaneous squamous-cell carcinoma in patients treated with PUVA	N Engl J Med	not comparative between treatment nodes
22494856	Stockfleth, E.	Recurrence rates and patient assessed outcomes of 0.5% 5-fluorouracil in combination with salicylic acid treating actinic keratoses	Eur J Dermatol	not treatment of skin cancer or <80% SCC or BCC
16650155	Streeton, C. L.	Treatment of basal cell carcinomas by general practitioners in Australia	Int J Dermatol	not comparative between treatment nodes
6556694	Swanson, N. A.	Basal cell carcinoma. Treatment modalities and recommendations	Prim Care	no primary data
4088894	Szymczyk, W.	[Effect of dose fractionation on 3 years results of roentgenotherapy of skin cancer]	Nowotwory	Not English (Polish)
17322605	Taherian, K.	Surgical excision of periocular basal cell carcinomas	Indian J Ophthalmol	not comparative between treatment nodes

UID	First Author	Title	Journal	Reason for Exclusion
15061853	Tan, S. R.	Effect of acitretin on wound healing in organ transplant recipients	Dermatol Surg	not comparative between treatment nodes
22547009	Tang, C.	Stereotactic radiosurgery for retreatment of gross perineural invasion in recurrent cutaneous squamous cell carcinoma of the head and neck	Am J Clin Oncol	not comparative between treatment nodes
24441673	Tang, J. Y.	Tazarotene: randomized, double-blind, vehicle-controlled, and open-label concurrent trials for basal cell carcinoma prevention and therapy in patients with basal cell nevus syndrome	Cancer prevention research (Philadelphia, Pa.)	not comparative between treatment nodes
22670904	Tang, J. Y.	Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome	N Engl J Med	not treatment of skin cancer or <80% SCC or BCC
24623654	Tanvetyanon, Tawee, et al.	"Postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck."	Head & neck 37.6 (2015): 840-845.	>20% metastatic/nodal involvement
1080961	Tarpley, J. L.	High dose methotrexate as a preoperative adjuvant in the treatment of epidermoid carcinoma of the head and neck. A feasibility study and clinical trial	Am J Surg	not treatment of skin cancer or <80% SCC or BCC
20101335	Teli, M. A.	Recurrence pattern in squamous cell carcinoma of skin of lower extremities and abdominal wall (Kangri cancer) in Kashmir valley of Indian subcontinent: impact of various treatment modalities	Indian J Dermatol	>20% recurrent or % recurrent not given
12832877	Thomas, D. J.	Excision margins for nonmelanotic skin cancer	Plast Reconstr Surg	not comparative between treatment nodes
19852120	Tierney, E. P.	Cost effectiveness of Mohs micrographic surgery: review of the literature	J Drugs Dermatol	no primary data
2090402	Tijl, J. W.	The optimal follow-up time for a basal cell carcinoma of the eyelid	Doc Ophthalmol	>20% recurrent or % recurrent not given
17700732	Tindholdt, T. T.	[Photodynamic therapy of facial basal cell carcinoma]	Tidsskr Nor Laegeforen	not comparative between treatment nodes
23035730	Tinelli, M.	What determines patient preferences for treating low risk basal cell carcinoma when comparing surgery vs imiquimod? A discrete choice experiment survey from the SINS trial	BMC Dermatol	not treatment of skin cancer or <80% SCC or BCC
24975199	Togsverd-Bo, Katrine, et al.	"Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients–a randomized controlled trial."	British Journal of Dermatology 172.2 (2015): 467-474.	not treatment of skin cancer or <80% SCC or BCC
9487802	Tope, W. D.	Protoporphyrin IX fluorescence induced in basal cell carcinoma by oral delta-aminolevulinic acid	Photochem Photobiol	no outcomes of interest
CN-00454732	Torres, A.	Imiquimod 5% cream preceeding surgery for BCC monitoring with confocal microscopy	Annales de Dermatologie Et de Venereologie	duplicate/conference abstract and we have full publication
CN-00478784	Torres, A.	Treatment of basal cell carcinoma using imiquimod 5% cream as an adjuvant therapy to	Journal of the	duplicate/conference abstract and we have full

UID	First Author	Title	Journal	Reason for Exclusion
		Mohs micrographic surgery. Abstract P5-19 The 12th Congress of the European Academy of Dermatology and Venereology. Barcelona, Spain 15-18th October 2003	European Academy of Dermatology and Venereology : JEADV	publication
16984216	Triesscheijn, M.	Optimizing meso-tetra-hydroxyphenyl-chlorin-mediated photodynamic therapy for basal cell carcinoma	Photochem Photobiol	not comparative between treatment nodes
2015753178	Trone, J. C.	Skin Cancers in Nonagenarian Patients: Special Focus on Radiotherapy	Clinical Oncology	not comparative between treatment nodes
11958891	Tsao, M. N.	Radiotherapy management for squamous cell carcinoma of the nasal skin: the Princess Margaret Hospital experience	Int J Radiat Oncol Biol Phys	not comparative between treatment nodes
20033810	Tsukuda, M.	Randomized controlled phase II comparison study of concurrent chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil versus CCRT with cisplatin, 5-fluorouracil, methotrexate and leucovorin in patients with locally advanced squamous cell carcinoma of the head and neck	Cancer Chemother Pharmacol	not treatment of skin cancer or <80% SCC or BCC
24397256	Tuerdi, M.	Standard surgical excision and reconstruction of giant basal cell carcinoma of the face: may be an alternative to the Mohs micrographic surgery	Journal of the European Academy of Dermatology and Venereology : JEADV	not comparative between treatment nodes
10219440	Tufano, R. P.	Malignant tumors of the nose and paranasal sinuses: hospital of the University of Pennsylvania experience 1990-1997	Am J Rhinol	not treatment of skin cancer or <80% SCC or BCC
21277787	Tyrrell, J.	The effect of air cooling pain relief on protoporphyrin IX photobleaching and clinical efficacy during dermatological photodynamic therapy	J Photochem Photobiol B	not comparative between treatment nodes
19881375	Unlu, R. E.	Is it really necessary to make wide excisions for basal cell carcinoma treatment?	J Craniofac Surg	not comparative between treatment nodes
2218385	Vaillant, L.	[Skin carcinoma of the face: surgery or radiotherapy?]	Rev Stomatol Chir Maxillofac	Not English (French)
22170313	van der Beek, N.	PpIX fluorescence combined with auto-fluorescence is more accurate than PpIX fluorescence alone in fluorescence detection of non-melanoma skin cancer: an intra-patient direct comparison study	Lasers Surg Med	not treatment of skin cancer or <80% SCC or BCC
21046543	van der Eerden, P. A.	Eighteen years of experience in Mohs micrographic surgery and conventional excision for nonmelanoma skin cancer treated by a single facial plastic surgeon and pathologist	Laryngoscope	>20% recurrent or % recurrent not given
11494691	van der Meer,	[Low 5-year recurrence rate after surgical	Ned	Not English (Dutch)

UID	First Author	Title	Journal	Reason for Exclusion
	G. T.	excision of 126 basal cell carcinomas with frozen section analysis upon indication]	Tijdschr Geneeskd	
25049028	van Oosten, E. J.	Different pain sensations in photodynamic therapy of nodular basal cell carcinoma Results from a prospective trial and a review of the literature	Photodiagnosis Photodyn Ther	not comparative between treatment nodes
2001338148	Van Zuuren, E. J.	Basal cell carcinoma on the dorsum of the hand: Report of 11 cases	Journal of the European Academy of Dermatology and Venereology	not comparative between treatment nodes
9012035	Veien, K.	[Results of treatment of non-melanoma skin cancer in a dermatologic practice. A prospective study]	Ugeskr Laeger	not comparative between treatment nodes
21707774	Veronese, F.	Basal cell carcinoma of the head region: therapeutical results of 350 lesions treated with Mohs micrographic surgery	J Eur Acad Dermatol Venereol	not comparative between treatment nodes
15377354	Vidal, D.	Efficacy of imiquimod for the expression of Bcl-2, Ki67, p53 and basal cell carcinoma apoptosis	Br J Dermatol	no outcomes of interest
15115500	Vidal, D.	Efficacy of imiquimod 5% cream for basal cell carcinoma in transplant patients	Clin Exp Dermatol	not comparative between treatment nodes
15347339	Vidal, D.	Open study of the efficacy and mechanism of action of topical imiquimod in basal cell carcinoma	Clin Exp Dermatol	not comparative between treatment nodes
17310012	Vidal, David, Xavier Matías-Guiu, and Agustín Alomar.	"Fifty-five basal cell carcinomas treated with topical imiquimod: outcome at 5-year follow-up."	Archives of dermatology 143.2 (2007): 264-276.	not comparative between treatment nodes
22508870	Viola, K. V.	Mohs micrographic surgery and surgical excision for nonmelanoma skin cancer treatment in the Medicare population	Arch Dermatol	no outcomes of interest
19726763	Von Hoff, Daniel D., et al.	"Inhibition of the hedgehog pathway in advanced basal-cell carcinoma."	New England Journal of Medicine 361.12 (2009): 1164-1172.	not comparative between treatment nodes
25925162	Waalboer-Spuij, R.	Patient Perception of Imiquimod Treatment for Actinic Keratosis and Superficial Basal Cell Carcinoma in 202 Patients	Dermatology	not comparative between treatment nodes
25865716	Wang, L.	Outcomes of Primary Squamous Cell Carcinoma of Major Salivary Glands Treated by Surgery With or Without Postoperative Radiotherapy	J Oral Maxillofac Surg	not treatment of skin cancer or <80% SCC or BCC
CN-01027501	Weinstock, M. A.	The veterans affairs topical tretinoin chemoprevention (VATTC) trial	British journal of dermatology	not treatment of skin cancer or <80% SCC or BCC
CN-00178586	Weissberg, J. B.	Radiation therapy (RT) and mitomycin C (MC) in the treatment of head and neck cancer:	Proc-Am-Assoc-	not treatment of skin cancer or <80% SCC or

UID	First Author	Title	Journal	Reason for Exclusion
		Prospective randomized trial	Cancer-Res	BCC
18698246	Wennberg, A. M.	Photodynamic therapy with methyl aminolevulinate for prevention of new skin lesions in transplant recipients: a randomized study	Transplantation	not treatment of skin cancer or <80% SCC or BCC
CN-00602278	Wennberg, AM	Results from a 15-month update of a multicentre study of methyl aminolaevulinate photodynamic therapy in immunocompromised organ transplant recipients with nonmelanoma skin cancer. Abstract P-79. British Association of Dermatologists 86th Annual Meeting	British journal of dermatology	duplicate/conference abstract and we have full publication
5587022	Wernsdorfer, R.	[Carcinomas of the external ear. Report on 170 cases]	Z Haut Geschlechtskr	no primary data
23760141	White, G. M.	Biopsy followed by immediate curettage and electrodesiccation of suspected basal cell carcinomas at the first visit	JAMA Dermatol	not comparative between treatment nodes
21219287	Wiegell, S. R., et al.	"A randomized, multicentre study of directed daylight exposure times of 1½ vs. 2½ h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp."	British Journal of Dermatology 164.5 (2011): 1083-1090.	not treatment of skin cancer or <80% SCC or BCC
18294318	Wiegell, S. R., et al.	"Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study."	British Journal of Dermatology 158.4 (2008): 740-746.	not treatment of skin cancer or <80% SCC or BCC
19416257	Wiegell, S. R., et al.	"Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial."	British Journal of Dermatology160.6 (2009): 1308-1314.	not treatment of skin cancer or <80% SCC or BCC
22250644	Wiegell, S. R., et al.	"Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study."	British Journal of Dermatology 166.6 (2012): 1327-1332.	not treatment of skin cancer or <80% SCC or BCC
1913451	Wilder, R. B.	Basal cell carcinoma treated with radiation therapy	Cancer	not comparative between treatment nodes
CN-01007534	Williams, H. C.	Surgical excision versus imiquimod 5% cream for basal-cell carcinoma (SINS): A multi-centre non-inferiority randomised controlled trial	Journal of investigative dermatology	duplicate/conference abstract and we have full publication
CN-00873112	Williams, H. C.	Surgical excision vs. imiquimod 5% cream for basal cell carcinoma: A multicentre noninferiority randomized controlled trial (Abstract DS03). 93rd Annual Meeting of the British Association of Dermatologists Liverpool United Kingdom. Conference Start: 20130709 Conference End: 20130711	British journal of dermatology	duplicate/conference abstract and we have full publication

UID	First Author	Title	Journal	Reason for Exclusion
15225948	Wilson, A. W.	Surgical management of incompletely excised basal cell carcinomas of the head and neck	Br J Oral Maxillofac Surg	not comparative between treatment nodes
CN-00452999	Woods, R. L.	Chemotherapy (CT for advanced squamous cell carcinomas) (SCCs) of head and neck: A randomised comparison of high dose versus low dose cis platinum (CIS DDP) in combination with bleomycin and methotrexate	Proceedings of the American Association for Cancer Research, 75th Annual Meeting . Toronto, Ontario, 9-12 May, 1984	not treatment of skin cancer or <80% SCC or BCC
16431060	Yin, M.	Analysis of 95 cases of squamous cell carcinoma of the external and middle ear	Auris Nasus Larynx	not treatment of skin cancer or <80% SCC or BCC
1587735	Zablow, A. I.	Electron beam therapy for skin cancer of the head and neck	Head Neck	not comparative between treatment nodes
25393353	Zeitouni, N. C.	A prospective study of pain control by a 2-step irradiance schedule during topical photodynamic therapy of nonmelanoma skin cancer	Dermatol Surg	not comparative between treatment nodes
21055053	Zhang, Z. X.	[Clinical analysis of 60 cases with maxillary squamous cell carcinoma]	Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi	not treatment of skin cancer or <80% SCC or BCC
55288		Bleomycin in advanced squamous cell carcinoma: a random controlled trial. Report of Medical Research Council Working Party on Bleomycin	Br Med J	No analysis by population of interest
22777303		Vismodegib (Erivedge) for basal cell carcinoma	Med Lett Drugs Ther	no primary data

Appendix C. Design Details

Table C-1. Design details

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
RCT							
Abbade 2015 (Conference abstract) (Brazil)	Unclear	Not reported	primary nodular BCC in the head and neck, <=2 in Ø	no histologic confirmation of nodular BCC, Gorlin syndrome or contraindication to surgical resection or PDT.	Biopsy/pathologic confirmed	Method of assessment not reported	92 lesions/68 lesions/68 lesions
Al-Niaimi 2015 26157307 (UK)	Single center	Not reported	>18 y/o, BCC > 1 x 1 cm2 requiring treatment with MMS	morphoeic, infiltrative and subtypes, a photosensitive skin disorder, hypersensitivity to MAL, participation in another investigational drug or research study within 30 days, and females of child-bearing potential	Method of diagnosis not reported	Visual assessment	19/19/19
Allen 1979 298425 (UK)	Single center	Not reported	BCC anywhere in the body	<18 y/o; previous deep x-ray tx or cryotherapy; lesion near the eye when the other eye sees less than 6/18.	Method of diagnosis not reported	Method of assessment not reported	31/31/31
Alpsoy 1996 8708151 (Turkey)	Unclear	Not reported	adults with histologically confirmed BCC	recurrent lesions, genetic or nevoid conditions, or lesions with deep tissue involvement	Biopsy/pathologic confirmed: histologically confirmed BCC	Method of assessment not reported	45/45/45
Arits 2013 23683751 (Netherlands)	Multicenter	No industry support	1 primary, histologically proven superficial BCC per patient	using immunosuppressive drugs, had genetic skin cancer disorders, tumour was located in the H zone or scalp, or were breastfeeding or pregnant	Biopsy/pathologic confirmed: 3 mm punch biopsy and was assessed by consensus	Method of assessment not reported	601/601/583
Avril 1997 9218740 (France)	Unclear	Not reported	previously untreated BCC of the face, Ø < 4 cm.	contraindication to surgery and radiotherapy, BCC on the scalp or the neck, pts with total removal of BCC at biopsy, pts w/ >=5 BCCs, LE <3 yrs	Biopsy/pathologic confirmed	Method of assessment not reported	360/360/347
Basset-Seguin 2008 18693158 (13 centers in 7	Multicenter	No industry support	>=18 y/o w/ previously untreated primary superficial	xeroderma pigmentosum, porphyria, Gorlin's syndrome, history of arsenic exposure,	Biopsy/pathologic confirmed	Method of assessment not reported	120/118/115

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
european countries)			BCC lesions suitable for cryotherapy. confirmed by histology using 4 mm punch biopsy. <=10 eligible lesions. Ø 6-15 mm on the face or scalp, <20 mm on the extremities or neck and <30 mm on the trunk, which were not pigmented, morpheaform or infiltrating.	allergy to MAL or other topical photosensitizers or excipients of the cream, participated in other investigational studies in last 30 days and pregnant or breast-feeding women. Concomitant treatment with immunosuppressive medication			
Bath-Hextall 2014 24332516 (UK)	Multicenter	Industry supplied materials	histologically confirmed, primary, previously untreated, nodular or superficial BCC not arising at sites at high risk for subclinical tumour spread	morphoeic or recurrent BCC and those with Gorlin syndrome	Biopsy/pathologic confirmed: Histologically proven BCC (usually a punch or shave biopsy specimen of no more than 25% of the total lesion, though sometimes at surgery)	Method of assessment not reported	501/501/485
Berroeta 2007 17573890 (United Kingdom)	Single center	No industry support	<= 2 cm, well-define, nodular BCC on anatomically noncritical sites	< 18 y/o; pregnancy; photosensitivity; morphoeic BCCs; high-risk site; recurrent BCCs; immunodeficiency; size > 2 cm.	Method of diagnosis not reported	Visual assessment: well defined <=2 cm	31/31/31
Beutner 1999 10570388 (USA)	Unclear	Industry funded	biopsy-confirmed BCC with clearly visible margins, nodular w/ area 0.5 - 1.5 cm^2, or superficial w/ area of 0.5-2 cm^2, and that was suitable for tx by surgical excision.	central facial/periorificial sites	Biopsy/pathologic confirmed	Method of assessment not reported	35/35/35

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
Brinkhuizen 2016 27067393 (Netherlands)	Single center	Industry supplied materials	Patients with histologically proven primary sBCC or (micro) nBCC >=4 mm, not located on the face or on the hairy scalp		Biopsy/pathologic confirmed	Visual assessment	128/128/119
Butler 2009 19018814 (texas, usa)	Single center	Industry funded	Immunocompetent, non-pregnant, >=18 y/o, primary nodular nasal BCCs, <1 cm	superficial, morpheaform, or micronodular histologic BCC	Biopsy/pathologic confirmed: histological confirmation of BCC before study enrollment with a 2-mm punch biopsy by a pathol-ogist.	Method of assessment not reported	31/31/31 (ITT) 28 actual
Cai 2015 25899562 (china)	Single center	No industry support	having skin BD upon biopsy	porphyria or photosensitivity	Biopsy/pathologic confirmed	Method of assessment not reported	18/18/18
Carija 2016 27516420	Single center	No industry support	>18 years, >2 BCCs, biopsy proven	lactating and pregnant women, heavily pigmented BCC, diagnosed porphyria	Biopsy/pathologic confirmed	assessment: traced onto graph paper and count squares	15/15/15
Choi 2016 26551044 (korea)	Single center	No industry support	≥18 y/o, untreated thin primary nBCC, maximum tumour depth of 2 mm in a biopsy specimen and clinical evaluation, surgical excision would be difficult because of bleeding abnormalities or cardiac problems.	>5 eligible lesions; lesions located in the midface region, nose, orbital areas or ears; Ø >15 mm; non-nodular; known allergies to MAL or lidocaine; pregnancy or lactation; active systemic infectious disease; immunosuppressive treatment; personal history of malignant melanoma; tendency toward melasma or keloid formation; any indication of poor compliance.	Biopsy/pathologic confirmed	Method of assessment not reported	39 (42 lesions)/39 (42 lesions)/34 patients (37 lesions)
Choi 2017 28199463	Single center	Not reported	> 18 years with previously untreated microinvasive SCC,	pregnancy or lactation; active systemic infectious disease; other inflammatory,	Biopsy/pathologic confirmed: 4 mm punch biopsy	Visual assessment: photographed for	45/45/40

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
			tumor invasion into the papillary dermis (Clark level II) according to a biopsy specimen and difficulty in surgical excision because of health problems	infectious, or neoplastic skin diseases in the treated area; allergy to MAL,other topical photosensitizers, or excipients of the cream; history of photosensitivity; use of immunosuppressive or photosensitizing drugs; participation in any other investigational study in the preceding 30 days; history or indicators of poor compliance. Histological findings of acantholysis, desmoplasia, perineural or lymphovascular invasion, and echographic features of regional lymph node metastasis		baseline measurement	
Cornell 1990 2229497 (US)	Multicenter	No industry support	superficial or noduloulcerative BCC confirmed by biopsy, 32-70 y/o, not pregnant, and in good general health.	previous therapy to the test lesion, immunosuppressive or cytotoxic therapy (within the prior 4 wks), or exogenous interferon/interferon-inducer except interferonalfa-2b (Intron A), BCC located in the perioral or central area of the face or penetrating to deep tissue	Biopsy/pathologic confirmed: punch or shave biopsy	Visual assessment: photographed and its size and anatomic location were precisely defined.	172/172/165
Edwards 1990 2107219 (U.S.)	Unclear	Industry supplied materials	clinically typical, sharply defined BCC easily excisable at the end of the study	any serious or debilitating illness, history of thromboembolic phenomena or CVD, received rt to the test site area or who had a history of arsenic ingestion, pregnant or nursing women, immunosuppressed, pts taking nonsteroidal anti-inflammatory medications	Biopsy/pathologic confirmed	Visual assessment: at randomization, immediately before treatment and at the beginning of each treatment week	29/29/29
Edwards 1990	Unclear	Industry	otherwise healthy	Morpheic BCC, recurrent	Biopsy/pathologic	Visual	65/65/63

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
2383027 (U.S.)		supplied materials	35-65 y/o; 1 clinically typical, sharply defined basal cell carcinoma with clearly visible margins, Ø 0.5 to 1.5 cm for nodular tumors or 2 cm for superficial lesions, per pt.	cancers, deeply invasive lesions, periorificial tumors, and central facial BCC; serious or debilitating illness, a history of thromboembolic or CVD, rt to the test site area, or a history of arsenic ingestion. Pregnancy, breast-feeding, and immunosuppression as a result of medication or illness, nonsteroidal anti-inflammatory medications	confirmed: confirmatory diagnostic shave or punch skin biopsy that removed less than 25% of the lesion	assessment: The size and a clinical description of each basal cell carcinoma were recorded. The lesion was then photographed.	
Eigentler 2007 17610993 (Germany)	Unclear	Not reported	adults w/ >=1 clinically typical and histologically confirmed primary nBCC Ø <=1.5 cm	micronodular, infiltrative, superficial, or morpheic BCC, BCCs w/ multicentric growth pattern, w/in 0.5 cm of the eyes	Biopsy/pathologic confirmed	Visual assessment: the lesion was documented by photography and the silhouette was traced on a plastic film.	102/102/90
Eimpunth 2014 (Conference abstract) (unclear)	Unclear	Not reported	biopsy proven, superficial or nodular BCCs located on trunk or extremities		Biopsy/pathologic confirmed	Method of assessment not reported	24/24/24
Foley 2009 20064185 (U.S. and australia)	Multicenter	Industry funded	18 y/o, primary nodular BCC verified by local histologic exam of 2-3 mm punch biopsy and suitable for a simple excision surgery.	periorbital area, ears, nasaolabial fold; Ø < 6mm (any site) or >15 mm (face or scalp), > 20 mm (extremities or neck), or > 30 mm (trunk); pigmented, morpheaform or infiltrating pattern. porphyria, Gorlin's syndrome, xeroderma pigmentosum, history of arsenic exposure or allergy to MAL, ALA, or excipients, participated in any other investigational study in the previous 30 days or were likely to be poorly compliant, pregnant or breast-feeding.	Biopsy/pathologic confirmed	Method of assessment not reported	131 (160 lesions)/131 (160 lesions)/128

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
				concomitant treatment with any immunosuppressive medication was prohibited.			
Garcia-Martin 2011 21242584 (Spain)	Unclear	Not reported	nodular BCC on the eyelid	previous tx, other dermatological diseases such as Gorlin syndrome or psoriasis, immunocompromised status, aggressive varieties of BCC such as morpheaform (sclerosing or infiltrative) BCC	Biopsy/pathologic confirmed: punch of diameter 4 mm	Visual assessment	27/27/27
Geisse 2002 12196749 (U.S.)	Multicenter	Industry funded	>=18 y/o, histologically confirmed superficial BCC 0.5-2.0 cm^2	w/in 1 cm of the hairline, eyes, nose, mouth, or ears; the anogenital area; hands and feet, previously treated, recurrent, or w/in 5 cm of another BCC tumor	Biopsy/pathologic confirmed: A biopsy specimen of no more than 25% of the tumor area was taken for histologic confirmation of sBCC.	Visual assessment	128/128/125
Geisse 2004 15097956 (U.S.)	Multicenter	Industry funded	>=18 y/o, primary, histologically-confirmed superficial BCC >= 0.5 cm2, Ø <= 2.0 cm on the limbs, trunk (excluding the anogenital area), neck, or head (excluding the H-zone)	any dermatological disease in the target sBCC site or surrounding area that could be exacerbated by imiquimod or cause difficulty with examination (such as subjects with nevoid basal cell carcinoma syndrome)	Biopsy/pathologic confirmed: confirmatory punch or shave biopsy < 25% of the tumor area	Visual assessment: clinically evident tumor margins and local landmarks	724/724/694
Haak 2015 24903544 (Denmark)	Single center	No industry support	>=18 y/o, previously untreated facial tumours. histologically verified nBCC either: Ø > 15 mm, located in the H-zone, located on severely sun-damaged skin with	lactating or pregnant women, porphyria, known allergy to MAL, Gorlin syndrome, immunosuppressive treatment, Fitzpatrick skin type IV–VI, history of keloid formation and conditions associated with risk of poor compliance	Biopsy/pathologic confirmed: histologically verified	Visual assessment: photographed and mapped on a template	32/32/32

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
			one or more co-existing actinic lesions requiring treatment				
Hall 1986 3514075 (UK)	Single center	Not reported	BCC proven by biopsy, considered suitable for tx w/ rt	Recurrent tumors, location on nose or pinna, electrons considered Tx of choice, lesion near eye and vision in contralateral eye <6/18	Biopsy/pathologic confirmed: "Proven by biopsy"	Method of assessment not reported	105/105/93
Ko 2014 24102369 (Korea)	Single center	No industry support	Korean, ≥ 18 y/o, biopsy-confirmed Bowen's Disease lesions on lower extremities, >=2 comparable symmetrical lesions of similar severity and <=twofold difference in number of lesions between the right and left sides.	porphyria, known allergies to the MAL cream or lidocaine, pregnancy, lactation, any active systemic infectious disease, immunosuppressive treatment, personal history of malignant melanoma, tendency towards melasma or keloid formation, prior treatment of the lesions w/in 4 wks, and any indication of poor compliance.	Biopsy/pathologic confirmed	Visual assessment: photographed, mapped and numbered	21/19/18
Kuijpers 2006 16865869 (Netherlands)	Single center	No industry support	nodular, primary BCC located anywhere but periocular area and hairy scalp; clinical Ø <20 mm.	pigmented BCC; contra-indications to surgery; hypersensitivity to daylight or creams; porphyria; >5 BCCs.	Method of diagnosis not reported	Method of assessment not reported	43/43/43
Kuijpers 2007 17451581 (Netherlands)	Single center	No industry support	>=18 y/o, untreated, primary histologically proven BCC, nodular or superficial, on the head and neck, <20mm Ø	Recurrent, not superficial or nodular, >20 mm Ø, contraindications to either procedure, presence of 5+ BCCs	Biopsy/pathologic confirmed	Method of assessment not reported	88/88/88
Marks 2001 11312429 (Australia and New Zealand)	Multicenter	Industry funded	>=18 y/o, biopsy-proven superficial BCC on head, neck, trunk or limbs, SA 0.5-2 cm^2, primary tumor, biopsy <25%	Infection, recurrent, w/in 1 cm of the hairline, eyes, nose, mouth, ears, anogenital region, hands, and feet	Biopsy/pathologic confirmed	Method of assessment not reported	99/99/99

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
			of the lesion				
Migden 2015 25981810 (worldwide)	Multicenter	Industry funded	>= 18 y/o; histologically confirmed, locally advanced BCC not amenable to rt or curative surgery; adequate bone marrow, liver function, and renal function	previous tx with sonidegib or another Hedgehog pathway inhibitor, major surgery, other antineoplastic therapy, taken an investigational agent w/in 4 wks before the start of the study, currently taking strong inhibitors or inducers of CYP3A4 or CYP3A5 expression or drugs metabolised by CYP2B6 or CYP2C9; gastrointestinal dysfunction or known malabsorption syndromes, neuromuscular disorders, or other uncontrolled medical disorders; treatment with drugs known to cause rhabdomyolysis (pravastatin allowed w/ extra caution); pregnancy or breastfeeding	Biopsy/pathologic confirmed	Visual assessment: standard annotated photography	269/230/230
Miller 1997 8996264 (USA)	Multicenter	No industry support	6-15 mm Ø, well-defined margins, <=50 mm from any other malignancy that would otherwise be treated with surgery or curettage/electrodesiccation	lesions already received tx, high-risk sites, tumors considered to be more appropriately treated w/ Mohs, deep tissue involved lesions, morpheaform lesions, lesions associated with basal cell nevus syndrome, known hypersensitivities or allergies to 5-FU, sulfites, epinephrine, or bovine collagen; history of autoimmune disease or immunosuppression; women who were pregnant or lactating	Biopsy/pathologic confirmed: punch or shave biopsy of no more than 25% of total legion	Visual assessment: 6-15mm in largest diameter, well-defined margins	122/122/116
Morton 1996 8977678 (Scotland)	Unclear	Not reported	<=21 mm Ø		Biopsy/pathologic confirmed: 4-mm punch biopsy	Method of assessment not reported	19/19/19

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
Morton 2006 16785375 (Europe)	Multicenter	Industry funded	>= 18 y/o, histologically confirmed SCC in situ	treated w/in the previous 3 mo or strongly pigmented, <6mm or >40 mm Ø, located on the genitalia	Biopsy/pathologic confirmed: biopsy specimen taken within 5 months, and with no evidence of any change in appearance suggestive of lesion progression	Visual assessment	229/229/209
Mosterd 2008 18717680 (Netherlands)	Single center	Not reported	>18 y/o, untreated nBCC w/ Ø <=20 mm	Pregnancy, LE <5 years, known skin cancer syndromes, use of phototoxic /photosensitive drugs, hypersensitivity to light or ALA cream, recurrent or pigmented BCC, not nodular BBC, and a localization on concave areas or hairy skin	Biopsy/pathologic confirmed: 3mm punch biopsy	Visual assessment	151/149/149
Mosterd 2008 19010733 (Netherlands)	Multicenter	No industry support	>= 1 untreated, histologically confirmed primary BCC >=1cm Ø located in the H-zone or a facial primary BCC of an aggressive histological subtype (ie, morpheaform, micronodular, trabecular, infiltrative, or BCC with squamous differentiation)	LE<3 yrs	Biopsy/pathologic confirmed	Visual assessment: overall and close-up photographs were taken before each treatment	443/374/251
Orenberg 1992 1430394 (USA)	Unclear	Not reported	Biopsy-proven nodular BCC, 06-1.5 cm Ø	Previous local tx or systemic cancer therapy w/in 6 mo; Gorlin's syndrome, morpheaform, pigmented or deeply invasive lesions; any serious or debilitating illness, chronic respiratory disease,	Biopsy/pathologic confirmed	Method of assessment not reported	20/20/20

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
				depressed bone marrow, autoimmunedisease, or w/ hypersensitivity to 5-FU, epinephrine, or bovine couagen; Pregnant or lactating women and subjects requiring the use of nonsteroidal antiinflammatory drugs, nonselective beta-blocking drugs, aspirin, and topical or systemic steroids			
Patel 2006 16713457 (United Kingdom)	Single center	Industry funded	biopsy-proven cutaneous SCC in situ; full-thickness epidermal dysplasia; no active treatment 1 mo; post-biopsy legion 1-20 cm^2; >=1 cm away from eye; had to be able to attend clinical trials room.		Biopsy/pathologic confirmed: biopsy specimen, which by conventional histologic examination showed full-thickness epidermal dysplasia	Method of assessment not reported	31/31/28
Rhodes 2004 14732655 (Europe)	Multicenter	Industry funded	>=18 y/o w/ perviously untreated primary nodular BCC suitable for simple excision surgery	> 10 eligible lesions; lesions in midface region, orbital areas, or ears; 6mm-15mm Ø (face and scalp), > 20mm Ø (extremities or neck), >30mm Ø (trunk); pigmented or morpheaform BCCs; polyphyria; Gorlin syndrome; history of arsenic exposure; in another study in past 30 days; likely to be poor compliers; taking immunosuppresive medication; pregnant or breasfeeding	Biopsy/pathologic confirmed	Visual assessment	103/103/101
Salim 2003 12653747 (UK)	Multicenter	Not reported	Bowen's disease	Not reported	Biopsy/pathologic confirmed	Method of assessment not reported	49/40/40
Salmanpoor 2012	Single	Not reported	Pathologically	Tumors with indications for	Biopsy/pathologic	Method of	55/55/55

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
(Iran)	center		confirmed BCC	Mohs	confirmed	assessment not reported	
Schleier 2007 25047438 (Germany (Friedrich-Schiller University Jena))	Single center	No industry support	histologically verified superficial BCC w/ no deep infiltration (<2 mm), no morpheic and pigmented BCC, and good compliance.	unclear histology, clinically nodular BCC, expected poor compliance, untreated diabetes mellitus, and pregnancy	Biopsy/pathologic confirmed	Method of assessment not reported	24/24/24
Schulze 2005 15888150 (Europe)	Multicenter	Industry funded	non-pregnant, >= 18 y/o; histologically confirmed primary sBCC on limbs, trunk, neck, or head; area >=0.5 cm^2 and Ø <=2.0 cm prior to biopsy.	clinically significant, unstable medical conditions; metastatic tumor or tumor with high probability of metastatic spread; tumor on anogenital area or w/in 1 cm of the hairline, nose, mouth, ears, and eyes; histological evidence morphoeic, severe squamous metaplasia, or any infliltrative or desmoplastic features; dermatological disease w/in 5 cm of target site margins that would be exacerbated by treatment and would affect assessment.	Biopsy/pathologic confirmed	Visual assessment: multiplying the two largest diameters perpendicular to each other	166/166/166
Shumack 2002 12224977 (12 weeks) (Australia and New Zealand; And United States)	Multicenter	Not reported	>=18 y/o, primary target tumor, histologically confirmed as nodular BCC. 0.5-1.5 cm^2 area and >1 cm from the eyes, nose, mouth, ear, and hairline.	BCC with morpheic infiltrating and micronodular patterns	Biopsy/pathologic confirmed: punch or shave biopsy of the target tumor.	Visual assessment: Target tumors were measured and photographed prior to the prestudy biopsy and rephotographed prior to treatment initiation and at each interval visit.	92/92/77
Shumack 2002 12224977 (6 weeks)	Multicenter	Not reported	>=18 y/o, primary target tumor,	BCC with morpheic infiltrating and micronodular patterns	Biopsy/pathologic confirmed: punch	Visual assessment:	92/92/77

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
(Australia and New Zealand; And United States)			histologically confirmed as nodular BCC. 0.5-1.5 cm^2 area and >1 cm from the eyes, nose, mouth, ear, and hairline.		or shave biopsy of the target tumor.	Target tumors were measured and photographed prior to the prestudy biopsy and re-photographed prior to treatment initiation and at each interval visit.	
Siller 2010 20546215 (8 private dermatology clinics Australia)	Multicenter	Industry funded	>=18 y/o, with one sBCC lesion suitable for surgical excision on the arm, shoulder, chest, face, neck, abdomen, back, leg or scalp. Lesions with pre- and post-biopsy Ø 4–15 mm and thickness <=4 mm	women of childbearing potential; recurrent or atypical lesions, immunosuppression, and prior, concomitant or anticipated therapy with the potential to confound the study results.	Biopsy/pathologic confirmed	Visual assessment	60/60/60
Spencer 2006 16393600 (United States)	Single center	Industry funded	>= 18 y/o; previously untreated histologically confirmed nBCC.	comorbidities that would interfere with or be exacerbated by treatment.	Biopsy/pathologic confirmed: histologically confirmed	Visual assessment	20/20/20
Sterry 2002 12452875 (nodular) (Europe)	Multicenter	Industry funded	>=18 y/o, primary tumour, histologically confirmed superficial or nodular BCC, area 0.5 cm^2-2.0 cm^2 for superficial or 0.25 cm^2-1.5 cm^2 for nodular	previous therapy to the target tumour or any dermatological conditions that would interfere with local assessments.	Biopsy/pathologic confirmed: prestudy confirmatory punch, deep shave, or wedge biopsy that removed no more than approximately 25% of the tumour	Visual assessment: measuring and multiplying the two largest perpendicular dimensions of the tumour. The tumour site and appropriate anatomic landmarks were mapped using a	183/177

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
						clear plastic sheet as a template to guide the excision at the end of the study	
Sterry 2002 12452875 (superficial) (Europe)	Multicenter	Industry funded	>=18 y/o, primary tumour, histologically confirmed superficial or nodular BCC, area 0.5 cm^2-2.0 cm^2 for superficial or 0.25 cm^2-1.5 cm^2 for nodular	previous therapy to the target tumour or any dermatological conditions that would interfere with local assessments.	Biopsy/pathologic confirmed: prestudy confirmatory punch, deep shave, or wedge biopsy that removed no more than approximately 25% of the tumour	Visual assessment: measuring and multiplying the two largest perpendicular dimensions of the tumour. The tumour site and appropriate anatomic landmarks were mapped using a clear plastic sheet as a template to guide the excision at the end of the study	183/177
Szeimies 2008 18624836 (United Kingdom/Germany/Switzerland/Australia)	Multicenter	Industry funded	>= 18 y/o; primary sBCC suitable for simple excision surgery; confirmed by histology; no histological evidence of aggressive growth patterns	> 5 eligible lesions; lesions located in nose, nasolabial, or orbial areas; lesions w/ Ø <8 mm or >20 mm; recurrent lesions; lesions located in severely sun-damaged skin where surgery was not suitable due to frequent recurrence/ occurrence of other BCCs in the same area; lesions located close to or involving a scar of SCC; pigmented, morpheaform or infiltrating lesions on the treated area; at risk in terms of precautions, warnings, and	Biopsy/pathologic confirmed: biopsy at screening	Method of assessment not reported	196/196/196

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
				contraindications as indicated in MAL-PDT package insert; pregnant or breastfeeding women.			
Thissen 2000 10940063 (Netherlands)	Single center	No industry support	superficial or nodular BCCs, clinically <2 cm Ø, localized anywhere in the head and neck area	recurrent BCCs, histologic subtypes not nodular or superficial, >2 cm Ø, >=5 BCCs, and contraindications to surgery or cryosurgery (eg, cold intolerance). LE <1 yr.	Method of diagnosis not reported	Visual assessment: Before treatment, the tumors were documented with photographs	96/96/96
Torres 2004 15606733 (loma linda, CA; boston, MA)	Multicenter	Industry funded	biopsy proven BCC; <=25% of the lesion removed at time of biopsy. 18 y/o, histologically confirmed, primary, superficial, nodular, or mixed superficial and nodular BCC. Target tumor consistent w/ BCC w/ no histologic evidence of aggressive growth patterns, including severe squamous metaplasia, morpheaform or infiltrative/desmoplastic features, or basosquamous features, and suitable for treatment with Mohs. area >=0.5 cm2 and Ø <2.0 cm and could be located on an acceptable area of the body as determined by the investigator.	previous therapy to the target tumor or dermatologic conditions that could interfere with skin assessments.	Biopsy/pathologic confirmed	Visual assessment: use of tattoo in center of lesion	72/72/69

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
Tran 2012 22511036 (US)	Single center	Not reported	Caucasian, Fitzpatrick skin type I or II, 46-84 y/o. Superficial, nodular, multicentric BCCs, and SCCIS 0.4–3 cm	Morpheaform, infiltrating, and recurrent BCCs and invasive SCCs or lesions on the head and neck, hands, feet, and genital areas.	Biopsy/pathologic confirmed	Visual assessment	20/20/20
van der Geer 2012 22385074 (Netherlands)	Single center	No industry support	>18 y/0ears w/ nodular (or nodular and partially superficial) BCC 1–5 cm Ø in the face	pregnant women, women who were breastfeeding, recurrent BCC, aggressive growth pattern, pts w/ BCC w/in 1 cm from the eyes, lips or mucosa of the nose, another skin tumour w/in 5 cm of the target tumour, and allergy to imiquimod 5% cream or components of the cream	Biopsy/pathologic confirmed	Phtotgraphy and computer assesment	70/70/70
Wang 2001 11298545 (England)	Single center	Industry funded	histopathologically verified BCC suitable for PDT and cryosurgery, 20-90 y/o	pregnancy/lactation; severe malignancies; daily intake of vitamins E or C, b-carotene, iron preparations, non-steroidal anti-inflammatory agents or strong analgesics in higher than specified doses; BCC on the nose; morphoeic growth; porphyria; abdominal pain of unknown aetiology; photosensitivity;and treatment of the BCC with topical steroids type III or IV within the last month.	Biopsy/pathologic confirmed	Method of assessment not reported	88/88/83
Wettstein 2013 23566745 (Switzerland)	Single center	Industry supplied materials	diagnosed clinically or by biopsy w/ primary nodular BCC of the face presenting at the University Hospital Basel between June 2007 and February	patients under steroid medication or immunosuppressive therapy; patients with direct defect closure; pathological analysis revealed incomplete tumour resection or another BCC sub-type than solid/nodular	Biopsy/pathologic confirmed	Confocal assessment	32/23/23

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
			2008				
NRCS							
Ahmed 2000 11069453 (UK)	Multicenter	Not reported	clinical diagnosis of Bowen's Disease	Patients with recurrent lesions and those on immunosuppression	Biopsy/pathologic confirmed: biopsy-proven	Method of assessment not reported	73/67
Ballester-Sanchez 2016 26985197 (Spain)	Single center	Industry funded	adults, primary superficial or nodular BCC w/ T1 and T2 clinical stage	Ø >20 mm , depth >4 mm, or located on irregular surfaces	Biopsy/pathologic confirmed: histopathologic examination	Visual assessment: clinically aided by dermoscope	40/40
Chren 2013 23190903 (U.S.)	Multicenter	No industry support	consecutive patients with nonrecurrent NMSC diagnosed in 1999 and 2000 and treated in 2 sites, a university-affiliated private dermatology practice and the dermatology clinic at the nearby VA medical center affiliated with the university		Biopsy/pathologic confirmed: Biopsies were performed either by dermatology faculty members or by dermatology residents	Method of assessment not reported	1253/1174
Cosgarea 2012 22738399 (Romania)	Single center	No industry support	Men or women >18 y/o, clinically diagnosised primary BCC, superficial or nodular BCC, with a maximum 3 mm above the skin level	recurrent, pigmented or morpheaform lesions; use of phototoxic/photosensitive drugs, hypersensitivity to light or ALA cream, pregnant or breastfeeding women	Biopsy/pathologic confirmed: histologically confirmed	Method of assessment not reported	72/72
Graells 2014 24139468 (Spain)	Single center	Not reported	patients treated for their first BCC at the hospital between January 2003 and December 2011	patients followed for less than 3 months	Biopsy/pathologic confirmed: histologically confirmed BCCs	Method of assessment not reported	623/621
Lippert 2013 23725586 (Czech Republic)	Single center	No industry support	one confirmed nBCC, and there was one tested nBCC per person, Ø 20-30 mm	tumors in the middle portion of the face and areas adjacent to the eyes and ears	Biopsy/pathologic confirmed: Verified by biopsy sample from the peripheral portion of the tumor, which was	Other: thickness measured using high-resolution ultrasound	56/56

Author Year PMID (Country/Region)	Number of centers	Funding	Inclusion criteria*	Exclusion criteria*	Method of diagnosis	Preoperative tumor size assessment	N enrolled/ randomized/ analyzed
					as small as possible so that the area intended for the experiment was not reduced,		
Pampena 2016 26589877 (Italy)	Single center	No industry support	Histologically verified NMSC	lymphatic or visceral metastases	Biopsy/pathologic confirmed: histologically confirmed	Method of assessment not reported	385/385
Shah 2009 19588534 (U.S.)	Single center	No industry support	male patients w/ biopsy-proven BCCs on the trunk and extremities	Morpheaform, infiltrative, and recurrent BCCs	Biopsy/pathologic confirmed: biopsy-proven	Method of assessment not reported	32/32
Sofen 2015 25913533 (U.S.)	Multicenter	Industry funded	>=21 y/o, new, operable, biopsy-confirmed, nodular BCC and willing to delay excision		Biopsy/pathologic confirmed: biopsy-confirmed	Method of assessment not reported	74/49
Sullivan 2003 14725659 (US)	Single center	Not reported	biopsy confirmed superficial BCC, Ø 0.8-2.0 cm on the neck, trunk, or limbs.	recurrent or previously treated tumors or tumors located on the head	Biopsy/pathologic confirmed	Method of assessment not reported	12/12
Wilson 2012 22145798 (U.S.)	Multicenter	No industry support	NMSCs identified by daily review of pathology records and defined according to final histopathologic diagnosis of BCC or SCC.	No "recurrent" or "possibly recurrent" skin cancers	Biopsy/pathologic confirmed	Method of assessment not reported	1777/1777

*y/o = years old; w/ = with, Ø = diameter; LE = life expectancy; tx = treatment; mo = month; rt = radiation therapy

Appendix D. Baselines

Table D-1. Baselines

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
RCT							
Abbade 2015	Surgical excision	NR		NR		BCC: nodular (100)	head and neck (100)
Abbade 2015	MAL-PDT	NR		MR		BCC: nodular (100)	head and neck (100)
Al-Niaimi 2015 26157307	PDT + MMS	61.4 (NR); range (44, 84)	200 mm2; range (100-459)	66.7		BCC: nodular (100)	face (100)
Al-Niaimi 2015 26157307	MMS	62.7 (NR); range (41, 89)	201 mm2; range (120, 408)	40		BCC: nodular (100)	face (100)
Allen 1979 298425	cryotherapy	NR		NR		BCC: unspecified (100)	NR
Allen 1979 298425	radiotherapy	NR		NR		BCC: unspecified (100)	NR
Alpsoy 1996 8708151	IFN alfa-2a	58.7 (NR); range (48, 73)	median 2.05 cm2; range (0.5, 8.75)	53		BCC: superficial(14), nodular (79), morphealike (7)	eyelid (27), nose (13), zygoma (27), forehead (13), cheek (13), trunk (7)
Alpsoy 1996 8708151	IFN alfa-2b	63.6 (NR); range (38, 70)	median 1.82 cm2; range (0.6, 8.2)	53		BCC: superficial(7), nodular (86), morphealike (7)	eyelid (20), nose (7), zygoma (20), forehead (20), cheek (27), trunk (7)
Alpsoy 1996 8708151	IFN alfa-2a + IFN alfa-2b	60.3 (NR); range (39, 74)	median 1.9 cm2; range (0.5, 8.9)	40		BCC: superficial(7), nodular (79), morphealike (14)	eyelid (20), nose (13), zygoma (27), forehead (13), cheek (20), trunk (7)
Arits 2013 23683751	MAL-PDT	median 63; range (26, 87)		52		BCC: superficial (100)	head/neck excluding H-zone (12), extremities (29), trunk (59), upper extremities (16), lower extremities (13)
Arits 2013 23683751	Imiquimod	median 62; range (30, 91)		49		BCC: superficial (100)	head/neck excluding H-zone (12), extremities (27), trunk (61), upper extremities (13), lower extremities (14)
Arits 2013 23683751	Fluorouacil	median 64; range (35, 86)		47		BCC: superficial (100)	head/neck excluding H-zone (15), extremities (24), trunk (60), upper extremities (13), lower extremities (11)
Avril 1997 9218740	surgery	66.5 (12.6)	diameter: 11.1	54		BCC: superficial (21),	nose (53), cheek, pre- and

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
			mm (5.7)			ulcerated (30), nodular (45), sclerosing (4)	retroauricular areas (21), eyelids, internal and external eye angles (19), forehead, temple, between eyebrows 36 (21), chin, cutaneous superior lip 10 (6), ear (3)
Avril 1997 9218740	radiotherapy	65,4 (11.5)	diameter: 11.7 (5.7)	46		BCC: superficial (23), ulcerated (29), nodular (43), sclerosing (5)	nose (28), cheek, pre- and retroauricular areas (24), eyelids, internal and external eye angles (20), forehead, temple, between eyebrows (17), chin, cutaneous superior lip (7), ear (3)
Basset-Seguin 2008 18693158	MAL-PDT	62 (NR); range (25, 86)		33	I 5; II 57; III 33; IV 5	BCC: superficial (100)	face/scalp (6), extremities (22), trunk/neck (72)
Basset-Seguin 2008 18693158	Cryotherapy	64 (NR); range (38, 90)		47	I 5; II 63; III 30; IV 2	BCC: superficial (100)	face/scalp (4), extremities (20), trunk/neck (76)
Bath-Hextall 2014 24332516	Imiquimod	NR	diameter: median 12 mm (IQR 9, 16)	41	I 14; II 37; III 42; IV 6	BCC: superficial (52), nodular (48)	face (37), trunk (38), neck (6), arm (6), leg (10), other (3)
Bath-Hextall 2014 24332516	excision	NR	diameter: median 10 mm (IQR 8, 15)	40	I 13; II 46; III 35; IV 6	BCC: superficial (50), nodular (50)	face (33), trunk (39), neck (9), arm (7), leg (9), other (3)
Berroeta 2007 17573890	Total	median 72; range (50, 89)		NR		BCC: nodular (100)	NR
Beutner 1999 10570388	imiquimod 2x/day	range (37, 81)		NR		BCC: superficial (86), nodular (14)	upper exremity (57), anterior upper trunk (14), neck (29)
Beutner 1999 10570388	imiquimod 1x/day	range (37, 81)		NR		BCC: superficial (75), nodular (25)	upper extremity (50), anterior upper trunk (25), posterior upper trunk (25)
Beutner 1999 10570388	imiquimod 3x/week	range (37, 81)		NR		BCC: superficial (100)	upper extremity (25), anterior upper trunk (25), posterior upper trunk (25), neck (25)
Beutner 1999 10570388	imiquimod 2x/week	range (37, 81)		NR		BCC: superficial (60), nodular (40)	lower extremity (20), anterior upper trunk (40), posterior upper trunk (20), neck (20)

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
Beutner 1999 10570388	imiquimod 1x/week	range (37, 81)		NR		BCC: superficial (50), nodular (50)	lower extremity (50), anterior upper trunk (25), posterior upper trunk (25)
Beutner 1999 10570388	vehicle (3 2x/day, 2 1x/day, 2 3x/week, 2 2x/week, 2 1x/week)	range (37, 81)		NR		BCC: superficial (91), nodular (9)	face (9), upper extremity (46), anterior upper trunk (9), neck (9), posterior lower trunk (27)
Brinkhuizen 2016 27067393	Diclofenac (results superficial/nodular)	63.0/78.5 (NR); range (54, 82)	61.7/49.5 mm2; range (30.0, 84.4)	25		BCC: superficial (50), nodular (50)	extremities (47), trunk/neck (53)
Brinkhuizen 2016 27067393	Calcitriol (results superficial/nodular)	65.5/68.5 (NR); range (55, 75)	54.2/59.7 mm2; range (34.3, 87.6)	22		BCC: superficial (50), nodular (41); micronodular or mixed (9)	trunk/neck (59), genetalia (41)
Brinkhuizen 2016 27067393	Diclofenac + Calcitriol (results superficial/nodular)	67.5/71 (NR); range (60, 79)	46.7/44.8 mm2; range (33.0, 101.3)	37.5		BCC: superficial (50), nodular (50)	trunk/neck (50), genetalia (44)
Brinkhuizen 2016 27067393	No treatment (results superficial/nodular)	61.5/66 (NR); range (49, 73)	59.7/53.4 mm2; range (39.1, 98.4)	37.5		BCC: superficial (50), nodular (44), micronodular or mixed (6)	extremities (53), trunk/neck (47)
Butler 2009 19018814	Vehicle group+MOHs	75.3 (11.4); range (48, 93)	30.1mm2 (9.5); range (19.2, 50.4)	43.8		BCC: nodular (100)	face (100)
Butler 2009 19018814	imiquimod 5% Cream group+MOHs	73.3 (10.5); range (42, 85)	33.5 mm2 (12.8); range (14.1, 57.6)	66.7		BCC: nodular (100)	hands (100)
Cai 2015 25899562	ALA-PDT + CO2 Laser	NR	diameter: 2.62 cm (0.94)	50		SCC: Bowen's (100)	NR
Cai 2015 25899562	CO2 Laser	NR	diameter: 2.58 cm (0.86)	62.5		SCC: Bowen's (100)	NR
Carija 2016 27516420	ALA-PDT	Median 71 (range 55, 78)	255.4 mm2 (209.2)	13.3	II and III 100	BCC: superficial (79), nodular (21)	Trunk/neck (96), extremities (4)
Carija 2016	ALA-PDT +	Median 71	216 mm2 (154.3	13.3	II and III 100	BCC: superficial (82),	Trunk/neck (76.5),

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
27516420	PDL	(range 55, 78)				nodular (18)	extremities (23.5)
Choi 2016 26551044	Er:YAG ablative fractional laser-primed MAL- PDT	NR		55	III 15; IV 65; V 20	BCC: nodular (100)	NR
Choi 2016 26551044	MAL-PDT	NR		36.8	III 10.5; IV 74.7; V 15.8	BCC: nodular (100)	NR
Choi 2017 28199463	Er:YAG ablative fractional laser-primed MAL- PDT	76.4 (6.2)	Diameter 11.5 mm (3.8)	71.4	III: 28.6; IV 57.1; V: 14.3	SCC: moderately differentiated (81), poorly differentiated (19)	Face/scalp (76.2), extremities (19.0), trunk/neck (4.8)
Choi 2017 28199463	MAL-PDT	75.1 (6.2)	Diameter 11.8 mm (4.1)	54.6	III: 29.1, IV: 54.2, V: 16.7	SCC: moderately differentiated (75), poorly differentiated (25)	Face/scalp (75.0), extremities (16.7), trunk/neck (8.3)
Cornell 1990 2229497	interferon	56	83 mm2	19		BCC: superficial (46), noduloulcerative (54)	head and face (25), extermities (12), trunk/neck (63)
Cornell 1990 2229497	placebo	57	75 mm2	14		BCC: superficial (45), noduloulcerative (55)	head and face (17), extermities (14), trunk/neck (59)
Edwards 1990 2107219	interferon gamma, 0.01	range (37, 69)		NR		BCC: superficial (47), nodular (53)	NR
Edwards 1990 2107219	interferon gamma, 0.05	range (37, 69)		NR		BCC: superficial (57), nodular (43)	NR
Edwards 1990 2383027	Interferon alfa-2b, 30 million IU	range (35, 65)		NR		BCC: superficial (50), nodular (50)	NR
Edwards 1990 2383027	Interferon alfa-2b, 10 million IU	range (35, 65)		NR		BCC: superficial (50), nodular (50)	NR
Eigentler 2007 17610993	imiquimod 5% 8 weeks	median 65; range (38, 88)	diameter: 8.2 mm; median8.0 mm; range (4, 15)	27	II 51; III 44.4; IV 4.4	BCC: nodular (100)	face (24.4), scalp (2.2), ear (8.9), trunk/neck (4.4), perioral (4.4), periorbital (8.9), nose (42), arm/shoulder (4.4)

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
Eigentler 2007 17610993	imiquimod 5% 12 weeks	median 63; range (39, 79)	diameter: 9.6 mm; median 9.0; range (5, 15)	33	1 4.4;II 52.2; III 41.3; IV 2.2	BCC: nodular (100)	face (19.6), scalp (2.2), ear (10.9), trunk/neck (8.7), perioral (2.2), periorbital (6.5), nose (37), arm/shoulder (4.4), leg/hip (4.3)
Eimpunth 2014	Total	range (29, 88)		33		BCC: unspecified (100)	NR
Foley 2009 20064185	methyl-aminolevulinatePDT	66 (NR); range (28, 88)	diameter: 8.8 mm; range (6, 20)	28.78	I 41; II 39; III-IV 20	BCC: nodular (100)	face/scalp (25), extremities (20), Trunk 32 (43%) Neck 9 (12%)
Foley 2009 20064185	placebo PDT	67 (NR); range (39, 88)	diameter: 9.0 mm; range (6, 22)	20	I 29; II 43; III-IV 28	BCC: nodular (100)	face/scalp (31), extremities (23), Trunk 34 (45%) Neck 1(1%)
Garcia-Martin 2011 21242584	imiquimod 5%	73.13 (NR); range (53, 84)	diameter: 7.6 mm; range (2-12)	33.3		BCC: unspecified (100)	eyelid (100)
Garcia-Martin 2011 21242584	radiotherapy	74.18 (NR); range (65, 83)	diameter: 7.41 mm; range (4-12)	41.7		BCC: unspecified (100)	eyelid (100)
Geisse 2002 12196749	Imiquimod 3x/wk	62 (NR); range (36, 85)	median 1.0 cm2	NR		BCC: superficial (100)	neck/face/forehead (4), upper extremity (not hand) (15), trunk (73), lower extremity/thigh (not foot) (8)
Geisse 2002 12196749	Imiquimod 5x/wk	55 (NR); range (38, 84)	median 0.6 cm2	NR		BCC: superficial (100)	neck/face/forehead (3), upper extremity (not hand) (31), trunk (55), lower extremity/thigh (not foot) (10)
Geisse 2002 12196749	Imiquimod 1x/day	56 (NR); range (35, 85)	median 0.7 cm2	NR		BCC: superficial (100)	neck/face/forehead (7), upper extremity (not hand) (21), trunk (64), lower extremity/thigh (not foot) (7)
Geisse 2002 12196749	Imiquimod 2x/day	69 (NR); range (51, 85)	median 1.0 cm2	NR		BCC: superficial (100)	neck/face/forehead (8), upper extremity (not hand) (54), trunk (31), lower extremity/thigh (not foot) (8)
Geisse 2002 12196749	vehicle (control)	58 (NR); range (38, 85)	median 0.8 cm2	NR		BCC: superficial (100)	neck/face/forehead (9), upper extremity (not hand)

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
							(34), trunk (47), lower extremity/thigh (not foot) (9)
Geisse 2004 15097956	Imiquimod 5x/wk	58.4 (13.1), median 59; range (31, 89)		37	I 15; II 54; III 26; IV 5	BCC: unspecified (100)	neck (4), trunk: anterior lower (1), trunk: anterior upper (17), trunk: posterior lower (7), trunk: posterior upper (24), lower extremity (excluding foot) (15), upper extremity (excluding hand) (31), chin (1), forehead (1)
Geisse 2004 15097956	Vehicle 5x/wk or 7x/wk	58.7 (12.4); range (32, 85)		38	I 19; II 43; III 32; IV 5	BCC: unspecified (100)	neck (1), trunk: anterior lower (1), trunk: anterior upper (20), trunk: posterior lower (6), trunk: posterior upper (20), lower extremity (excluding foot) (10.5), upper extremity (excluding hand) (39), cheek (1), chin (1), forehead (1)
Geisse 2004 15097956	Imiquimod 7x/wk	59.4 (12.27); median 58; range (29, 88)		41	I 16; II 46; III 34; IV 4	BCC: unspecified (100)	neck (5), trunk: anterior lower 3, trunk: anterior upper (13), trunk: posterior lower (8), trunk: posterior upper (26), lower extremity (excluding foot) (11), upper extremity (excluding hand) (33), cheek (1), chin (1), forehead (1) Face: nose 1 (1%)
Haak 2015 24903544	MAL PDT	NR	diameter: median 8.5 mm (IQR 6, 10.5)	37.5	I ; II 56; III 44	BCC: nodular (100)	nose (37), forehead (31), cheek (6), oral area (13), periorbital area (13)
Haak 2015 24903544	AFXL MAL PDT	NR	diameter: median 7 mm (IQR 6, 8)	68.8	I ; II 69; III 31	BCC: nodular (100)	nose (56), forehead (19), cheek (13), oral area (6), periorbital area (6)
Hall 1986 3514075	Radiotherapy		diameter: 19 <1 cm, 25 1-2 cm, 5	NR		BCC: unspecified (100)	face and neck (82), eyelid (6), trunk (12)

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
			>2 cm				
Hall 1986 3514075	Cryotherapy		diameter: 19 <1 cm, 23 1-2 cm, 2 >2 cm	NR		BCC: unspecified (100)	face and neck (65), eyelid (17), trunk (17)
Ko 2014 24102369	Er:YAG AFL PDT	68.9 (13.2)		52.4	III 9.5; IV 71.4; V 19.1	SCC: Bowen's (100)	extremities (100)
Ko 2014 24102369	MAL-PDT	68.9 (13.2)		52.4	III 9.5; IV 71.4; V 19.1	SCC: Bowen's (100)	extremities (100)
Kuijpers 2006 16865869	ALA-PDT (total)	68.4 (NR); median 73; range (39, 87)	diameter: 8.1 mm (4.12)	34.9		BCC: nodular (100)	forehead/temple+nose/paranasal (36.4), cheek/chin/lips (9.1), ears (9.1), extremities (9.1), trunk/neck (36.4)
Kuijpers 2006 16865869	MAL-PDT (total)	68.4 (NR); median 73; range (39, 87)	diameter: 8.4 (3.28)	34.9		BCC: nodular (100)	forehead/temple+nose/paranasal (38.1), cheek/chin/lips (4.8), ears (14.3), extremities (4.8), trunk/neck (38.1)
Kuijpers 2006 16865869	ALA-PDT (debulking subgroup)	68.4 (NR); median 73; range (39, 87)		34.9		BCC: nodular (100)	NR
Kuijpers 2006 16865869	ALA-PDT (no debulking subgroup)	68.4 (NR); median 73; range (39, 87)		34.9		BCC: nodular (100)	NR
Kuijpers 2006 16865869	MAL-PDT (debulking subgroup)	68.4 (NR); median 73; range (39, 87)		34.9		BCC: nodular (100)	NR
Kuijpers 2006 16865869	MAL-PDT (no debulking subgroup)	68.4 (NR); median 73; range (39, 87)		34.9		BCC: nodular (100)	NR
Kuijpers 2007 17451581	Curettage + Cryosurgery	67 (NR); range (34, 92)	diameter: 5.4 mm (2.9)	43		BCC: nodular (100)	Forehead/temple, Cheek/chin, Periocular (80), Lips/mouth (4), Ears/periauricular (8), Neck, chest/back (8)
Kuijpers 2007 17451581	Surgical excision	67 (NR); range (34, 92)	diameter: 5.3 mm (2.6)	43		BCC: superficial (8), nodular (92)	Forehead/temple, Cheek/chin, Periocular (76), Lips/mouth (6),

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
							Ears/periauricular (6), Neck, chest/back (12)
Marks 2001 11312429	Total	61 (NR); range (23, 83)	range (0.5, 2 cm2)	27	II 46; III 32	BCC: superficial (98); nodular (1); follicular (1)	Upper extremities (32), upper trunk (28), head/neck/lower limbs (40)
Migden 2015 25981810	sonidegib 200	median 67; range (25, 92)		39		BCC: advanced (91), metastatic (9)	head and neck (100)
Migden 2015 25981810	sonidegib 800	median 65; range (24, 93)		36		BCC: advanced (71), metastatic (29)	head and neck (100)
Miller 1997 8996264	Total	61 (NR); range (29, 86)	80 mm2; range 18, 225	20		BCC: superficial (31), nodular (69)	head (7), extremities (40), trunk/neck (52)
Morton 1996 8977678	cryotherapy	76 (NR); range (62, 88)	82 mm2; range (30, 360)	84		SCC: Bowen's (100)	hands (5), face (15), legs (80)
Morton 1996 8977678	photodynamic	76 (NR); range (62, 88)	150 mm2; range (25, 441)	84		SCC: Bowen's (100)	hands (5), face (10), legs (85)
Morton 2006 16785375	MAL PDT	71.9 (NR); range (43, 89)	diameter: 18.9 mm; range (5, 40mm)	62	I 10; II 47; III 38; IV 5	SCC: Bowen's (100)	face/scalp (23), extremities (65), trunk/neck (12)
Morton 2006 16785375	PDT placebo	73.4 (NR); range (53, 88)	diameter: 19.3 mm; range (8, 40mm)	65	I 24; II 53; III 18; IV 6	SCC: Bowen's (100)	face/scalp (25), extremities (67), trunk/neck (8)
Morton 2006 16785375	Cryotherapy	74.0 (NR); range (45, 99)	diameter: 19.4 mm; range (6, 45mm)	59	I 4; II 49; III 39; IV 9	SCC: Bowen's (100)	face/scalp (29), extremities (57), trunk/neck (14)
Morton 2006 16785375	Fluorouracil	72.5 (NR); range (39, 86)	diameter: 20.9 mm; range (9, 37mm)	63	I 20; II 37; III 40; IV 3	SCC: Bowen's (100)	face/scalp (19), extremities (69), trunk/neck (11)
Mosterd 2008 18717680	ALA-PDT	64.0 (NR); range (24, 83)	diameter: 8.9 mm (4.0 mm); median(IQR) range ()	48.2		BCC: nodular (100)	face (53); "rest of the body" (47%)
Mosterd 2008 18717680	Surgical excision	65.1 (NR); range (21, 91)	diameter: 9.3 mm (4.3 mm); median(IQR) range ()	50		BCC: nodular (100)	face (51); "rest of the body" (49%)
Mosterd 2008 19010733	MMS	67.4 (12.7)	1.28 cm2 (1.36); diameter: 13.76 mm (6.43)	39.7		BCC: unspecified (100), 51.5% aggressive	frontal/temporal (26), cheek/chin (9), (peri)nasal (34), lips/perioral (7), periocular (8), ears (4), periauricular (12)

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
Mosterd 2008 19010733	Surgical excision	68.7 (12.2)	1.77 cm2 (1.28); diameter: 15.97 mm (8.17)	38.2		BCC: unspecified (100), 43.1% aggressive	frontal/temporal (32), cheek/chin (8), (peri)nasal (30), lips/perioral (4), periocular (8), ears (8), periauricular (10)
Orenberg 1992 1430394	7.5 mg 5-FU	60 (NR); range (22, 78)	123.9 mm2	5		BCC: nodular (100)	face (30), extemities (30), trunk/neck (40)
Orenberg 1992 1430394	15 mg 5-FU	60 (NR); range (22, 78)	76.4 mm2	5		BCC: nodular (100)	face (10), scalp (10), lip (10), ear (30), extemities (10), trunk/neck (30)
Patel 2006 16713457	imiquimod 5%	74 (8); range (54, 83)	429 mm2 (489); range (23, 1776)	40		SCC: Bowen's (100)	NR
Patel 2006 16713457	vehicle	74 (8); range (60, 86)	248 mm2 (166); range (84, 555)	87.5		SCC: Bowen's (100)	NR
Rhodes 2004 14732655	MAL PDT	69 (NR); range (40, 95)		38	I 8; II 50; III 40; IV 2	BCC: nodular (100)	face/scalp (40), extremities (11), trunk/neck (49)
Rhodes 2004 14732655	excision	67 (NR); range (38, 82)		41	I 8; II 43; III 43; IV 6	BCC: nodular (100)	face/scalp (58), extremities (9), trunk/neck (29)
Salim 2003 12653747	PDT	76 (NR); range (65, 88)		80		SCC: Bowen's (100)	extremities (100)
Salim 2003 12653747	5-FU	76 (NR); range (65, 88)		80		SCC: Bowen's (100)	face (12), extremities (88)
Salmanpoor 2012	Surgical excision	57.3 (NR); range (21, 84)		37		BCC: unspecified (100)	face and scalp (100)
Salmanpoor 2012	Curettage	57.3 (NR); range (21, 84)		37		BCC: unspecified (100)	face and scalp (100)
Salmanpoor 2012	Electodessication and curettage	57.3 (NR); range (21, 84)		37		BCC: unspecified (100)	face and scalp (100)
Schleier 2007 25047438	ALA-thermogel PDT	69.9 (NR); range (42, 96)		46.15		BCC: superficial (100)	face (54.17), scalp (20.83), lip (2.78), eyelid (1.39), extremities (9.72), trunk/neck (11.11)
Schleier 2007 25047438	mALA-thermogel PDT	71.8 (NR); range (49, 88)		36.36		BCC: superficial (100)	face (52.5), scalp (30), extremities (5), trunk/neck (12.5)
Schulze 2005 15888150	imiquimod 5%	64.3 (13.06); median 67; range (25, 83)		39	I 5; II 48; III 42; IV 5; V 1	BCC: superficial (100)	cheek (1), forehead (0), extremities (including hand) (20), trunk/neck

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
							(70)
Schulze 2005 15888150	vehicle	64.5 (11.43); median 68; range (31, 86)		39	I 1; II 46; III 41; IV 10; V 1	BCC: superficial (100)	cheek (1), forehead (5), scalp (1), extremities (including hand) (30), trunk/neck (61)
Shumack 2002 12224978 (12 weeks)	vehicle cream	NR	median 0.8 cm2	42		BCC: nodular (100)	face (17), trunk/neck (54.2), upper extremity (not hand) (25), lower extremity (not foot) (4)
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week	NR	median 0.8 cm2	75		BCC: nodular (100)	face (25), trunk/neck (75)
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Once daily for 7 days per week	NR	median 0.7 cm2	10		BCC: nodular (100)	face (29), trunk/neck (33), upper extremity (not hand) (19), lower extremity (not foot) (10)
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Once daily for 5 days per week	NR	median 0.7 cm2	35		BCC: nodular (100)	face (48), trunk/neck (26), Upper extremity (not hand) (17), lower extremity (not foot) (9)
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Once daily for 3 days per week	NR	median 0.7 cm2	30		BCC: nodular (100)	face (40), trunk/neck (35), upper extremity (not hand) (20), lower extremity (not foot) (5)
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week	NR	median 0.6 cm2	0		BCC: nodular (100)	face (100)
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5%	63 (41.1)	median 0.8 cm2	13		BCC: nodular (100)	face (28), trunk/neck (11.11), Upper extremity

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
	cream - Once daily for 3 days per week						(not hand) (25), lower extremity (not foot) (13)
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week	69 (11.2)	median 0.8 cm2	13		BCC: nodular (100)	face (32), trunk/neck (39), Upper extremity (not hand) (26), lower extremity (not foot) (3)
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Once daily for 7 days per week	66 (12.4)	median 0.8 cm2	29		BCC: nodular (100)	face (11), trunk/neck (48), Upper extremity (not hand) (26), lower extremity (not foot) (3)
Siller 2010 20546215	total	59 (NR); range (34, 86)	diameter: 9 mm; range (4, 15mm)	27		BCC: superficial (100)	NR
Spencer 2006 16393600	imiquimod 5%	NR		40		BCC: nodular (100)	face (60), ear (10), unspecified other (30)
Spencer 2006 16393600	vehicle	NR		10		BCC: nodular (100)	face (50), ear (20), unspecified other (30)
Sterry 2002 12452875 (nodular)	Imiquimod (2 days/week) with occlusion	66 (13.2); NR	median: 0.6 cm2	50		BCC: nodular (100)	Face (10), Scalp (1), extremities (2), trunk/neck (9)
Sterry 2002 12452875 (nodular)	Imiquimod (3 days/week) with occlusion	66 (14.6); NR	median: 0.7 cm2	30		BCC: nodular (100)	Face (18), extremities (2), trunk/neck (3)
Sterry 2002 12452875 (nodular)	Imiquimod (2 days/week) without occlusion	67 (8.9); NR	median: 1.0 cm2	24		BCC: nodular (100)	Face (9), extremities (1), trunk/neck (10)
Sterry 2002 12452875 (nodular)	Imiquimod (3 days/week) without occlusion	66 (13.2); NR	median: 0.6 cm2	46		BCC: nodular (100)	Face (11), extremities (5), trunk/neck (8)
Sterry 2002 12452875 (superficial)	Imiquimod (2 days/week) with occlusion						

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
Sterry 2002 12452875 (superficial)	Imiquimod (3 days/week) with occlusion						
Sterry 2002 12452875 (superficial)	Imiquimod (2 days/week) without occlusion						
Sterry 2002 12452875 (superficial)	Imiquimod (3 days/week) without occlusion						
Szeimies 2008 18624836	MAL-PDT	64.5 (12.7); range (33, 85)	diameter: 12.5 mm (3.7)	36.0		BCC: superficial (100)	face/scalp (11.1), extremities (28.9), trunk/neck (60)
Szeimies 2008 18624836	excision	63.1 (13.9); range (31, 92)	diameter: 12.6 mm (3.7)	31.3		BCC: superficial (100)	face/scalp (4.5) , extremities (25.0), trunk/neck (70.5)
Thissen 2000 10940063	cryotherapy	NR		NR		BCC: superficial (17), nodular (83)	face (46), eyelid (4), ear (4), trunk/neck (6), forehead/temple (34), chin/perioral (6)
Thissen 2000 10940063	surgical excision	NR		NR		BCC: superficial (12), nodular (88)	face (43), eyelid (8), trunk/neck (14), forehead/temple (25), chin/perioral (10)
Torres 2004 15606733	imiquimod, 2 weeks	NR	median 0.9 cm2 (IQR 0.2, 2.0)	33.3		BCC: superficial (42), nodular (58)	NR
Torres 2004 15606733	imiquimod, 4 weeks	NR	median 0.8 cm2 (IQR 0.5, 1.3)	41.7		BCC: superficial (33), nodular (67)	NR
Torres 2004 15606733	imiquimod, 6 weeks	NR	median 1.2 cm2 (IQR 0.5, 2.7)	33.3		BCC: superficial (17), nodular (83)	NR
Torres 2004 15606733	vehicle controlled-pooled	NR	median 1.2 cm2 (IQR 0.5, 2.7)	19.4		BCC: superficial (33), nodular (67)	NR
Tran 2012 22511036	S1: PDL 15 j/cm2	NR	88 mm2 (SE 12.1)	57	I and II 100%	BCC: superficial (12.5), nodular (62.5), multifocal (12.5); SCC: in situ (12.5)	extremities (12), trunk/neck (88)
Tran 2012 22511036	S2: PDL 7.5 j/cm2	NR	105 mm2 (SE 23.6)	43	I and II 100%	BCC: nodular (50), multifocal (27.5); SCC: in situ (12.5)	extremities (50), trunk/neck (50)
Tran 2012 22511036	No treatment	NR	94 mm2 (SE 15.2)	43	I and II 100%	BCC: nodular (57), multifocal (29); SCC: in	extremities (43), trunk/neck (57)

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
						situ (16)	
van der Geer 2012 22385074	Imiquimod + Mohs	69 (NR); range (95%CI 65, 73)		37	1 29;II 66	BCC: nodular (100)	H-zone (57), nose (23), ear 4 (11), scalp + frontal (23), other regions (cheek, temporal, chin) (43)
van der Geer 2012 22385074	no treatment + Mohs	68 (NR); range (95%CI 64, 72)	median 110 mm2 (IQR 80, 160)	31	1 26;II 66	BCC: nodular (100)	H-zone (66), nose (26), ear (17), scalp + frontal (14), other regions (cheek, temporal, chin) (43)
Wang 2001 11298545	Total	range (42, 88)		50		BCC: superficial and nodular	legs (11), arms (7), trunk (54), head/neck (28)
Wettstein 2013 23566745	Ringer's lactate (control group)	59 (NR); range (34, 86)	2.5 cm2 (1.72)	26.67		BCC: nodular (100)	nose (46.2), cheek (23.1), frontal (7.7), ear (23.1)
Wettstein 2013 23566745	interferon alpha-2b	59 (NR); range (34, 86)	3.1 cm2 (2.51)	26.67		BCC: nodular (100)	nose (50), cheek (10), frontal (20), ear (20)
NRCS							
Ahmed 2000 11069453	Curettage	74; 46, 89	336 mm2; 30-1890	82		SCC: Bowen's (100)	extremities (38), trunk (2), head/neck (4)
Ahmed 2000 11069453	Cryotherapy	74; 46, 89	336 mm2; 30-1890	82		SCC: Bowen's (100)	extremities (29), trunk (4), head/neck (3)
Ballester-Sanchez 2016 26985197	brachytherapy 36.6 Gy	70 (3); NR	diameter: 11.54 (0.96)	50	II: 9 (45%), III: 11 (55%)	BCC: superficial/multicentric (50%), BCC: nodular (50%)	head/neck (15), trunk/extremities (5)
Ballester-Sanchez 2016 26985197	brachytherapy 42 Gy	79 (2); NR	diameter: 12.2 (0.68)	40	II: 10 (50%), III: 10 (50%)	BCC: superficial/multicentric (40%), BCC: nodular (60%)	head/neck (15), trunk/extremities (5)
Chren 2013 23190903	electrodessication and curettage	NR	diameter: 9.0 mm (5.6)	21	I or II: 97 (41.1)	BCC: unspecified (83), SCC: unspecified (17)	H-Zone of face (10.7); other (unspecified) (89.3)
Chren 2013 23190904	excision	NR	diameter: 9.5 mm (6.1)	21	I or II: 180 (38.2)	BCC: unspecified (69), SCC: unspecified (31)	H-Zone of face (25.9); other (unspecified) (74.1)
Chren 2013 23190905	Mohs	NR	diameter: 7.8 mm (4.4)	33	I or II: 196 (42)	BCC: unspecified (77), SCC: unspecified (23)	H-Zone of face (64.6); other (unspecified) (35.4)
Cosgarea 2012 22738399	ALA PDT	65; 51, 85		47	I: 3, II: 21, III: 12, IV: 1	BCC: superficial/multicentric (64.5%), BCC: nodular	NR

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
						(35.5%)	
Cosgarea 2012 22738399	surgical excision	66; 49, 90		47.5	I: 3, II: 19, III: 13, IV: 1	BCC: superficial/multicentric (63%), BCC: nodular (37%)	face/scalp (21), extremities (3), trunk/neck (24)
Graells 2014 24139468	Imiquimod	NR		50.7		BCC: superficial(60), nodular (2), Infiltrative/micronodular/ morphea form/sclerosing (38)	exremities (7.14), trunk/neck (92.86)
Graells 2014 24139468	Surgery	NR		43.27		BCC: superficial(17), nodular (32), Infiltrative/micronodular/ morphea form/sclerosing (51)	exremities (5.64), trunk/neck (94.37)
Lippert 2013 23725586	Total	61.9 (NR); NR		43		BCC: nodular (100)	49 head (not H-zone or adjacent to the eyes or ears) cheeks, or neck; 7 other parts of the body
Pampena 2016 26589877	3675 cGy	81.3 (8.7)		45.8		BCC: unspecified (66), SCC: unspecified (34)	exremities (8.9), trunk (2.1), head/neck (89)
Pampena 2016 26589878	4500 cGy	73.3 (10.2)		35.6		BCC: unspecified (80.5), SCC: unspecified (19.5)	exremities (5.4), trunk (5.4), head/neck (89.2)
Shah 2009 19588534	Pulse dye laser	NR		NR		BCC: superficial/multicentric (43%), BCC: nodular (47.5%), BCC: infiltrative/micronodular/ morpheaform/sclerosing (9.5%)	extremities (2), trunk/neck (19)
Shah 2009 19588534	no treatment	NR		NR		BCC: superficial and nodular	NR
Sofen 2015 25913533	vismodegib 12 weeks	60.5 (11.2); 43, 81	diameter: median: 1.2 cm; range: 1-3	21		BCC: nodular (100)	Scalp/head/neck and cape area (100%)
Sofen 2015 25913533	vismodegib 12 weeks + 24 weeks observation	65.2 (13.3); 40, 86	diameter: median: 1.5; range: 1-2	12		BCC: nodular (100)	Scalp/head/neck and trunk/limbs (100%)

Author Year PMID	Arm	Age, mean (SD); range	Lesion area, mean (SD); range	Female, %	Fitzpatrick score %	Lesion type (%)	Lesion location (%)
Sofen 2015 25913533	vismodegib 16 weeks	65.1 (11.8); 47, 89	diameter: median: 1.2; range: 1-3	32		BCC: nodular (100)	Scalp/head/neck and trunk/limbs (100%)
Sullivan 2003 14725659	imiquimod 5%	63; 57, 78	diameter: 9.5 mm	33		BCC: superficial (100)	Trunk/neck (4), forearm (2)
Sullivan 2003 14725659	vehicle	59; 52, 62	diameter: 7.5 mm	33		BCC: superficial (100)	Trunk/neck (4), forearm (2)

Appendix E. Arm Details

Table E-1. Arm details

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
RCTs									
Abbade 2015	Surgical excision	excision (4 mm)							
Abbade 2015	MAL-PDT				630nm	2 sessions in 1 week, MAL, "previously the lesions were shaved"			
Al-Niaimi 2015 26157307	PDT + MMS	Mohs 2-10 weeks following PDT treatment			non-coherent red light/average wavelength 631 nm at 70-100 mW/cm2 to 37 J/cm2	2 sessions 1 week apart to 74 J/cm2, 160 mg/g MAL, preparing the site with topical acetone and light abrasion with curettage			
Al-Niaimi 2015 26157307	MMS	Mohs within 3 months of the baseline screening visit							
Allen 1979 298425	cryotherapy		Cryotherapy (liquid nitrogen spray from the Brymil cryospray)						
Allen 1979 298425	radiotherapy			Photons (gamma or x), 9 times a week for one month					
Alpsoy 1996 8708151	IFN alfa-2a						IFN alfa-2a (Intralesional) 3 times/weekly (total 10 injections)	1.5 megaunits of intralesional IFN if the lesion was less than 2 cm2, 3 megaunits, if	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								greater than 2 cm2	
Alpsoy 1996 8708151	IFN alfa-2b						IFN alfa-2b (Intralesional) 3 times/weekly (total 10 injections)	1.5 megaunits of intralesional IFN if the lesion was less than 2 cm2, 3 megaunits, if greater than 2 cm2	
Alpsoy 1996 8708151	IFN alfa-2a + IFN alfa-2b						IFN alfa-2a and 2b (injected alternately) (Intralesional) 3 times/weekly (total 10 injections)	1.5 megaunits of intralesional IFN if the lesion was less than 2 cm2, 3 megaunits, if greater than 2 cm2	
Arits 2013 23683751	MAL-PDT				LED 630 nm for 7 min at to 37 J/cm2, total dose 74 J/cm2	2 sessions 1 week apart, 16% MAL, non-traumatic surface preparation			
Arits 2013 23683751	Imiquimod						Imiquimod 5% (Topical) daily 5 days/week for 6 weeks	apply in a thin layer to the tumour including 5–10 mm of the surrounding skin with no occlusive dressing applied. Patients were advised to apply the cream at least 1 h before going to bed and to wipe it off after 8 h.	
Arits 2013	Fluorouacil						Fluorouacil 5%	apply in a thin	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
23683751							(Topical) twice daily (morning and evening) for 4 weeks	layer to the tumour including 5–10 mm of the surrounding skin, with no occusive dressing applied. Patients were advised to wipe off the remnants before applying a new layer. There was no time limit on how long the cream was to remain applied	
Avril 1997 9218740	surgery	Frozen section (2 mm)							
Avril 1997 9218740	radiotherapy			Photons (gamma or x) for Interstitial brachythera py (65-70 Gy delivered at the reference isodose, according to the Paris dosimetry method, over 5-7 days) or Superficial contacthera					

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
				py (for BCC < 2mm, 2 sessions, each delivering 18-20 Gy with a 2-week interval) or Conventional radiotherapy (2-4 Gy, 3-4 times per week, up to a total dose of 60 Gy)					
Basset-Seguin 2008 18693158	MAL-PDT				(Curelight®; PhotoCure ASA, Oslo Nor-way)/570-670 nm to 75 J/cm	standard was one session; crust). Lesions with non-complete response were treated again with two MAL PDT sessions 7 days apart apart to *depends on number of sessions. , 160 mg/g MAL, the lesions were prepared by slight surface debridement using a curette or scalpel blade to facilitate access of the cream and light. Lesion preparation was			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						always very superficial and insufficient to cause pain.A 1 mm layer of MAL cream was applied to each lesion and 5 mm of surrounding tissue, and then covered with an adhesive occlusive dressing for 3 hours. The dressings were then removed and the cream washed off with 0.9% saline solution before illumination			
Basset-Seguin 2008 18693158	Cryotherapy (2 freeze thaw cycles)		Cryotherapy (Cryotherapy was performed using a hand-held liquid nitrogen spray and a double freeze-thaw cycle. After an initial ice field forma- tion with a 3 mm rim of clinically healthy tissue, the ice field was maintained for up to 20 seconds. The procedure was						

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
			repeated after a thaw of 2-3 times the freeze duration. Lesions with non-complete response or repeat double freeze-thaw cryo- therapy and then evaluated 3 months later; 2 passes)						
Bath-Hextall 2014 24332516	Imiquimod						Imiquimod 5% (Topical) once daily for 6 (superficial - clinically diagnosed) or 12 (nodular) weeks	before bed	
Bath-Hextall 2014 24332516	excision	excsision (4 mm)							
Berroeta 2007 17573890	PDT	excision (4-5 mm)			630 nm to 125 mW cm^-2	20%; > 50 mg cm^-2 ALA, gentle superficial curettage, 5-aminolaevulinic acid fir 6 h under occlusion			
Berroeta 2007 17573890	excision								
Beutner 1999 10570388	imiquimod 2x/day						imiquimod 5% (Topical) twice daily for 10 weeks (median)		
Beutner	imiquimod						imiquimod 5%		

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
1999 10570388	1x/day						(Topical) once daily for 13 weeks (median)		
Beutner 1999 10570388	imiquimod 3x/week						imiquimod 5% (Topical) three times weekly for 14.5 weeks (median)		
Beutner 1999 10570388	imiquimod 2x/week						imiquimod 5% (Topical) twice weekly for 16 weeks (median)		
Beutner 1999 10570388	imiquimod 1x/week						imiquimod 5% (Topical) once weekly for 16 weeks (median)		
Beutner 1999 10570388	vehicle (3 2x/day, 2 1x/day, 2 3x/week, 2 2x/week, 2 1x/week)						vehicle cream 5% (Topical) 3 2x/day, 2 1x/day, 2 3x/week, 2 2x/week, 2 1x/week for 16 weeks (median)		
Brinkhuizen 2016 27067393	Diclofenac						diclofenac sodium 3% gel in hyaluronic acid 2.5% (Topical) twice daily for 8 weeks		
Brinkhuizen 2016 27067393	Calcitriol						Calcitriol 3 u?g/g (Topical) twice daily for 8 weeks		
Brinkhuizen 2016 27067393	Diclofenac + Calcitriol						diclofenac sodium + Calcitriol 3% gel in hyaluronic acid 2.5% + 3 ?ug/g (Topical) twice daily for 8 weeks	diclofenac gel application was followed by calcitriol ointment with a 2-minute interval	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
Brinkhuizen 2016 27067393	No treatment								
Butler 2009 19018814	Vehicle group+MOHs	Mohs					Vehicle (Topical) nightly for 6 weeks		
Butler 2009 19018814	imiquimod 5% Cream group+MOHs	Mohs					Imiquimod (Topical) nightly for 6 weeks		
Cai 2015 25899562	ALA-PDT + CO2 Laser		CO2 Laser Therapy without curettage (vaporization under local anesthesia, power ranging between 2 and 3 W. lesions vaporized to the leveled of the papillary dermis in nonhairy areas and to the level fo the midreticular dermis in hairy areas. during process vaporized tissues were erased with a cotton swab soaked with broogeramine to expose the fresh wound.)		red light from laser radiation source (qishi Laser institute)/630 nm to 180 j/cm^2	1-3 treatment sessions one week intervals apart, 20% ALA, vaporization under local anesthesia, power ranging between 2 and 3 W. lesions vaporized to the leveled of the papillary dermis in nonhairy areas and to the level fo the midreticular dermis in hairy areas. during process vaporized tissues were erased with a cotton swab soaked with broogeramine to expose the fresh wound; ala hydrochloride applied to lesion and surrounding area (0 to 4 mm away from margin). lesion			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						sites maintained under occlusion for 5h using and occlusive and light shielding dressing. After occlusion, dressing removed and ALA washed of with 0.9% saline solution. depending on response of pts, treatments done 1, 2, 3 times (separated by weekly intervals)			
Cai 2015 25899562	CO2 Laser		CO2 Laser Therapy without curettage (vaporization under local anesthesia, power ranging between 2 and 3 W. lesions vaporized to the leveled of the papillary dermis in nonhairy areas and to the level fo the midreticular dermis in hairy areas. during process vaporized tissues were erased with a cotton swab soaked with						

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
			broogeramine to expose the fresh wound.) depending on response of pts, treatments done 1, 2, 3 times (separated by weekly intervals)						
Carija 2016 27516420	PDT-ALA				150 J/cm2	1 session 3-5 minutes, 20% ALA, surface crusts removed and abraded			
Carija 2016 27516420	PDT-ALA + PDL				150 J/cm2	1 session 3-5 minutes, 20% ALA, surface crusts removed and abraded; Pulsed dye laser, three passes			
Choi 2016 26551044	Er:YAG ablative fractional laser-primed MAL- PDT				Aktilite CL128/ 632nm to 37 J/m^2	1 session, 16% MAL, lesions were then cleansed with saline gauze, and a lidocaine–prilocaine 5% cream (EMLA; Astra Pharmaceuticals, LP, Westborough, MA, USA) was applied to the treatment area for 30 min under occlusion. After the anaesthetic cream was			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						removed, AFL was performed using a 2940 nm Er:YAG AFL (Joule; Sciton Inc., Palo Alto, CA, USA) with a 550 lm ablation depth, level one coagulation, 22% treatment density and a single pulse. Immediately after AFL, a 1 mm thick layer of methyl aminolevulinate (16% Metvix cream; PhotoCure ASA, Oslo, Norway) was applied to the lesion and to 5 mm of the surrounding healthy tissue. The area was covered with an occlusive dressing (Tegaderm; 3M Co., Saint Paul, MN, USA) for 3 h, after which the remaining cream was removed with saline gauze.			
Choi 2016 26551044	MAL-PDT				Aktilite CL128/ 632 nm to 37 J/cm^2	2 sessions 7 days apart, 16% MAL, 1 mm thick layer of methyl			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						aminolevulinate (16% Metvix cream; PhotoCure ASA, Oslo, Norway) was applied to the lesion and to 5 mm of the surrounding healthy tissue. The area was covered with an occlusive dressing (Tega-derm; 3M Co., Saint Paul, MN, USA) for 3 h, after which the remaining cream was removed with saline gauze.			
Choi 2017 28199463	Er:YAG ablative fractional laser-primed MAL- PDT				37 J/cm2	1 session, 17% MAL; Aktilite CL128; 632nm; pretreatment with 2940-nm Er:YAG AFL			
Choi 2017 28199463	MAL-PDT				74 J/cm2	2 sessions 7 days apart, 17% MAL; Aktilite CL128; 632nm			
Cornell 1990 2229497	interferon						interferon alfa-2b 1.5 million IU (Intralesional) 3 times per week for 3 weeks	Each test site was cleansed with alcohol, and the area underlying visible skin changes by the tumor and the substance of each lesion was	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								injected with 0.15 ml of the test solution	
Cornell 1990 2229497	placebo						phosphate buffers, humanalbumin,and glycine. (Intralesional) 3 times per week for 3 weeks	Each test site was cleansed with alcohol, and the area underlying visible skin changes by the tumor and the substance of each lesion was injected with 0.15 ml of the test solution	
Edwards 1990 2107219	interferon gamma, 0.01						interferon gamma 0.01 (Intralesional) 3 times/week on alternate days for 3 weeks		
Edwards 1990 2107219	interferon gamma, 0.05						interferon gamma 0.05 (Intralesional) 3 times/week on alternate days for 3 weeks		
Edwards 1990 2383027	Interferon alfa-2b, 30 million IU						Interferon alfa-2b 30 million IU (Intralesional) weekly for 3 weeks	Patients were given 650 mg of acetaminophen orally at the time of injection	
Edwards 1990 2383027	Interferon alfa-2b, 10 million IU						Interferon alfa-2b 10 million IU (Intralesional) once	Patients were given 650 mg of acetaminophen orally at the time of injection	
Eigentler 2007 17610993	imiquimod 5% (8 weeks)						imiquimod 5% (Topical) thrice weekly for 8		

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
							weeks		
Eigentler 2007 17610993	imiquimod 5% (12 weeks)						imiquimod 5% (Topical) thrice weekly for 12 weeks		
Eimpunth 2014	pulsed dye laser				fluence of 7.5 J/cm2, 3-ms pulse width	one session of double stacked-pulses of PDL treatment using 10 mm spot size at the office visit. Lesions were treated with 1 single session and included a 6-mm margin of normal skin around the clinically apparent tumor			
Eimpunth 2014	no treatment								
Foley 2009 20064185	methyl-aminolevulinatePDT				CureLight/570-670 nm at 50-200mW/cm^2 to 75 j/cm^2	1-2 treatment cycles (assessed 3- 6 months) 1 week apart, 160 mg/g MAL, the surfaceof the lesion was prepared by gentle tumorsurface debridement using a curette, which removedthe stratumcorneuma nd surfaceof the friable tumor tissue. A layer of cream(MAL or placebo),1 mm thick, was appliedto each lesion and 5 mm of surroundingtissue and covered with an adhesive occlusivedressing			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						(e.g. Tegaderm, 3M, St Paul, MN, USA). After 3 h, the dressings were removed and the creamwas washedoff with 0.9% saline solution, immediately followed by illumination			
Foley 2009 20064185	placebo PDT				CureLight/570-670 nm at 50-200mW/cm^2 to 75 j/cm^2	1-2 treatment cycles (assessed 3- 6 months) 1 week apart, placebo, the surface of the lesion was prepared by gentle tumor surface debridement using a curette, which removed the stratum corneum and surface of the friable tumor tissue, to facilitate access of the cream and light to the tissue. The purpose of this debridement was to debulk rather than remove the tumor. placebo),1 mm thick, was appliedto each			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						lesion and 5 mm of surroundingtissue and covered with an adhesive occlusivedressing (e.g. Tegaderm, 3M, St Paul, MN, USA). After 3 h, the dressings were removed and the creamwas washedoff with 0.9% saline solution, immediately followed by illumination			
Garcia-Martin 2011 21242584	imiquimod 5%						Imiquimod 5% (Topical) 5 times per week for 6 weeks	plus carbomer 0.2% cream	
Garcia-Martin 2011 21242584	radiotherapy			Photons (gamma or x) to 4000-7000 cGy, 10-15 sessions, 2-3 times per week for 5 weeks					
Geisse 2002 12196749	Imiquimod 3x/wk						Imiquimod 5% (Topical) 3x/week for 12 weeks	mean total dose: 43mg	
Geisse 2002 12196749	Imiquimod 5x/wk						Imiquimod 5% (Topical) 5x/week for 12 weeks	mean total dose: 43mg	
Geisse	Imiquimod						Imiquimod 5%	mean total	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
2002 12196749	1x/day						(Topical) daily for 12 weeks	dose: 69mg	
Geisse 2002 12196749	Imiquimod 2x/day						Imiquimod 5% (Topical) twice daily for 12 weeks	mean total dose: 146mg	
Geisse 2002 12196749	vehicle (control)						vehicle (Topical) varied for 12 weeks		
Geisse 2004 15097956	Imiquimod 5x/wk						Imiquimod 5% (Topical) 5 times/week for 6 weeks		
Geisse 2004 15097956	Imiquimod 7x/wk						Imiquimod 5% (Topical) 7 times/week for 6 weeks		
Geisse 2004 15097956	Vehicle 5x/wk or 7x/wk						vehicle 5% (Topical) 5 or 7 times/week for 6 weeks		
Haak 2015 24903544	MAL PDT				LED for 8 min to 37 J/cm2	2 sessions 7-10 days apart to 74 J/cm2, 16% MAL, partial debulking was performed with a ring curette (M.H.) and areas compressed until bleeding stopped			
Haak 2015 24903544	AFXL MAL PDT				LED for 8 min to 37 J/cm2	2 sessions 7-10 days apart to 74 J/cm2, 16% MAL, partial debulking was performed with a ring curette (M.H.) and areas compressed until bleeding stopped. UltraPulse? fractional CO2			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						laser system using a DeepFx handpiece to deliver two stacked pulses of 40 mJ per pulse at a density of 5%			
Hall 1986 3514075	Radiotherapy			For lesions >1 cm, External Photons (gamma or x) to 3750 Gy, 10 treatments over 12 days. NR <1 cm					
Hall 1986 3514075	Cryotherapy		Cryotherapy without curettage (Cry-Owen spray gun for face and trunk; Brymil cryospray near the eye)						
Ko 2014 24102369	Er:YAG AFL PDT				Aktilite/632 to 37 J cm^-2	1 session, 16% MAL, AFL therapy was performed using a 2940-nm Er: YAG AFL (Joule?; Sciton Inc., Palo Alto, CA, U.S.A.) at 550– 600 lm ablation depth, level 1 coagulation, 22% treatment density and a single			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						pulse. Immediately afterwards, a 1-mm thick layer of MAL (16% Metvix? cream; PhotoCure ASA, Oslo, Norway) was applied to the lesion and to 5 mm of surrounding healthy tissue. The area was covered with an occlusive dressing (Tegaderm?; 3M, Saint Paul, MN, U.S.A.) for 3 h, after which the remaining cream was removed with saline gauze			
Ko 2014 24102369	MAL-PDT				Aktilite/632 to 37 J cm^-2	2 sessions 7 days apart to 37J cm ^ -2 (x2), 16% MAL, a 1-mm thick layer of MAL (16% Metvix? cream; PhotoCure ASA, Oslo, Norway) was applied to the lesion and to 5 mm of surrounding healthy tissue. The area was covered with an occlusive			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						dressing (Tegaderm?; 3M, Saint Paul, MN, U.S.A.) for 3 h, after which the remaining cream was removed with saline gauze			
Kuijpers 2006 16865869	ALA-PDT (total) (no subgroup stratification, combination of arms 2 and 3)	3mm			broadband, metal halogen light; 600-730 nm at 100 mwatt/cm^2, total dose 75 J/cm^2	2 sessions 7 days apart, 20% ALA, 20% 5-ALA on tumor + 5mm margin in non-transparent layer 2mm thick, covered with polyurethane and opaque dressing for 3 hours then cleaned with saline			0
Kuijpers 2006 16865869	ALA-PDT (debulking subgroup) (ALA-PDT + allocation to debulking group)	3mm			broadband, metal halogen light; 600-730 nm at 100 mwatt/cm^2, total dose 75 J/cm^2	2 sessions 7 days apart , 20% ALA, 20% 5-ALA on tumor + 5mm margin in non-transparent layer 2mm thick, covered with polyurethane and opaque dressing for 3 hours then cleaned with saline; debulking group: all tumor tissue above skin level with Stiefel sharp curette nr. 4 after topical anesthesia			1
Kuijpers	ALA-PDT (no	3mm			broadband, metal	2 sessions 7 days			0

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
2006 16865869	debulking subgroup) (ALA-PDT + no allocation to debulking group)				halogen light; 600-730 nm at 100 mwatt/cm^2 total dose 75 J/cm^2	apart, 20% ALA, 20% 5-ALA on tumor + 5mm margin in non-transparent layer 2mm thick, covered with polyurethane and opaque dressing for 3 hours then cleaned with saline			
Kuijpers 2006 16865869	MAL-PDT (total) (MAL-PDT + no stratification by subgroup, combination of arms 5+6)	3mm			broadband, metal halogen light; 600-730 nm at 100 mwatt/cm^2, total dose 75 J/cm^2	7 days apart, 16% MAL, 16% MAL on tumor + 5mm margin in non-transparent layer 2mm thick, covered with polyurethane and opaque dressing for 3 hours then cleaned with saline			0
Kuijpers 2006 16865869	MAL-PDT (debulking subgroup) (MAL-PDT + allocation to debulking group)	3mm			broadband, metal halogen light; 600-730 nm at 100 mwatt/cm^2, total dose 75 J/cm^2	7 days apart, 16% MAL, 16% MAL on tumor + 5mm margin in non-transparent layer 2mm thick, covered with polyurethane and opaque dressing for 3 hours then cleaned with saline; debulking group: all tumor tissue above skin level with Stiefel sharp curette nr. 4 after topical			1

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
						anesthesia			
Kuijpers 2006 16865869	MAL-PDT (no debulking subgroup) (MAL-PDT + no allocation to debulking group)	3mm			broadband, metal halogen light; 600-730 nm at 100 mwatt/cm^2, total dose 75 J/cm^2	7 days apart, 16% MAL, 16% MAL on tumor + 5mm margin in non-transparent layer 2mm thick, covered with polyurethane and opaque dressing for 3 hours then cleaned with saline			0
Kuijpers 2007 17451581	Curettage + Cryosurgery		Cryotherapy (Curettage with sharp curette. Cryo with liquid nitrogen with neoprene open cone)						
Kuijpers 2007 17451581	Surgical excision	excision (3 mm)							
Marks 2001 11312429	Imiquimod BID						Imiquimod 5% (Topical) BID for 6 weeks		
Marks 2001 11312429	Imiquimod OD						Imiquimod 5% (Topical) OD for 6 weeks		
Marks 2001 11312429	Imiquimod BID 3/week						Imiquimod 5% (Topical) BID 3 times per week for 6 weeks		
Marks 2001 11312429	Imiquimod OD 3/week						Imiquimod 5% (Topical) OD 3 times per week for 6 weeks		
Migden 2015 25981810	sonidegib 200						sonidegib 200 mg (Oral) once daily for until documented	Dose interruptions of 21 days or fewer, or dose	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
							disease progression (as confi rmed by independent central review), intolerable toxic eff ects, withdrawal of consent, death, discontinuation at an investigator's discretion, dose interruption lasting longer than 21 days (unless the patient was responding to study treatment and had not progressed, in which case resumption of treatment was permitted at the investigator's discretion), use of a prohibited medication, start of another antineoplastic therapy, or study termination.	reductions were permitted for toxic eff ects deemed to be related to study treatment	
Migden 2015 25981810	sonidegib 800						sonidegib 800 mg (Oral) once daily for until documented disease progression (as confi rmed by	Dose interruptions of 21 days or fewer, or dose reductions were permitted for toxic eff ects	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
							independent central review), intolerable toxic eff ects, withdrawal of consent, death, discontinuation at an investigator's discretion, dose interruption lasting longer than 21 days (unless the patient was responding to study treatment and had not progressed, in which case resumption of treatment was permitted at the investigator's discretion), use of a prohibited medication, start of another antineoplastic therapy, or study termination.	deemed to be related to study treatment	
Miller 1997 8996264	1.0 mL 5-FU weekly/6 weeks						5-FU/epi 1.0 mL (Intralesional) once weekly for 6 weeks		
Miller 1997 8996264	0.5 mL 5-FU weekly/6 weeks						5-FU/epi 0.5 mL (Intralesional) once weekly for 6 weeks		
Miller 1997	1.0 mL 5-FU 2x weekly/3						5-FU/epi 1.0 mL (Intralesional)		

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
8996264	weeks						twice weekly for 3 weeks		
Miller 1997 8996264	1.0 mL 5-FU twi 2x weekly/3 weeks						5-FU/epi 0.5 mL (Intralesional) twice weekly for 3 weeks		
Miller 1997 8996264	0.5 mL 5-FU 2x weekly/4 weeks						5-FU/epi 0.5 mL (Intralesional) twice weekly for 4 weeks		
Miller 1997 8996264	0.5 mL 5-FU 3x weekly/2 weeks						5-FU/epi 0.5 mL (Intralesional) three times weekly for 2 weeks		
Morton 1996 8977678	cryotherapy		Cryotherapy (Liquid nitrogen was applied to lesions via a hand-held 'Cryac' spray. After initial iceiicld formation, the freeze was maintained for 20 SH A single freeze-thaw cycle technique was employed with a 2-3 mm rim of clinically healthy tissue included in the treatment field.)						
Morton 1996 8977678	photodynamic				300 W xenon short arc plasma discharge for 30 min to 125 J/cm2	1 session, 20% ALA			
Morton 2006	MAL PDT				noncoherent red light wavelength,	2 sessions 1 week apart, 160			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
16785375					570-670nm to 75J/cm2	mg/g MAL, gentle surface debridement with a curette.			
Morton 2006 16785375	PDT placebo				noncoherent red light wavelength, 570-670nm to 75J/cm2	2 sessions 1 week apart, placebo cream, gentle surface debridement with a curette. Retreated at 12 weeks if partial response			
Morton 2006 16785375	Cryotherapy or Fluorouracil		Cryotherapy without curettage (Cryotherapy was performed with a handheld liquid nitrogen spray, using a single freeze/thaw cycle. After an initial ice field formation with a 2-mm rim of clinically healthy tissue, the ice field was maintained for a minimum of 20 seconds; 1 pass)				Fluorouracil 5% (Topical) once daily during the first week and twice daily weeks 2-4 for 4 weeks	Retreated at 12 weeks if partial response	
Mosterd 2008 18717680	ALA-PDT				broadband metal–halogen light source/585–720 nm for 15 min at 100 mW cm-2 to 75 J cm-2, total dose 150	2 sessions 60 minutes apart, 20% ALA, debulking 3 weeks before procedure			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
					J cm-2				
Mosterd 2008 18717680	Surgical excision	excision (3 mm)							
Mosterd 2008 19010733	MMS	Mohs (3 mm)							
Mosterd 2008 19010733	Surgical excision	excision (3 mm)							
Orenberg 1992 1430394	7.5 mg 5-FU (0.25 ml of MPI 5003 (7.5 mg 5-FU) intralesionally)						5-FU 30 mg/ml (Intralesional) weekly for up to 6 weeks		
Orenberg 1992 1430394	15 mg 5-FU (0.5 ml of MPI 5003 (15 mg 5-FU) intralesionally)						5-FU 30 mg/ml (Intralesional) weekly for up to 6 weeks		
Patel 2006 16713457	imiquimod 5%						imiquimod 5% (Topical) daily for 16 weeks	wash with tap water and pat dry before applying nightly	
Patel 2006 16713457	vehicle						vehicle (Topical) daily for 16 weeks	wash with tap water and pat dry before applying nightly	
Rhodes 2004 14732655	MAL PDT				red light, 570-670 nm at 50-200 mW, total dose 75 J/cm2	2 sessions 1 week apart, MAL, surface crust or scale was removed with a scalpel blade			
Rhodes 2004 14732655	excision	excision (5 mm)							
Salim 2003	PDT (ALA PDT)				Xenon lamp 630 ± 15 nm for 12-	1 session, 20% ALA			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
12653747					40 min at 50–90 mW/cm2 to 100 J/cm2				
Salim 2003 12653747	5-FU (Efudix)						5-FU (Topical) Daily for 1 week then BID for 3 weeks for 4 weeks total treatment		
Salmanpoor 2012	Surgical excision	excision (4 mm)							
Salmanpoor 2012	Curettage								NR
Salmanpoor 2012	Electodessication and curettage		Diathermy (2 mm cauttery margins after curettage; dessication)						
Schleier 2007 25047438	ALA-thermogel PDT				diode laser, Ceralas 635 PDT at 0.1 W/cm^2 to 120 J/cm ^2	1-3 times based on response at follow up, 10% ALA, ALA dissolved in thermogel 1 hour before treatment. combination gel applied 3 mm beyond visible margin of tumor. the gel layer was 5 mm thick. the area was covered with plaster and protected from light. three hours after application , residue was removed.			
Schleier 2007 25047438	mALA-thermogel PDT				diode laser, Ceralas 635 PDT at 0.1 W/cm^2 to	1-3 times based on response at follow up, 10%			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
					120 J/cm ^2	methyl-ALA, methyl-ALA dissolved in thermogel 1 hour before treatment. combination gel applied 3 mm beyond visible margin of tumor. the gel layer was 5 mm thick. the area was covered with plaster and protected from light. three hours after application , residue was removed.			
Schulze 2005 15888150	imiquimod 5%						imiquimod 5% (Topical) daily for 6 weeks		
Schulze 2005 15888150	vehicle						vehicle cream (Topical) daily for 6 weeks		
Shumack 2002 12224978 (12 weeks)	vehicle cream						vehicle Placebo (Topical) twice daily for 7 days per week or once daily for 7 days per week or once daily for 5 days per week for 12 weeks		
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week						imiquimod 5% (Topical) Twice daily for 7 days per week for 12 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to normal sleeping hours according	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								to the dosing regimen to which they were assigned. The target tumor was washed with mild soap just prior to cream application, and the cream was rubbed into and around (approximately up to 1 cm) the tumor. The cream remained in place for at least 8 hours without occlusion.	
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Once daily for 7 days per week						imiquimod 5% (Topical) Once daily for 7 days per week for 12 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to normal sleeping hours according to the dosing regimen to which they were assigned. The target tumor was washed with mild soap just prior to cream application, and the cream was	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								rubbed into and around (approximately up to 1 cm) the tumor. The cream remained in place for at least 8 hours without occlusion.	
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Once daily for 5 days per week						imiquimod 5% (Topical) Once daily for 5 days per week for 12 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to normal sleeping hours according to the dosing regimen to which they were assigned. The target tumor was washed with mild soap just prior to cream application, and the cream was rubbed into and around (approximately up to 1 cm) the tumor. The cream remained in place for at least 8 hours without occlusion.	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
Shumack 2002 12224978 (12 weeks)	imiquimod (IMQ) 5% cream - Once daily for 3 days per week						imiquimod 5% (Topical) Once daily for 3 days per week for 12 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to normal sleeping hours according to the dosing regimen to which they were assigned. The target tumor was washed with mild soap just prior to cream application, and the cream was rubbed into and around (approximately up to 1 cm) the tumor. The cream remained in place for at least 8 hours without occlusion.	
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week						Imiquimod 5% (Topical) Twice daily for 7 days per week for 6 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to normal sleeping hours according to the dosing regimentowhich theywereassign	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								ed.Thetargettu morwaswashed with mild soap just prior to cream application, and the cream was rubbed into and around (approximately up to 1 cm) the tumor. The cream remained in place for at least 8 hours without occlusion.	
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Once daily for 3 days per week						Imiquimod 5% (Topical) Once daily for 3 days per week for 6 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to normal sleeping hours according to the dosing regimentowhich theywereassign ed.Thetargettu morwaswashed with mild soap just prior to cream application, and the cream was rubbed into and around (approximately up to 1 cm) the tumor. The	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								cream remained in place for at least 8 hours without occlusion.	
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Twice daily for 3 days per week						Imiquimod 5% (Topical) Twice daily for 3 days per week for 6 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to normal sleeping hours according to the dosing regimentowhich theywereassign ed.Thetargettu morwaswashed with mild soap just prior to cream application, and the cream was rubbed into and around (approximately up to 1 cm) the tumor. The cream remained in place for at least 8 hours without occlusion.	
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Once daily for 7 days per week						Imiquimod 5% (Topical) Once daily for 7 days per week for 6 weeks	Patients applied topical 5% imiquimod cream to 1 target tu- mor just prior to	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								normal sleeping hours according to the dosing regimentowhich theywereassigned.Thetargettumorwaswashed with mild soap just prior to cream application, and the cream was rubbed into and around (approximately up to 1 cm) the tumor. The cream remained in place for at least 8 hours without occlusion.	
Siller 2010 20546215	vehicle gel, treatment arm A; day 1 and 2 (subjects randomized to apply vehicle cream (control) on day 1 and 2.)						vehicle cream (Topical) 2X for N/A	Day 1 and Dat 2; investigator applied gel directly to sBCC using a micropipette and a circular template. volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20 micrograms/cm 2)	
Siller 2010	ingenol						ingenol	Day 1 and Day	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
20546215	mebutate gel, 0.0025%, treatment arm A-days 1 and 2 (subjects randomized to apply 0.0025% ingenol mebutate on days 1 and 2.)						mebutate 0.0025% (Topical) 2x for N/A	2; investigator applied gel directly to sBCC using a micropipette and a circular template. volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20 micrograms/cm 2)	
Siller 2010 20546215	ingenol mebutate gel, 0.01%, treatment arm A- day 1 and 2 (subjects randomized to apply 0.01% ingenol mebutate on days 1 and 2.)						ingenol mebutate 0.01% (Topical) 2x for N/A	Day 1 and Day 2; investigator applied gel directly to sBCC using a micropipette and a circular template. volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20 micrograms/cm 2)	
Siller 2010 20546215	ingenol mebutate gel, 0.05%, treatment arm A-day 1 and 2 (subjects randomized to apply						ingenol mebutate 0.05% (Topical) 2x for N/A	Day 1 and Day 2; investigator applied gel directly to sBCC using a micropipette and a circular template.	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
	0.05% ingenol mebutate on days 1 and 2.)							volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20 micrograms/cm 2)	
Siller 2010 20546215	vehicle gel, treatment arm B- day 1 and 8 (subjects randomized to apply vehicle cream (control) on day 1 and 8.)						vehicle (Topical) 2x for N/A	Day 1 and Day 8; investigator applied gel directly to sBCC using a micropipette and a circular template. volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20 micrograms/cm 2)	
Siller 2010 20546215	ingenol mebutate gel, 0.0025%, treatment arm B-days 1 and 8 (subjects randomized to apply 0.0025% ingenol mebutate on days 1 and 8.)						ingenol mebutate 0.0025% (Topical) 2x for N/A	Day 1 and Day 8; investigator applied gel directly to sBCC using a micropipette and a circular template. volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								micrograms/cm 2)	
Siller 2010 20546215	ingenol mebutate, 0.01%, treatment arm B- day 1 and 8 (subjects randomized to apply 0.01% ingenol mebutate on days 1 and 8.)						ingenol mebutate 0.01% (Topical) 2x for N/A	Day 1 and Day 8; investigator applied gel directly to sBCC using a micropipette and a circular template. volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20 micrograms/cm 2)	
Siller 2010 20546215	ingenol mebutate gel, 0.05%, treatment arm B-day 1 and 8. (subjects randomized to apply 0.05% ingenol mebutate on days 1 and 8.)						ingenol mebutate 0.05% (Topical) 2x for N/A	Day 1 and Day 8; investigator applied gel directly to sBCC using a micropipette and a circular template. volume of gel based on longest post-biopsy lesion diameter (ranged btw 0.25-5.20 micrograms/cm 2)	
Spencer 2006 16393600	imiquimod 5%						imiquimod 5% (Topical) daily for 1 month		3 cycles
Spencer 2006	vehicle						vehicle (Topical) daily for 1 month		3 cycles

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
16393600									
Sterry 2002 12452875	Imiquimod (2 days/week) with occlusion						Imiquimod 5% (Topical) 2 days/week for 6 weeks	bedtime; left on for 8 hours; with occlusive dressing	
Sterry 2002 12452875	Imiquimod (3 days/week) with occlusion						Imiquimod 5% (Topical) 3 days/week for 6 weeks	bedtime; left on for 8 hours; with occlusive dressing	
Sterry 2002 12452875	Imiquimod (2 days/week) without occlusion						Imiquimod 5% (Topical) 2 days/week for 6 weeks	bedtime; left on for 8 hours; without occlusive dressing	
Sterry 2002 12452875	Imiquimod (3 days/week) without occlusion						Imiquimod 5% (Topical) 3 days/week for 6 weeks	bedtime; left on for 8 hours; without occlusive dressing	
Sterry 2002 12452875 (nodular)	Imiquimod (2 days/week) with occlusion						Imiquimod 5% (Topical) 2 days/week for 6 weeks	bedtime; left on for 8 hours; with occlusive dressing	
Sterry 2002 12452875 (nodular)	Imiquimod (3 days/week) with occlusion						Imiquimod 5% (Topical) 3 days/week for 6 weeks	bedtime; left on for 8 hours; with occlusive dressing	
Sterry 2002 12452875 (nodular)	Imiquimod (2 days/week) without occlusion						Imiquimod 5% (Topical) 2 days/week for 6 weeks	bedtime; left on for 8 hours; without occlusive dressing	
Sterry 2002 12452875 (nodular)	Imiquimod (3 days/week) without occlusion						Imiquimod 5% (Topical) 3 days/week for 6 weeks	bedtime; left on for 8 hours; without occlusive dressing	
Sullivan 2003 14725659	imiquimod 5%						imiquimod 5% (Topical) nightly on weekdays for 10 applications	schedule immediate exicision if irritation	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
								developed	
Sullivan 2003 14725659	vehicle						vehicle cream NR (Topical) nightly on weekdays for 10 +- 3 applications		
Szeimies 2008 18624836	MAL-PDT				large-field LED for 7-10 min to 37 J/cm^2	2 sessions, 160 mg/g MAL, without bleeding or pain, to remove scales and crusts and roughen legion surface, followed by layer of 1 mm thick MAL to lesion and surrounding 5-10 mm area			
Szeimies 2008 18624836	excision	excsision (3 mm)							
Thissen 2000 10940063	cryotherapy		Cryotherapy with curettage (treated with liquid nitrogen)						
Thissen 2000 10940063	surgical excision	excision (3 mm)							
Torres 2004 15606733	imiquimod, 2 weeks (pt applied imiquimod 5x/week x 2 weeks prior to MOHs.)	Mohs					imiquimod 5% (Topical) 5x/week for 2 weeks	apply cream to target tumor area and 1cm of skin surrounding tumor	
Torres 2004 15606733	imiquimod, 4 weeks (pt applied imiquimod 5 x/week x 4 weeks prior to	Mohs					imiquimod 5% (Topical) 5x/week for 4 weeks	apply cream to target tumor area and 1cm of skin surrounding tumor	

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
	MOHs)								
Torres 2004 15606733	imiquimod, 6 weeks (pt applied imiquimod 5x/week x 6 weeks prior to MOHs)	Mohs					imiquimod 5% (Topical) 5x/week for 6 weeks	apply cream to target tumor area and 1cm of skin surrounding tumor	
Torres 2004 15606733	vehicle controlled-pooled (applied study cream 5x/week for 2, 4, or 6 weeks prior to MOHs.)	Mohs					vehicle cream (Topical) 5x/week for 2, 4, and 6 weeks	apply cream to target tumor area and 1cm of skin surrounding tumor	
Tran 2012 22511036	S1: PDL 15 j/cm2				595 nM pulsed-dye laser: pulse energy of 15 J/cm2, 3-millisecond pulse length	no dynamic cooling, using a 7-mm spot size with 10% overlap of pulses and two passes; 4 mm margin			
Tran 2012 22511036	S2: PDL 7.5 j/cm2				595 nM pulsed-dye laser: 7.5 J/cm2, 3-millisecond pulse length	no dynamic cooling, using a 10-mm spot size with 10% overlap of pulses and double-stacked pulses with a repetitive pulse rate of 1.5 Hz; 4 mm margin			
Tran 2012 22511036	No treatment								
van der Geer 2012 22385074	Imiquimod + Mohs	Mohs					Imiquimod 5% (Topical) daily/5 days per week for 4 weeks		
van der Geer 2012	no treatment + Mohs	Mohs							

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
22385074									
Wang 2001 11298545	ALA-PDT				635nm at 80+/-20 mW/cm2 to 60 J/cm2	1 session, 20% ALA. When the stratum corneum was intact, it was carefully scraped off with a scalpel. Lipids were removed using 96% ethanol. Crusts were softened with isotonic saline and then lifted off.			
Wang 2001 11298545	cryosurgery		Cryotherapy without curettage (CRY-AC spray)						
Wettstein 2013 23566745	Mohs + Ringer's lactate (control group)	excision (NR)					Ringer 1x10^6 IU (Intralesional) once for N/A	immediately after surgical excision	
Wettstein 2013 23566745	Mohs + interferon alpha-2b	excision (NR)					inf alpha-2b 1x10^6 IU (Intralesional) once for N/A	immediately after surgical excision	
NRCS									
Ahmed 2000 11069453	Curettage	excsision (3 mm)							
Ahmed 2000 11069453	Cryotherapy		Cryotherapy without curettage (Liquid nitrogen with a 3mm margin; the freeze was then maintained for						

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
			5±10 s. The lesion was allowed to thaw fully and the freeze was repeated;)						
Ballester-Sanchez 2016 26985197	brachytherapy 36.6 Gy			Photons (gamma or x) to 36.6 Gy, Brachytherapy/Plesiotherapy, 6 sessions, 2x/week for 3 weeks					
Ballester-Sanchez 2016 26985197	brachytherapy 42 Gy			Photons (gamma or x) to 42 Gy, Brachytherapy/Plesiotherapy, 6 sessions, 2x/week for 3 weeks					
Chren 2013 23190903	electrodessication and curettage	Mohs	Diathermy (electrodessication and curettage; 3 passes)						
Chren 2013 23190904	excision	excsision (median 3.0 mm)							
Chren 2013 23190905	Mohs								
Cosgarea 2012 22738399	ALA PDT				red led to 37 J/cm2	2 sessions 1 month apart to 74 J/cm2, 20% ALA			
Cosgarea 2012	surgical excision	excsision (3 mm)							

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
22738399									
Graells 2014 24139468	Imiquimod						Imiquimod NR (Topical) 5 days per week for 6 weeks		
Graells 2014 24139468	Surgery								
Lippert 2013 23725586	Laser ablation + AFP + PDT				630 nm	2 sessions 14 days apart, ALA, AFP with a CO2 laser. Tumor ablation was performed using a gallium arsenide 980-nm diode laser with a 3- to 9-W output in continual mode using local anesthesia with 4% supracaine; this procedure was controlled using high-resolution ultrasound. This treatment was followed by a 7-day interval during which the necrotic layer after the ablation separated (bloc penetration of ALA), and partial tissue granulation occurred.			
Lippert 2013 23725586	Laser ablation + PDT		CO2 Laser Therapy (AFP was performed using a CO2 fractional laser with a 10,600-		630 nm	2 sessions 14 days apart, ALA. Tumor ablation			

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
			nm wavelength (mode, SX; SX index, 8; density, 15%; power, 15 W))			was performed using a gallium arsenide 980-nm diode laser with a 3- to 9-W output in continual mode using local anesthesia with 4% supracaine; this procedure was controlled using high-resolution ultrasound. This treatment was followed by a 7-day interval during which the necrotic layer after the ablation separated (bloc penetration of ALA), and partial tissue granulation occurred			
Pampena 2016 26589877	3675 cGy			External Photons (gamma or x) to 3675 cGy, 7 sessions weekly					
Pampena 2016 26589878	4500 cGy			External Photons (gamma or x) to 4500 cGy, 15 sessions daily					
Shah 2009	Pulse dye laser		CO2 Laser Therapy (595						

Author, year, PMID	Arm	Surgical interventions (margins)	Thermal interventions (description)	Radiation	Photodynamic Therapy dose	Photodynamic Therapy description	Medical interventions description	Medical interventions other	Curettage number of passes
19588534			nm Pulse dye lasereach pass at 15 J/cm2 pulse length of 3 ms; 4 passes at 2 week intervals)						
Shah 2009 19588534	no treatment								
Sofen 2015 25913533	vismodegib 12 weeks						vismodegib 150 mg/d (Oral) for 12 weeks		
Sofen 2015 25913533	vismodegib 12 weeks + 24 weeks observation						vismodegib 150 mg/d (Oral) for 12 weeks	+ 24 weeks observation period	
Sofen 2015 25913533	vismodegib 16 weeks						vismodegib 150 mg/d (Oral) for 16 weeks	8 weeks + 4 weeks observation + 8 weeks	
Sullivan 2003 14725659	imiquimod 5%						imiquimod 5% (Topical) nightly on weekdays for 10 applications	schedule immediate exicision if irritation developed	
Sullivan 2003 14725659	vehicle						vehicle cream NR (Topical) nightly on weekdays for 10 +- 3 applications		

Appendix F. Risk of Bias

Table F-1. Risk of bias in RCTs

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
Abbade 2015 (Conference abstract) (Brazil)	No Data	No Data	Yes	No	No	No Data	Yes	No	No	No Data	No	Moderate
Al-Niaimi 2015 26157307 (UK)	Unsure	Yes	Yes	No	No	Yes	No	Yes	Yes	No	(12 month results mentioned in the protocol not given; recurrence rates not given by arm; only 1 AE given)	cosmetic outcomes : low recurrenc e: moderate to high
Allen 1979 298425 (UK)	Yes ("subjects randomly assigned in a coded, controlled trial.")	Yes ("randomly coded allocation of treatment")	No Data (No Table 1 / patient characteri stics reported.)	Yes (Subjects could not be blinded to treatment allocation (Cryotherap y vs. Radiothera py))	No Data (No mention is made of blinding providers; Review Authors do not discuss whether this would impact the outcome.)	No Data (No mention is made of blinding outcome assessors; Review Authors do not discuss whether this would impact the outcome.)	No Data (No dropouts reported.)	No Data (Only Recurr ence was reporte d, but it was reporte d complet ely for both arms of the trial.)	No Data (See above)	No Data (No Adverse Events were reported)	Low RoB (Outcome of interest, recurrence, was reported by arm.)	High
Alpsoy 1996 8708151	Unsure	Unsure	Yes	Unsure	Unsure	Unsure	Yes	No	No	Yes		High

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
(Turkey)												
Arits 2013 23683751 (Netherlands)	Yes	Yes	Yes	No (patients were not blinded)	No (caregivers were not blinded)	Yes (all outcome assessors (except for AEs, which were assessed by patients) were blinded)	Yes	No	No	Yes	No	Low
Avril 1997 9218740 (France)	Unsure (method of randomization not reported)	Yes	Yes	No (The lack of blinding is concerning for patient and physician reported cosmetic outcomes, but they also report outcomes from third-party blinded assessors)	No (The lack of blinding is concerning for patient and physician reported cosmetic outcomes, but they also report outcomes from third-party blinded assessors)	No (The lack of blinding is concerning for patient and physician reported cosmetic outcomes, but they also report outcomes from third-party blinded assessors)	Unsure (ITT not reported, low number of dropouts)	Yes (23% and 27% lost to followup by mean followup time of 41 months)	No (similar rates between arms)	No (they were reported, but not well defined)	(Neither paper reported AEs adequately)	High
Basset-Seguin 2008 18693158 (13 centers in 7 european countries)	Unsure	Yes	Yes	No	No	Unsure	No	No	No	Yes		Low to moderate for all outcomes
Bath-Hextall 2014 24332516 (UK)	Yes	Yes	Yes	No	No	Yes	Yes (Modified ITT: all randomized	Yes	No	Yes	No	Low

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
							patients who received at least 1 applicatio n of imiquimo d or surgery and for whom the outcome was available)					
Berroeta 2007 17573890 (United Kingdom)	Yes	Yes	No Data	No	No	Yes	Yes	No	No	Yes	Yes (Said they measured at multiple timepoints but only reported 1 year)	Moderate
Beutner 1999 10570388 (USA)	No Data	No Data	No (Group sizes are very small)	Unsure	Yes	No Data	Yes (no dropouts or crossove r)	No	No	Yes	No	Moderate to high due to small sample size and baseline difference s
Brinkhuizen 2016 27067393 (Netherlands)	Yes	Yes	No (superficia l not similar, nodular similar	No	No	Yes	Yes	No	No	Yes	None immediatel y apparent	Low to moderate

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
			enough)									
Butler 2009 19018814 (texas, usa)	Yes	Yes	Yes	Yes	Yes	Yes	No (3 patients who failed to complete the study were included as treatment failures. this is not ITT.)	No	No (3 patients in imiquimod group and 0 patients in vehicle groupp)	Yes	No	Low for all outcomes
Cai 2015 25899562 (china)	Unsure	Yes	Yes	Unsure	Yes	Yes	Unsure (study states: "patients randomly assigned to two groups accordin g to their hospital identificat ion number" did not mention a specific computer generator)	No	No	No (no table for adverse events; study loosely describes ae in the body of the text for study arm)		Low for efficacy; high for AEs
Carija 2016 27516420 (Croatia)	No	No	Yes	unsure	Yes	Yes	No	No	No	Yes	Yes	Moderate for all outcomes

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
Choi 2016 26551044 (Korea)	Unsure (did not elaborate on how subjects were randomized)	Yes	Yes	Yes	Yes	Yes	No (five subjects dropped out prematurely for unrelated reasons to study and were analyzed as treatment failures. discussed with gaelen who did not think it effected outcomes or data based on bounding analysis.)	No	No	Yes	No	Low for all outcomes
Choi 2017 28199463 (Korea)	Yes	No	Yes	No	No	Yes	Yes	No	No	Yes	No	Low for all outcomes
Cornell 1990 2229497 (U.S.)	Yes	No Data	Yes (Location might be slightly different, disadvantages the treatment group)	Yes	No	Yes	Yes	No	No	Yes	No	Low for all outcomes

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
Edwards 1990 2107219 (U.S.)	Unsure (not reported; randomization done in blocks by lesion type (superficial or nodular))	Unsure (not reported)	Unsure (baseline data not reported)	Unsure (not reported)	Unsure (not reported)	Unsure (not reported)	Yes	No	No	Yes	(Adverse events and cosmetic outcomes were not presented by arm.)	This paper lacks detail on study design, so it is unclear whether it was properly conducted Moderate to high
Edwards 1990 2383027 (U.S.)	Unsure (not reported; subjects randomized in blocks based on lesion type)	Unsure (not reported)	Unsure (no baseline details given)	Yes	Yes	Yes	Yes (no drop outs, no crossovers)	No	No	No (Adverse events were not defined and were not given by arm)	(There appears to be some selective reporting: cosmetic outcomes were only reported in a subset of patients and not by arm, adverse events were not reported by arm. <- seems to be true in all studies)	This is an older study and a very short report, so things may have been done right but not adequately reported Moderate to high
Eigentler 2007	No Data	No Data	Unsure	No	No Data	No Data	No	No	No	Unsure (partial		Moderate to low

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
17610993 (Germany)										reporting, but they say there's no difference between arms)		
Eimpunth 2014 (Conference abstract) (unclear)	No Data	No Data	No Data	No	No Data	No Data	Yes	No	No	No	(probably)	It is very difficult to assess quality based on the abstract alone
Foley 2009 20064185 (U.S. and australia)	Yes	Yes	Unsure (They did note a significant difference btw groups in the distributio n of Fitzpatrick skin phototype ($p<0.05$), largely caused by greater proportion of patients with skin type 1 in the MAL group)	Yes	Yes	Yes	No (3 dropouts (2 in MAL and 1 in placebo) inconsist ent and unclearly presente d.)	No	No	Yes	No	Low for all outcomes

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
Garcia-Martin 2011 21242584 (Spain)	Unclear RoB	Unclear RoB	Low RoB	High RoB	Moderate RoB	Unclear RoB	Low RoB	Low RoB		Low RoB	(opthomologist rated cosmetic outcome prespecified in the methods but not reported in the results)	Low to moderate due to lack of blinding
Geisse 2002 12196749 (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes (Some AEs were not reported for vehicle groups)	(not immediately apparent)	Low for all outcomes
Geisse 2004 15097956 (U.S.)	Yes	Yes	No (ages and locations of tumors differ)	Yes	Yes	Yes	Yes	No	No	No (AE reporting was there, but inconsistent (sometimes by arm, sometimes with numbers, etc))	(I don't see any sign of overt selective reporting)	Low; moderate for AEs
Haak 2015 24903544 (Denmark)	Yes	Yes	Yes	No	No	Yes (except patient cosmetic outcomes)	Yes	No	No	Yes	(none immediately obvious)	Low for all outcomes
Hall 1986 3514075 (UK)	No (Not mentioned how randomized)	No (Not mentioned)	No (Difference in size and	No (Not possible to blind)	No (Not possible to blind)	No (Not mentioned)	No (Only analyzed patients with	Unsure (Only gives dropout	No Data (Only gives dropouts for whole study not per	No	No	Unsure Differential missingn

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
			location)				follow-up data)	s for whole study not per group)	group)			ess not reported
Ko 2014 24102369 (Korea)	Unsure	No	Yes	No	Unsure	Yes	Unsure (ITT population was 19. they had one dropout (unclear how many lesions) who violated protocol and counted as treatment failure. bc the exact number of lesions randomized for the 19 pts was not abailable for ITT eval, pp was used for data extraction.)	No	No	Yes	(not immediately apparent)	Low

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
Kuijpers 2006 16865869 (Netherlands)	Yes	Yes	Maybe (4 superficial BCC in surgery arm. All others nodular.)	No (Not possible)	No (Not possible)	Unsure (3rd blinded party did assessments "where possible")	No (Not true intention to treat, complete r analysis)	Yes (13/51 tumors in the cryo group lost to follow-up 2/49 in surgical group)	Yes (Cryo group had 13 missing at 5 years vs. 2 in excision group)	No	(Missing systematic reporting of AEs)	Moderate to high due to missingn ess
Kuijpers 2007 17451581 (Netherlands)	No Data ("randomly assigned" is only mention)	Unsure	Yes (seem similar enough)	Unsure	Unsure	Yes (pathologist was blinded)	Yes (no dropouts)	No	No	No	No (no reporting of adverse events other than pain)	Low for effectiven ess outcomes and moderate for AEs
Marks 2001 11312429 (Australia and New Zealand)	No (Not reported)	No (Not reported)	Unsure (Minimal data given in table 1)	No (Open-label)	Unsure (Open-label)	Unsure (Open-label)	No (Not true ITT but number of dropouts is low)	No	No	Yes	(Unclear - no protocol available but all outcomes of interest available)	Moderate to high
Migden 2015 25981810 (worldwide)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (both ITT and as treated results reported)	No (Very high dropout rate; most due to advers e events. Boundi ng	No (dropout rates and reasons were similar across arms)	Yes	(Possible; only a small number (7) of QOL results reported; NCT record does not call for any QOL results.)	Moderate due to dropouts

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
								analysis suggest there is high risk of bias due to dropouts)				
Miller 1997 8996264 (USA)	Unclear RoB (randomization procedure undefined)	Unclear RoB (randomization procedure undefined)	No Data	Low RoB (open label but outcomes aren't likely influenced)	Low RoB (open label but outcomes aren't likely influenced)	Low RoB (open label but outcomes aren't likely influenced)	Unsure (FLAG some drop outs related to treatment)	Yes (drops outs occurred either prior to completion or were unrelated to treatment)	Yes	Low RoB	No (adverse events selectively reported or not stratified, cosmetic outcome not fully reported, histologic clearance is reported fully)	Moderate for clearance, high for other outcomes
Morton 1996 8977678 (Scotland)	Unsure (not fully randomized)	Unsure	Yes	No	No	No (only one outcome assessor was reported to be blinded and that outcome was given at the fewest timepoints)	No (per protocol, not too many dropouts for 1 year, unclear for 2 years)	Yes (possibly for long-term)	Yes (possibly for long-term)	Yes	(It feels like there may be some selective reporting in the aesthetic outcomes)	Low to moderate due to lack of blinding and long term dropouts
Morton 2006 16785375 (Europe)	No Data (Not reported)	No Data (Not reported)	Unsure (Lesions size was	No (unblinded)	No (unblinded)	No (unblinded)	Yes (no dropouts)	No	No	Yes	(Does not appear to be any)	Older study with poor

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
			different; this was accounted for in a regression .)									reporting. Lack of blinding may affect AE reporting, but unlikely to affect clearance or recurrence high due to poor reporting
Mosterd 2008 18717680 (Netherlands)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	(Aesthetic outcomes only reported in combined recurrent/primary arm. Subgroup analysis for more severe cancers missing followup Ns;)	Low to maybe moderate because of loss to followup.
Mosterd 2008 19010733 (Netherlands)	Yes	Yes	Unsure (Very few baseline details were given. Those that	No (No blinding)	No (No blinding)	No (No blinding)	Yes	Yes (48 months >30% missingness)	Yes (48 months differential)	No (AEs were not defined)	(The lack of specificity in AE and baseline data reporting	Moderate for early followup and high for later followup

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
			are given are similar.)								may suggest selective reporting)	
Orenberg 1992 1430394 (USA)	Unclear RoB	Unclear RoB	No	Low RoB	Low RoB	Low RoB	Unsure (No dropouts/ protocol breaks reports)	No	No	High RoB	Yes	High, Lots of uncertainty, very small study
Patel 2006 16713457 (United Kingdom)	Yes	Yes	No (legion size different between groups)	Yes	Yes	Yes	No	Yes (3/15)	Yes (20% in one arm, no dropout in other arm)	No (not well-defined, not reported by arm)		High, blinding is good but groups are not similar, there is differential missingness, and outcomes are not reported by arm
Rhodes 2004 14732655 (Europe)	Yes	Yes	No (location of lesions differed significantly; this matters because a subgroup analysis by location of lesion	No	No	No (could lead to bias as lack of cure was established clinically and both investigators and patients assessed cosmetic outcomes)	No (per protocol analysis was done. The authors state that an ITT analysis was nearly	Yes (No for the early followup; yes for followup beyond 1 year)	No	Yes	(hard to tell)	High, especially given that the funding came from a PDT source

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
			was done)				identical)					
Salim 2003 12653747 (UK)	No (Not reported)	No (Not reported)	No (Lesion location not similar. Other characteristics not provided)	No (Not reported)	No (Not reported)	No (Not reported)	Yes	No	Yes (Dropouts occurred only in the 5-FU group)	No	(Did not report AE assessments from each visit)	High risk of bias due to between-group difference slocation and selective reporting of AEs
Salmanpoor 2012 (Iran)	No (Not reported)	No (Not reported)	No Data (No Table 1 or other comparison)	Unsure (Not reported)	Unsure (Not reported)	Unsure (Not reported)	Yes (No dropouts reported)	No (No missing data reported)	No (No missing data reported)	Not Applicable (No AEs discussed)	(No AEs reported)	High
Schleier 2007 25047438 (Germany (Friedrich-Schiller University Jena))	Yes	No	Yes	Yes	Yes	Yes	Unsure	No		Yes (pain specifics unavailable)		Moderate for all outcomes
Schulze 2005 15888150 (Europe)	Yes (randomized to imiquimod or vehicle in a 1 : 1 ratio according to a computer-generated randomization schedule)	Yes (Study personnel remained blinded to the randomization until the database was complete and locked.)	Yes	Yes (Subjects, study personnel and the sponsor's clinical research team were blinded to study cream identity and treatment	No	Unsure	Yes	Yes	Yes	No	Yes	Low

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
				assignment)								
Shumack 2002 12224977 (12 weeks) (Australia and New Zealand; And United States)	No (92 patients randomized to Imiquimod and placebo according to the dosing scheme: - once daily for 3 days per week (20 Active, 8 Vehicle) -once daily for 5 days per week (23 A, 6 V) - once daily for 7 days per week (21 A, 10 V))	No Data (method of allocation concealment was not reported)	No (Twice daily for 7 days per week group (4 active, 0 control) Mean age is different from range of age in other groups and combined vehicle)	Yes	No Data ("double blind")	No Data ("double blind")	Yes (15 were discontinued from the study. Post treatment excision results were obtained for 11 of these. Intention to Treat was reported.)	No (Clearance outcome was partially reported. Reported for combined vehicle separate from dosing regimen groups, where only results of imiquimod patients were reported.)	No	No (AE were defined but # of counts within each arm was not completely reported.)	Yes (AE were defined but # of counts within each arm was not completely reported.)	Low for clearance outcomes , unclear for AEs
Shumack 2002 12224977 (6 weeks) (Australia and New Zealand; And United	Yes (99 patients randomized to Imiquimod and placebo according to the dosing	No Data	No (Noticeable difference in age for Twice daily for 7	Yes	No Data	No Data	Yes (9 patients were discontinued from the study,	No	No	Yes	No	Low Adverse events reported but not for every arm

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
States)	scheme: - once daily for 3 days per week (32) -twice daily for 3 days per week (31) - once daily for 7 days per week (35) - twice daily for 7 days per week (1))		days/ week arm (n=1))				but only 4 did not undergo post-treatment excision 5 of 99 enrolled did not undergo post treatment excision. ITT not reported.)					
Siller 2010 20546215 (8 private dermatology clinics Australia)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	No	Yes		Low for all outcomes
Spencer 2006 16393600 (United States)	No Data (randomization not reported)	No Data	Unsure (very low n)	No Data	No Data	No (blinding not reported)	Yes (no dropouts)	No	No	No	No (not all time points reported.)	High risk of bias
Sterry 2002 12452875 (nodular) (Europe)	Yes	Yes	Yes	No	No	Unsure	No	No	Yes	No (Few AEs reported by arm; in general unclear AE reporting)	(Not immediately evident)	Low for efficacy and moderate to high for AEs
Sterry 2002 12452875 (superficial)	Yes	Yes	No	No	No	Unsure	No	No	Yes	No (Few AEs reported		Low to moderate for

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
(Europe)										by arm; in general unclear AE reporting)		efficacy and moderate to high for AEs
Szeimies 2008 18624836 (United Kingdom/Germany/Switzerland/Australia)	Yes	Yes	Yes	No	No	No	Unsure (per protocol analysis)	No	Yes (some outcomes)	No		Low to moderate
Thissen 2000 10940063 (Netherlands)	No Data	No Data	Yes	No (Not possible to blind patients to treatment allocation (cryosurgery vs. surgical excision))	No Data (It is not reported if providers were blinded, might be high RoB for clinical recurrence outcome)	Unsure (cosmetic results were independently assessed by 5 professionals who were "not involved in the trial and who were blinded to the treatment")	Yes (few drop-outs not reported by arm (3 did not appear for control visits and 1 died), not related to treatment or outcome)	No (Clearance is fully reported by arm.)	No	Yes (AEs: secondary wound infections; moderate to severe swelling of treated area. (Reported by Arm))	No	Moderate to high because of blinding only
Torres 2004 15606733 (loma linda, CA; boston, MA)	Yes (computer-generated schedule)	No	Yes	Yes	Yes	Unsure (histologist)	Yes	No		No (Not well reported)	No (probably not)	Low for all outcomes
Tran 2012 22511036 (US)	No Data	No Data	No (groups were not similar at baseline,	Yes	No	No	Yes	No	No	Yes	(unclear)	Moderate to high due to nonsimilar

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
			though the differences were not statistically significant (probably because of the small sample size))									baselines
van der Geer 2012 22385074 (Netherlands)	Yes	Yes	Yes	No (no mention of blinding)	No (no mention of blinding)	No (High RoB, no mention of blinding, and only clinical clearance outcome)	Yes	No	No	Yes	(none that i could spot easily)	Moderate
Wang 2001 11298545 (England)	No Data	Unsure	Unsure (The two treatment groups were comparable concerning medical history of the patients and status at the medical examination.)	No (No blinding regimen was possible due to the nature of the treatment procedures.)	No (No blinding regimen was possible due to the nature of the treatment procedures.)	No Data	Yes	No	No	Yes		Low to moderate due to poor reporting
Wettstein 2013	Yes	No Data	Yes	Yes	Yes	No Data	Yes	No	No	Yes	(Low)	Low

Study	Adequate generation of a randomized sequence reported	Adequate allocation concealment reported	Group similarity at baseline	Adequate blinding of PATIENTS reported	Adequate blinding of PROVIDERS reported	Adequate blinding of OUTCOME ASSESSORS reported	Intention to treat analysis ?	Incom-plete results data	Incomplete results data: Differential missingness	Adverse events (of interest) precisely defined	Selective Reporting	Overall, by outcome
23566745 (Switzerland)												

Table F-2. NRCS

Study	Group similarity at baseline	Adequate blinding of outcome assessors	Incomplete results data	Differential missingness	Adverse events (of interest) precisely defined		Selective Reporting	Overall, by outcome
Ahmed 2000 11069453 (UK)	Unsure (Baseline data not given by arm except lesion location, which was balanced)	No		Unsure (okay for clinical clearance and pain; problematic for recurrence)	Unsure (dropouts not given by arm)			High (primarily because of unclear reporting)
Ballester-Sanchez 2016 26985197 (Spain)	Unsure (ages differ significantly; exact location of tumors not given)	No	No	No	Unsure (only 2 AEs reported, but those were reported well)	Unsure (Unclear results reporting)		Moderate
Chren 2013 23190903 (U.S.)	No (Patients, tumors, and care differed in the treatment groups (Table 1). For example, tumors treated with destruction were much less likely to be located in the H-zone of the face, and much less likely to have	Yes (primary source of data on recurrence was the medical record. patients who consented were examined a median of 8.6 years after treatment by a dermatologist (MMC) blinded to treatment type.)	No (Patients lost to follow-up were similar to those with follow-up in most features but were more likely to be female (38% vs. 26%), to have worse mental health status (median SF-12 Mental Component	No	No (Adverse events were not reported in any of the 4 papers from this study)	(Consecutive patients)		Low

Study	Group similarity at baseline	Adequate blinding of outcome assessors	Incomplete results data	Differential missingness	Adverse events (of interest) precisely defined		Selective Reporting	Overall, by outcome
	histological risk factors for recurrence.)		Score 41.2 vs 51.5), and to have BCC rather than SCC (89% vs 75%).)					
Cosgarea 2012 22738399 (Romania)	Yes	No	No	No	No	Yes (Baseline numbers for skin type and # lesions per patient do not add up)	No	Moderate
Graells 2014 24139468 (Spain)	No (The imiquimod and surgery groups differed: higher frequency of superficial BCCs in patients treated with imiquimod vs. surgery, the proportion of patients with a history of multiple BCCs and current multiple BCCs was higher in the group of patients who received imiquimod.)	No	Unsure (For "subsequent BCC" outcome, 67 subjects were lost to follow-up (10.7% of whole group), but distribution of missing by arm is not reported.)	No	Unsure (AE was only defined for Imiquimod. Imiquimod-induced inflammation was classified as mild (not requiring any change in treatment), moderate (requir- ing the addition of a corticosteroid-antibiotic cream but no change in imiquimod treatment), or intense (requiring the temporary or permanent withdrawal of treatment).)	Yes (Multivariate analysis did not include variables such as: size, histology, or location of BCC), all of which may explain the difference in risk between imiquimod and surgery.)	No (Lack of clinical clearance was not reported for surgery arm. Adverse Events were only defined for Imiquimod arm. No AEs reported for surgery arm.)	High
Lippert 2013 23725586 (Czech Republic)	Yes	No	No	No	Unsure (AEs not reported in depth)		Unsure (Cosmetic outcomes not reported by arm)	Moderate to low (outcome assessors not blinded; AEs and cosmetic outcomes given very short shrift)

Study	Group similarity at baseline	Adequate blinding of outcome assessors	Incomplete results data	Differential missingness	Adverse events (of interest) precisely defined		Selective Reporting	Overall, by outcome
Pampena 2016 26589877 (Italy)	Yes (nothing > 20% differential, mean age may be of concern)	Yes (OS and DFS likely not affected by blinding. Cosmetic outcome assessor blinded)	No (no missing)	No (no missing)	No Data (no AEs)		No (all 3 outcomes reported)	Low (NRCS, no Aes)
Shah 2009 19588534 (U.S.)	Unsure (stated, but baselines not given for controls)	No	No	No	No (AEs not reported)			Moderate
Sofen 2015 25913533 (U.S.)	Unsure (From the baseline table, yes, but the number in each region for each arm is not given.)	No	Yes	Yes	Yes		No	Moderate (NRCS, no Aes)
Sullivan 2003 14725659 (US)	(some differences, but most likely due to small sample size)	Yes (dermatologist and pathologist blinded)	No (no missing)	No (no missing)	No Data (none reported)	(small sample size (6 per arm))	Yes (no AEs)	Moderate
Wilson 2012 22145798 (U.S.)	No (Statistically significant difference between patients at private site and VA site in terms of Age (private patients are younger), gender (private patients are more female), annual income (private patients are less likely to	No Data (Blinding of outcome assessors not reported.Exposure of interest was treatment center: private treatment center or VA center.)	Low Risk (No loss of follow-up reported.)	Low Risk	No Data (Authors do not mention AEs at all.)	No	No	Low (Differences at Baseline were controlled for in multivariate analysis. It is reported that it is unlikely that Clinical differences of patients accounted for all the variation in care between the treatment centers)

Study	Group similarity at baseline	Adequate blinding of outcome assessors	Incomplete results data	Differential missingness	Adverse events (of interest) precisely defined		Selective Reporting	Overall, by outcome
	be poor), tumor size (private tumors are smaller in diameter), histologic type (private tumors are less likely to be SCC), location (private tumors are less likely to be on head and neck), and H-zone (private tumors are less likely to be in the h-zone of the face).)							

Appendix G. Summary Results From Unadjusted NRCS

Table G-1. Summary results from unadjusted NRCS

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
Rank 1973 4700671	1942	BCC	A. Surgical Excision without interoperative evaluation	unclear whether the n here is lesions or patients	Recurrence	3/566 (0.5)		*A vs. D1: 0.14 (0.04, 0.47)*	n	
Rank 1973 4700671	1942	BCC	D1. External beam radiation	unclear whether the n here is lesions or patients	Recurrence	31/857 (3.6)			n	
Rank 1973 4700671	1942	SCC	A. Surgical Excision without interoperative evaluation	unclear whether the n here is lesions or patients	Recurrence	4/288 (1.4)		A vs. D1: 0.45 (0.13, 1.56)	n	
Rank 1973 4700671	1942	SCC	D1. External beam radiation	unclear whether the n here is lesions or patients	Recurrence	7/231 (3)			n	
Chernosky 1978 663726	1898	BCC + SCC	A. Surgical Excision without interoperative evaluation		Recurrence		6/494 (1.21)	A vs. D1: 0.47 (0.17, 1.31)	n	
Chernosky 1978 663726	1898	BCC + SCC	D1. External beam radiation		Recurrence		10/395 (2.53)	D1 vs. C2: 1.53 (0.77, 3.07)	n	
Chernosky 1978 663726	1898	BCC + SCC	C2. Diathermy/electrodessication		Recurrence		46/2763 (1.66)	A vs. C2: 0.73 (0.31, 1.71)	n	
Mazeron 1988 3146781	1326	BCC + SCC (nose)	D2. Brachytherapy/Pleisiotherapy	interstitial implantation	Recurrence		19/578 (3.3)	D2 vs. D1 (ortho): 0.68 (0.38, 1.21)	y	cosmetic outcomes

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
Mazeron 1988 3146781	1326	BCC + SCC (nose)	D1. External beam radiation	orthovoltage	Recurrence		31/648 (4.7)	*D1 (ortho) vs. D1 (mega): 0.21 (0.12, 0.4)*	y	cosmetic outcomes
Mazeron 1988 3146781	1326	BCC + SCC (nose)	D1. External beam radiation	megavoltage	Recurrence		19/100 (19)	*D2 vs. D1 (mega): 0.14 (0.07, 0.29)*	y	cosmetic outcomes
Knox 1967 6020491	1417	BCC	D1. External beam radiation	xray	Lack of cure		7/144 (4.8)	A vs. D1: 0.66 (0.25, 1.73)	n	
Knox 1967 6020491	1417	BCC	A. Surgical Excision without interoperative evaluation		Lack of cure		11/339 (3.2)	A vs. C2: 1.84 (0.85, 3.96)	n	
Knox 1967 6020491	1417	BCC	C2. Diathermy/electrodessication		Lack of cure		17/948 (1.8)	*D1 vs. C2: 2.8 (1.14, 6.87)*	n	
Knox 1967 6020491	1417	SCC	D1. External beam radiation	xray	Lack of cure		8/101 (7.9)	A vs. D1: 0.52 (0.19, 1.38)	n	
Knox 1967 6020491	1417	SCC	A. Surgical Excision without interoperative evaluation		Lack of cure		9/211 (4.3)	*A vs. C2: 3.42 (1.26, 9.32)*	n	
Knox 1967 6020491	1417	SCC	C2. Diathermy/electrodessication		Lack of cure		7/545 (1.3)	*D1 vs. C2: 6.61 (2.34, 18.67)*	n	
Tourli 2016 26870972	1380	BCC (head and neck region)	A. Surgical Excision without interoperative evaluation	wide excision	Recurrence		5/380 (1.4)	*A vs B: 5.65 (1.34, 23.75)*	n	
Tourli 2016 26870972	1380	BCC (head and neck region)	B. Surgical Excision with interoperative evaluation	delayed Mohs	Recurrence		3/1274 (0.23)		n	
Ashby 1989 2702595	1154	BCC + SCC	A. Surgical Excision without		Lack of cure	18/614 (2.9)		*A vs. D1: 0.46 (0.25,*	n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
			interoperative evaluation					*0.83)*		
Ashby 1989 2702595	1154	BCC + SCC	D1. External beam radiation		Lack of cure	30/482 (6.2)		D1 vs. C1: 0.73 (0.09, 5.85)	n	
Ashby 1989 2702595	1154	BCC + SCC	C1. Cryotherapy		Lack of cure	1/12 (8.3)		A vs. C1: 0.33 (0.04, 2.71)	n	
Futoryan 1995 7773598	1047	BCC + SCC	B. Surgical Excision with interoperative evaluation		infection		13/530 (2.5)	A vs. B: 0.86 (0.38, 1.95)	y	
Futoryan 1995 7773598	1047	BCC + SCC	A. Surgical Excision without interoperative evaluation		infection		11/517 (2.1)		y	
Honeycutt 1973 4750203	484	SCC	C2. Diathermy/electrodessication		Recurrence		3/281 (1.1)		n	
Honeycutt 1973 4750203	484	SCC	D1. External beam radiation		Recurrence		0/18 (0)		n	
Honeycutt 1973 4750203	484	SCC lip	C2. Diathermy/electrodessication		Recurrence		3/29 (10.3)	A vs. C2: 1.24 (0.18, 8.31)	n	
Honeycutt 1973 4750203	484	SCC lip	A. Surgical Excision without interoperative evaluation		Recurrence		2/16 (12.5)		n	
Jebodhsingh 2012 22560426	385	BCC (periocular)	A. Surgical Excision without interoperative evaluation		Recurrence	51/346 (15)		A vs. B: 2.31 (0.69, 7.73)	n	
Jebodhsingh 2012 22560426	385	BCC (periocular)	B. Surgical Excision with interoperative evaluation	Mohs	Recurrence	3/43 (8)			n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
Van Hezewijk 2010	333	BCC + SCC	D1. External beam radiation	54 gy	Recurrence		5/159 (3.1)	D1 (high dose) vs. D1 (low dose): 0.86 (0.29, 2.56)	n	cosmetic outcomes
Van Hezewijk 2010	333	BCC + SCC	D1. External beam radiation	44 gy	Recurrence		10/275 (3.6)		n	cosmetic outcomes
Hansen 2008 18363722	298	Bowen's	A. Surgical Excision without interoperative evaluation	elliptical or shave excision	Recurrence		8/188 (4.3)		n	
Hansen 2008 18363722	298	Bowen's	C1. Cryotherapy		Recurrence		2/24 (8.3)		n	
Hansen 2008 18363722	298	Bowen's	C3. Curettage + diathermy	Curettage and fulgaration	Recurrence		2/46 (4.3)		n	
Hansen 2008 18363722	298	Bowen's	F1. Topical or intralesional 5-FU...Define:	topical	Recurrence		1/24 (4.2)		n	
Hansen 2008 18363722	298	Bowen's	B. Surgical Excision with interoperative evaluation	Mohs	Recurrence		2/83 (2.4)		n	
Hansen 2008 18363722	298	Bowen's	C2. Diathermy/electrodessication		Recurrence		0/16 (0)		n	
Hansen 2008 18363722	298	Bowen's	F2. Topical or intralesional Imiquimod...Define:	topical	Recurrence		0/7 (0)		n	
Pereira 2013 23486132	289	NMSC	A. Surgical Excision without interoperative evaluation		Recurrence	29/289 (10)		*A vs. B: 3.61 (1.47, 8.86)*	n	
Pereira 2013	289	NMSC	B. Surgical	Mohs	Recurrence	6/200 (3)			n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
23486132			Excision with interoperative evaluation							
Nevrkla 1974 4425623	200	BCC	A. Surgical Excision without interoperative evaluation		Recurrence	1/35 (2.9)		A vs. D1: 0.44 (0.05, 3.68)	y	
Nevrkla 1974 4425623	200	BCC	D1. External beam radiation	low-voltage x-rays	Recurrence	8/129 (6.2)		D1 vs D2: 0.73 (0.18, 2.9)	y	
Nevrkla 1974 4425623	200	BCC	D2. Brachytherapy/Pleisiotherapy	implant of radium needles or radon seeds	Recurrence	3/36 (8.3)		A vs. D2: 0.32 (0.03, 3.27)	y	
Werlinger 2002 12472494	191	SCC	A. Surgical Excision without interoperative evaluation		Recurrence		0/20 (0)		n	
Werlinger 2002 12472494	191	SCC	C3. Curettage + diathermy	Curettage & Desiccation	Recurrence		2/56 (3.6)		n	
Werlinger 2002 12472494	191	BCC	A. Surgical Excision without interoperative evaluation		Recurrence		1/90 (1.1)	A vs. C3: 0.37 (0.04, 3.63)	n	
Werlinger 2002 12472494	191	BCC	C3. Curettage + diathermy	Curettage & Desiccation	Recurrence		3/102 (2.9)		n	
McIntosh 1983 6647186	186	BCC	A. Surgical Excision without interoperative evaluation		Recurrence		5/62 (8.1)	A vs. D1: 4.25 (0.8, 22.65)	n	
McIntosh 1983 6647186	186	BCC	D1. External beam radiation		Recurrence		2/99 (2)	D1 vs. C1: 0.33 (0.04, 2.44)	n	
McIntosh 1983	186	BCC	C1. Cryotherapy		Recurrence		2/34 (5.9)	A vs. C1: 1.4 (0.26, 7.65)	n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
6647186										
Harrison 1987 3676083	123	BCC	A. Surgical Excision without interoperative evaluation		Recurrence	2/15 (13.3)		A vs. C3: 1.85 (0.15, 23.07)	y	
Harrison 1987 3676083	123	BCC	C3. Curettage + diathermy	Curettage and cautery	Recurrence	1/13 (7.7)			y	
Mebed 2010 21503006	120	BCC+SCC	A. Surgical Excision without interoperative evaluation	with and without adjuvant radiotherapy	Recurrence	2/103 (1.9)			y	
Mebed 2010 21503006	120	BCC+SCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional	Recurrence	3/7 (42.9)			y	
Mebed 2010 21503006	120	BCC+SCC	D1. External beam radiation		Recurrence	0/8 (0)			y	
Tarstedt 2016 26841041	116	Bowen's	E1. PDT: MAL + red light...Define:		Lack of clinical clearance		4/18 (22.2)	E1 vs. E2: 2.29 (0.22, 24.14)	n	
Tarstedt 2016 26841041	116	Bowen's	E2. PDT: ALA + blue light...Define:		Lack of clinical clearance		1/9 (11.1)		n	
Tarstedt 2016 26841041	116	nodal BCC	E1. PDT: MAL + red light...Define:		Lack of clinical clearance		4/25 (16)	E1 vs. E2: 1.02 (0.2, 5.2)	n	
Tarstedt 2016 26841041	116	nodal BCC	E2. PDT: ALA + blue light...Define:		Lack of clinical clearance		3/19 (15.8)		n	
Tarstedt 2016 26841041	116	superficial BCC	E1. PDT: MAL + red light...Define:		Lack of clinical clearance		5/39 (12.8)	E1 vs. E2: 1.08 (0.23, 4.97)	n	
Tarstedt 2016 26841041	116	superficial BCC	E2. PDT: ALA + blue light...Define:		Lack of clinical clearance		3/25 (12)		n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
Avila 1977 589557	97	BCC+SCC (pinna)	A. Surgical Excision without interoperative evaluation		Recurrence	2/50 (4)		A vs. D1: 0.27 (0.05, 1.42)	y	
Avila 1977 589557	97	BCC+SCC (pinna)	D1. External beam radiation	x-rays	Recurrence	6/45 (13.3)			y	
Wang 2016	95	BCC	E3. PDT other (specify)...Define:	PDT combined with the application of the topical photosensitizer ALA and systemic light-sensitive drug HPD	Lack of clinical clearance	0/9 (0)	0/14 (0)		n	
Wang 2016	95	BCC	E3. PDT other (specify)...Define:	HPD-PDT	Lack of clinical clearance	2/13 (15.4)	2/13 (15.4)		n	
Wang 2016	95	BCC	E2. PDT: ALA + blue light...Define:	ALA-PDT following CO2 laser vaporization	Lack of clinical clearance	0/14 (0)	0/14 (0)		n	
Wang 2016	95	SCC	E3. PDT other (specify)...Define:	PDT combined with the application of the topical photosensitizer ALA and systemic light-sensitive drug HPD	Lack of clinical clearance		1/26 (3.8)		n	
Wang 2016	95	SCC	E3. PDT other (specify)...Define:	HPD-PDT	Lack of clinical clearance	0/10 (0)	0/10 (0)		n	
Wang 2016	95	SCC	E2. PDT: ALA + blue	ALA-PDT following CO2	Lack of clinical clearance		2/18 (11.1)		n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
			light...Define:	laser vaporization						
Cox 1995 7669642	91	Bowen's	C1. Cryotherapy		Recurrence		6/82 (7.3)		y	
Cox 1995 7669642	91	Bowen's	D1. External beam radiation		Recurrence		0/59 (0)		y	
Kowalzick 1994	87	BCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional 1 MU/weekly for 3 weeks	Lack of clinical clearance	4/7 (57.1)			y	
Kowalzick 1994	87	BCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional 3 MU/weekly for 3 weeks	Lack of clinical clearance	6/7 (85.7)			y	
Kowalzick 1994	87	BCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional 0.5 MU/twice weekly for 3 weeks	Lack of clinical clearance	6/7 (85.7)			y	
Kowalzick 1994	87	BCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional 1 MU/twice weekly for 3 weeks	Lack of clinical clearance	6/10 (60)			y	
Kowalzick 1994	87	BCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional 3 MU/twice weekly for 3 weeks	Lack of clinical clearance	5/10 (50)			y	
Kowalzick 1994	87	BCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional 0.5 MU/three times weekly for 3 weeks	Lack of clinical clearance	5/14 (35.7)			y	
Kowalzick 1994	87	BCC	F3. Topical or intralesional Interferon (INF)...Define:	intralesional 1 MU/three times weekly for 3 weeks	Lack of clinical clearance	2/14 (14.3)			y	
Reschly 2010 20677531	75	SCC (males over age 60)	C3. Curettage + diathermy	Curettage & Electrodesiccation	Recurrence		0/14 (0)		n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
Reschly 2010 20677531	75	SCC (males over age 60)	A. Surgical Excision without interoperative evaluation		Recurrence		1/16 (6)		n	
Bean 1984 6463702	70	BCC+SCC (hand)	A. Surgical Excision without interoperative evaluation		Recurrence		2/67 (3)		n	metastasis
Bean 1984 6463702	70	BCC+SCC (hand)	D1. External beam radiation		Recurrence		1/3 (33.3)		n	metastasis
Bean 1984 6463702	70	BCC+SCC (hand)	F1. Topical or intralesional 5-FU...Define:		Recurrence		3/3 (100)		n	metastasis
Bean 1984 6463702	70	BCC+SCC (hand)	C2. Diathermy/electrodessication		Recurrence		1/3 (33.3)		n	metastasis
Bean 1984 6463702	70	BCC+SCC (hand)	C1. Cryotherapy		Recurrence		1/3 (33.3)		n	metastasis
Cham 1991 1913614	41	BCC	F5. Medical other...Define:	BEC (Curaderm)	Lack of clinical clearance		0/39 (0)		y	
Cham 1991 1913614	41	BCC	F5. Medical other...Define:	placebo	Lack of clinical clearance		2/2 (100)		y	
Aguilar 2010 20456549	67	BCC+SCC	A. Surgical Excision without interoperative evaluation		Lack of clinical clearance (1-efficacy)		1/34 (2.5)	A vs. E1: 0.25 (0.02, 2.58)	n	costs
Aguilar 2010 20456549	67	BCC+SCC	E1. PDT: MAL + red light...Define:		Lack of clinical clearance (1-efficacy)		3/28 (10.5)	E1 vs. F2: 0.84 (0.15, 4.61)	n	costs
Aguilar 2010 20456549	67	BCC+SCC	F2. Topical or intralesional Imiquimod...Define:	topical	Lack of clinical clearance (1-efficacy)		3/24 (12.5)	A vs. F2: 0.21 (0.02, 2.18)	n	costs
Marks 2004	67	BCC	F2. Topical or intralesional Imiquimod...Define:	topical 5 times/week	Lack of clinical clearance	0/36 (0)			y	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
Marks 2004	67	BCC	F2. Topical or intralesional Imiquimod...Define:	topical 7 times/week	Lack of clinical clearance	2/30 (7)			y	
Kadakia 2016 26780196	53	SCC (scalp) immunocompromised	A. Surgical Excision without interoperative evaluation	Surgical excision or Mohs with post-operative radiation	Recurrence	8/45 (17.8)		A + D1 vs A: 0.36 (0.07, 1.83)	y	metastasis/ death
Kadakia 2016 26780196	53	SCC (scalp) immunocompromised	A. Surgical Excision without interoperative evaluation	Surgical excision or Mohs	Recurrence	3/8 (37.5)			y	metastasis/ death
Shiffman 1975 1125865	52	SCC (pinna)	A. Surgical Excision without interoperative evaluation		Recurrence	2/31 (6.5)		A vs. C3: 0.19 (0.03, 1.19)	n	metastasis
Shiffman 1975 1125865	52	SCC (pinna)	C3. Curettage + diathermy	curettage + electrodessication or surgery	Recurrence	4/15 (26.7)			n	metastasis
Ibbotson 2012 22971196	40	BCC	E1. PDT: MAL + red light...Define:		Lack of clinical clearance	8/20 (40)		E1 vs. E2: 1.24 (0.34, 4.46)	y	
Ibbotson 2012 22971196	40	BCC	E2. PDT: ALA + blue light...Define:		Lack of clinical clearance	7/20 (35)			y	
Yoon 1992 1463102	40	SCC	A. Surgical Excision without interoperative evaluation	excision only	Recurrence	8/13 (62)		A vs. B: 3.52 (0.76, 16.39)	n	metastasis/ death
Yoon 1992 1463102	40	SCC	B. Surgical Excision with interoperative evaluation	Mohs	Recurrence	5/16 (31)			n	metastasis/ death
Glass 1974	24	epidermoid	A. Surgical		Recurrence	2/19 (10.5)		A vs. D1:	n	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
4808574		carcinoma; incompletely excised	Excision without interoperative evaluation					0.47 (0.03, 6.57)		
Glass 1974 4808574	24	epidermoid carcinoma; incompletely excised	D1. External beam radiation	radiotherapy	Recurrence	1/5 (20)			n	
Valentine 2011 21077899	40	BCC	E1. PDT: MAL + red light...Define:	10 gp2					y	
Valentine 2011 21077899	40	BCC	E2. PDT: ALA + blue light...Define:	10 gp1					y	
Valentine 2011 21077899	40	Bowen's	E1. PDT: MAL + red light...Define:	10 gp 4					y	
Valentine 2011 21077899	40	Bowen's	E2. PDT: ALA + blue light...Define:	10 gp 3					y	
Halnan 1968 5710508	104	BCC + SCC	A. Surgical Excision without interoperative evaluation	10 lesions					y	cosmetic outcomes
Halnan 1968 5710508	104	BCC + SCC	D1. External beam radiation	x-ray therapy = 58 lesions					y	cosmetic outcomes
Halnan 1968 5710508	104	BCC + SCC	D2. Brachytherapy/Pleisiotherapy	radon gold see implant = 38 lesions					y	cosmetic outcomes
Bu 2016 27888160	20	BCC	E2. PDT: ALA + blue light...Define:	Excision + ALA PDT	Recurrence	0/10 (0)				
Bu 2016 27888160	20	BCC	A. Surgical Excision without interoperative evaluation	Excision + excision	recurrence	0/10 (0)				
Haseltine 2016	61	BCC + SCC	D2. Brachytherapy/Pl		Lack of clinical clearance	0/8 (0)		D2 vs D1: 0.04 (0,	y	cosmetic outcomes

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
27504127			eisiotherapy					21.14)		
Haseltine 2016 27504127	61	BCC + SCC	D1. External beam radiation	hypofractionation	Lack of clinical clearance	7/29 (24)		D2 vs D1: 0.05 (0, 27.38)	y	cosmetic outcomes
Haseltine 2016 27504127	61	BCC + SCC	D1. External beam radiation	standard fractionation	Lack of clinical clearance	4/20 (20)		D1 vs D1:1.27 (0.32, 5.09)	y	cosmetic outcomes
Salido-Vallejo 2016 26369617	86	SCC (infiltrating)	F5. Medical other...Define:	Methotrexate + excision	tumor area reduction	43	neg 0.52 cm2 (0.85)	mean difference -1.01 (-1.38, -0.64) P<0.001	y	
Salido-Vallejo 2016 26369617	86	SCC (infiltrating)	A. Surgical Excision without interoperative evaluation	excision only	tumor area reduction	43	0.49 cm2 (0..88)		y	
Overmark 2016 26073523	239	SCC (in situ)	A. Surgical Excision without interoperative evaluation		recurrence		1/125 (0.8)	A vs. C1: 0.16 (0.02, 1.61)		
Overmark 2016 26073523	239	SCC (in situ)	C1. Cryotherapy		recurrence		3/64 (4.7)	C1 vs E1: 0.23 (0.06, 0.85)		
Overmark 2016 26073523	239	SCC (in situ)	E1. PDT: MAL + red light...Define:		recurrence		13/74 (18)	A vs E1: 0.04 (0, 0.3)		
Nassiripour_2016_28163737	630	BCC + SCC	A. Surgical Excision without interoperative evaluation		recurrence	28/354 (7.9)		A vs B: 0.9 (0.51, 1.59)		
Nassiripour_2016_28163737	630	BCC + SCC	B. Surgical Excision with interoperative evaluation		recurrence	24/276 (8.7)				
Marconi 2016	597	BCC + SCC	D1. External beam radiation	2 Gy	lack of histological clearance		32/500 (6.4)	D1 (high dose) vs. D1 (low dose):	y	

Author year PMID	Total N (patients)	Lesion type (location)	Treatment	Treatment notes	Outcome (lack of clearance/ recurrence)	n patients (in arm)/N patients (in arm) (% patients)	n lesions (arm)/N lesions (in arm) (% lesions)	Odds Ratio (95% CI)	Adverse events reported (y/n)	Aditional outcomes reported
								0.26 (0.12, 0.54)		
Marconi 2016	597	BCC + SCC	D1. External beam radiation	> 2 Gy	lack of histological clearance		9/521 (1.7)		y	

Appendix H. Adverse Events Reported

Arm type	Outcome Description	# studies reporting outcome
cryotherapy	Blistering	3
cryotherapy	wound infection	3
cryotherapy	Necrosis	4
cryotherapy	Ulceration	4
cryotherapy	inflammation/swelling	5
cryotherapy	scarring	5
cryotherapy	pain	24
excision	bleeding	5
excision	cataract and lachrymal duct stenosis	1
excision	crusting	10
excision	dyspigmentations and telangiectasia	2
excision	Ectropion	1
excision	edema/oedema	5
excision	erosion	6
excision	Erythema	14
excision	headache	1
excision	inflammation/swelling	5
excision	itching	10
excision	malaise	1
excision	necrosis	4
excision	pain	25
excision	photosensitivity reaction	1
excision	Radiodystrophy	1
excision	scabbing	1
excision	scaling	4
excision	soreness	1
excision	spots or pimples	1
excision	skin infection	1
excision	skin irritation	9
excision	swelling	1
excision	weeping	1
excision	wound dehiscence	2
excision	wound infection	3
laser	dyspigmentation	2
laser	hypopigmentation	2
laser	Purpura	2
laser	blistering	3
laser	bullae	3
laser	scarring	5

Arm type	Outcome Description	# studies reporting outcome
laser	crusting	10
laser	Erythema	13
medical	Alanine aminotransferase elevation	1
medical	alkaline phosphatase elevation	2
medical	application site reaction	5
medical	arthralgia	1
medical	back pain	1
medical	bleeding	5
medical	Blink discomfort and dry eye	1
medical	Burning	9
medical	crusting	10
medical	Desquamation	1
medical	diarrhea	2
medical	discharge	1
medical	drainage	1
medical	Ectropion	1
medical	edema/oedema	5
medical	erosion	6
medical	Erythema	14
medical	excoriation/flaking	2
medical	fatigue	2
medical	fever	1
medical	headache	4
medical	hypopigmentation	2
medical	induration	1
medical	inflammation/swelling	5
medical	Intense conjunctival irritation	1
medical	itching	10
medical	lesions at remote site	1
medical	leukopenia	1
medical	loss of eyelashes	1
medical	malaise/cold or flu like symptoms	3
medical	nausea	3
medical	necrosis	4
medical	pain	25
medical	Paresthesia	1
medical	Pruritus	2
medical	pustules	1
medical	rash	3
medical	redness	2
medical	scabbing	4

Arm type	Outcome Description	# studies reporting outcome
medical	Scaling	4
medical	sensitivity	1
medical	sinusitis	1
medical	skin irritation	9
medical	soreness	1
medical	spots or pimples	1
medical	swelling	1
medical	Telangiectasia	1
medical	tenderness	2
medical	thrombocytopenia	1
medical	Ulceration	4
medical	upper respiritory tract infection	1
medical	Vesicles	3
medical	weeping	2
medical	Wound dehiscence	2
medical	Wounds	1
PDT	oozing	1
PDT	photosensitivity reaction	1
PDT	skin infection	1
PDT	squamae	1
PDT	tingling	1
PDT	warmth	1
PDT	hypopigmentation	1
PDT	hyperpigmentation	3
PDT	Infection	2
PDT	redness	2
PDT	wound dehiscence	2
PDT	Blistering	3
PDT	bullae	3
PDT	stinging	3
PDT	vesicles	3
PDT	wound infection	3
PDT	bleeding	4
PDT	scaling	4
PDT	Ulceration	4
PDT	necrosis	4
PDT	edema/oedema	5
PDT	erosion	6
PDT	scarring	6
PDT	inflamation/swelling	5
PDT	burning	9

Arm type	Outcome Description	# studies reporting outcome
PDT	skin irritation	10
PDT	itching	9
PDT	crusting	10
PDT	Erythema	13
PDT	pain	25
radiotherapy	Blink discomfort and dry eye	1
radiotherapy	cataract and lachrymal duct stenosis	1
radiotherapy	Intense conjunctival irritation	1
radiotherapy	loss of eyelashes	1
radiotherapy	Radiodystrophy	1
radiotherapy	slight pain in lower eyelid	1
radiotherapy	dyspigmentations and telangiectasia	2
radiotherapy	Ectropion	2
radiotherapy	Necrosis	4
radiotherapy	scarring	5

Appendix I. Study-Level Results

Table I-1. Recurrence, all BCC

Study	Arm	Lesion Location	n/N	Result
11298545 Wang	(E) cryosurgery	NR	6/39	OR 0.7 (0.4, 1.22)
11298545 Wang	(C) ALA-PDT	NR	11/44	OR 0.7 (0.4, 1.22)
14732655 Rhodes	(A,B) excision	face/scalp (58), extremities (9), trunk/neck (29)	0/35	OR 0.08 (0.01, 0.52)
14732655 Rhodes	(E) MAL PDT	face/scalp (40), extremities (11), trunk/neck (49)	0/31	OR 0.08 (0.01, 0.52)
17451581 Kuijpers	(A,B) Surgical excision	Forehead/temple, Cheek/chin, Periocular (76), Lips/mouth (6), Ears/periauricular (6), Neck, chest/back (12)	4/47	OR 0.42 (0.14, 1.25)
17451581 Kuijpers	(C) Curettage + Cryosurgery	Forehead/temple, Cheek/chin, Periocular (80), Lips/mouth (4), Ears/periauricular (8), Neck, chest/back (8)	9/38	OR 0.42 (0.14, 1.25)
18693158 Basset-Seguin	(E) Cryotherapy	face/scalp (4), extremities (20), trunk/neck (76)	19/93	OR 0.7 (0.4, 1.22)
18693158 Basset-Seguin	(C) MAL-PDT	face/scalp (6), extremities (22), trunk/neck (72)	22/100	OR 0.7 (0.4, 1.22)
18717680 Mosterd	(A,B) Surgical excision	face (51); \rest of the body\ (49%)	0/88	OR 0.08 (0.01, 0.52)
18717680 Mosterd	(E) ALA-PDT	face (53); \rest of the body\ (47%)	25/83	OR 0.08 (0.01, 0.52)
21242584 Garcia-Martin	(D) radiotherapy	eyelid (100)	0/12	OR 1.24 (0.02, 67.04)
21242584 Garcia-Martin	(F) imiquimod 5%	eyelid (100)	0/15	OR 1.24 (0.02, 67.04)
24903544 Haak	(E) AFXL MAL PDT	nose (56), forehead (19), cheek (13), oral area (6), periorbital area (6)	3/16	OR 0.7 (0.4, 1.22)
24903544 Haak	(C) MAL PDT	nose (37), forehead (31), cheek (6), oral area (13), periorbital area (13)	7/16	OR 0.7 (0.4, 1.22)
3514075 Hall	(D) Cryotherapy	face and neck (65), eyelid (17), trunk (17)	17/44	OR 14.8 (3.17, 69)
3514075 Hall	(C) Radiotherapy	face and neck (82), eyelid (6), trunk (12)	2/49	OR 14.8 (3.17, 69)
9218740 Avril	(A,B) surgery	nose (53), cheek, pre- and retroauricular areas (21), eyelids, internal and external eye angles (19), forehead, temple, between eyebrows 36 (21), chin, cutaneous superior lip 10 (6), ear (3)	1/174	OR 0.12 (0.01, 0.96)
9218740 Avril	(D) radiotherapy	nose (28), cheek, pre- and retroauricular areas (24), eyelids, internal and external eye angles (20), forehead, temple, between eyebrows (17), chin, cutaneous superior lip (7), ear (3)	8/173	OR 0.12 (0.01, 0.96)
Abbade	(A,B) Surgical excision	head and neck (100)	0/35	OR 0.08 (0.01, 0.52)
Abbade	(E) MAL-PDT	head and neck (100)	2/33	OR 0.08 (0.01, 0.52)
Salmanpoor	(A,B) Surgical excision	face and scalp (100)	2/24	OR 0.42 (0.14, 1.25)
Salmanpoor	(A,B) Surgical excision	face and scalp (100)	2/24	OR 0.36 (0.06, 2.23)

Study	Arm	Lesion Location	n/N	Result
Salmanpoor	(C) Electodessication and curettage	face and scalp (100)	2/25	OR 0.35 (0.06, 2.13)
Salmanpoor	(C) Electodessication and curettage	face and scalp (100)	2/25	OR 0.42 (0.14, 1.25)
Salmanpoor	(H) Curettage	face and scalp (100)	4/20	OR 0.36 (0.06, 2.23)
Salmanpoor	(H) Curettage	face and scalp (100)	4/20	OR 0.35 (0.06, 2.13)
Carija	(E) ALA PDT + PDL	extremities (23.5), trunk/neck (76.5)	5/25	OR 0.79 (0.46, 1.34)
Carija	(C) ALA PDT	extremities (3.6), trunk/neck (96.4)	1/22	OR 0.79 (0.46, 1.34)
Bath-Hextall	(F2) Imiquimod	Face (37), Trunk (38), Neck (6), Arm (6), Leg (10), Other (3)	11/206	OR 4.94 (1.08, 22.58)
Bath-Hextall	(A) Excision	Face (33), Trunk (39), Neck (9) Arm (7), Leg (9), Other (3)	2/177	OR 4.94 (1.08, 22.58)

Table I-2. Lack of histological clearance, all BCC

Study	Arm	Lesion Location	n/N	Result
10570388 Beutner	(F) imiquimod 5%	NR	20/24	OR 0.16 (0.02, 1.56)
10570388 Beutner	(I,J) vehicle (3 2x/day, 2 1x/day, 2 3x/week, 2 2x/week, 2 1x/week)	face (9), upper extremity (46), anterior upper trunk (9), neck (9), posterior lower trunk (27)	1/11	OR 0.16 (0.02, 1.56)
10940063 Thissen	(A,B) surgical excision	face (43), eyelid (8), trunk/neck (14), forehead/temple (25), chin/perioral (10)	0/48	OR 0.13 (0.01, 2.67)
10940063 Thissen	(C) cryotherapy	face (46), eyelid (4), ear (4), trunk/neck (6), forehead/temple (34), chin/perioral (6)	3/48	OR 0.13 (0.01, 2.67)
11298545 Wang	(C) cryosurgery	NR	6/39	OR 0.62 (0.26, 1.49)
11298545 Wang	(E) ALA-PDT	NR	11/44	OR 0.62 (0.26, 1.49)
12196749 Geisse	(F) Imiquimod 5%	NR	23/94	OR 0.16 (0.02, 1.56)
12196749 Geisse	(I,J) vehicle (control)	neck/face/forehead (9), upper extremity (not hand) (34), trunk (47), lower extremity/thigh (not foot) (9)	26/31	OR 0.16 (0.02, 1.56)
12224977-12 week Shumack	(F) Imiquimod 5%	NR	21/68	OR 0.16 (0.02, 1.56)
12224977-12 week Shumack	(I,J) vehicle cream	face (17), trunk/neck (54.2), upper extremity (not hand) (25), lower extremity (not foot) (4)	21/24	OR 0.16 (0.02, 1.56)
15097956 Geisse	(F) Imiquimod 5%	NR	49/346	OR 0.16 (0.02, 1.56)
15097956 Geisse	(I,J) Vehicle 5x/wk or 7x/wk	neck (1), trunk: anterior lower (1), trunk: anterior upper (20), trunk: posterior lower (6), trunk: posterior upper (20), lower extremity (excluding foot) (10.5), upper extremity (excluding hand) (39), cheek (1), chin (1), forehead (1)	335/346	OR 0.16 (0.02, 1.56)
15888150 Schulze	(F) imiquimod 5%	cheek (1), forehead (0), extremities (including hand) (20), trunk/neck (70)	17/84	OR 0.16 (0.02, 1.56)
15888150 Schulze	(I,J) vehicle	cheek (1), forehead (5), scalp (1), extremities (including hand) (30), trunk/neck (61)	77/82	OR 0.16 (0.02, 1.56)

Study	Arm	Lesion Location	n/N	Result
20064185 Foley	(I,J) methyl-aminolevulinatePDT	face/scalp (25), extremities (20), Trunk (32), Neck (9)	20/75	OR 0.13 (0.06, 0.27)
20064185 Foley	(E) placebo PDT	face/scalp (31), extremities (23), Trunk (34), Neck (1)	55/75	OR 0.13 (0.06, 0.27)
20546215 Siller	(F) ingenol mebutate gel	NR	37/48	OR 0.16 (0.02, 1.56)
20546215 Siller	(I,J) vehicle gel, treatment arm B- day 1 and 8	NR	5/6	OR 0.16 (0.02, 1.56)
22511036 Tran	(I,J) PDL	NR	8/14	OR 0.25 (0.06, 1.01)
22511036 Tran	(C) No treatment	extremities (43), trunk/neck (57)	4/6	OR 0.25 (0.06, 1.01)
23683751 Arits	(F) MAL-PDT	head/neck excluding H-zone (12), extremities (29), trunk (59), upper extremities (16), lower extremities (13)	10/126	OR 6.16 (1.32, 28.69)
23683751 Arits	(E) Imiquimod	head/neck excluding H-zone (12), extremities (27), trunk (61), upper extremities (13), lower extremities (14)	2/145	OR 6.16 (1.32, 28.69)
24903544 Haak	(C) AFXL MAL PDT	nose (56), forehead (19), cheek (13), oral area (6), periorbital area (6)	6/16	OR 0.62 (0.26, 1.49)
24903544 Haak	(E) MAL PDT	nose (37), forehead (31), cheek (6), oral area (13), periorbital area (13)	7/16	OR 0.62 (0.26, 1.49)
27067393 Brinkhuizen	(F) Calcitriol	trunk/neck (59), genetalia (41)	16/16	OR 0.16 (0.02, 1.56)
27067393 Brinkhuizen	(I,J) No treatment	extremities (53), trunk/neck (47)	16/16	OR 0.16 (0.02, 1.56)
Abbade	(A,B) Surgical excision	head and neck (100)	0/35	OR 0.12 (0.01, 2.47)
Abbade	(E) MAL-PDT	head and neck (100)	3/33	OR 0.12 (0.01, 2.47)
Eimpunth	(I,J) pulsed dye laser	NR	4/14	OR 0.25 (0.06, 1.01)
Eimpunth	(C) no treatment	NR	8/10	OR 0.25 (0.06, 1.01)

Table I-3. Lack of clinical clearance, all BCC

Study	Arm	Lesion Location	n/N	Result
11298545 Wang	(C) cryosurgery	NR	5/39	OR 0.61 (0.1, 3.56)
11298545 Wang	(E) ALA-PDT	NR	2/44	OR 0.61 (0.1, 3.56)
14732655 Rhodes	(A,B) excision	face/scalp (58), extremities (9), trunk/neck (29)	1/52	OR 0.25 (0.08, 0.74)
14732655 Rhodes	(E) MAL PDT	face/scalp (40), extremities (11), trunk/neck (49)	1/53	OR 0.25 (0.08, 0.74)
15888150 Schulze	(F) imiquimod 5%	cheek (1), forehead (0), extremities (including hand) (20), trunk/neck (70)	19/84	OR 0.04 (0.02, 0.07)
15888150 Schulze	(I,J) vehicle	cheek (1), forehead (5), scalp (1), extremities (including hand) (30), trunk/neck (61)	77/82	OR 0.04 (0.02, 0.07)
17573890 Berroeta	(A,B) excision	NR	4/19	OR 0.25 (0.08, 0.74)
17573890 Berroeta	(E) PDT	NR	8/21	OR 0.25 (0.08, 0.74)

Study	Arm	Lesion Location	n/N	Result
18624836 Szeimies	(A,B) excision	face/scalp (4.5) , extremities (25.0), trunk/neck (70.5)	0/117	OR 0.25 (0.08, 0.74)
18624836 Szeimies	(E) MAL-PDT	face/scalp (11.1), extremities (28.9), trunk/neck (60)	11/118	OR 0.25 (0.08, 0.74)
18693158 Basset-Seguin	(C) Cryotherapy	face/scalp (4), extremities (20), trunk/neck (76)	5/98	OR 0.61 (0.1, 3.56)
18693158 Basset-Seguin	(E) MAL-PDT	face/scalp (6), extremities (22), trunk/neck (72)	3/103	OR 0.61 (0.1, 3.56)
20546215 Siller	(F) ingenol mebutate gel	NR	36/48	OR 0.04 (0.02, 0.07)
20546215 Siller	(I,J) vehicle gel, treatment arm B- day 1 and 8	NR	6/6	OR 0.04 (0.02, 0.07)
21242584 Garcia-Martin	(D) radiotherapy	eyelid (100)	0/12	OR 1.24 (0.02, 67.04)
21242584 Garcia-Martin	(F) imiquimod 5%	eyelid (100)	0/15	OR 1.24 (0.02, 67.04)
2229497 Cornell	(F) interferon	head and face (25), extermities (12), trunk/neck (63)	22/118	OR 0.04 (0.02, 0.07)
2229497 Cornell	(I,J) placebo	head and face (17), extermities (14), trunk/neck (59)	33/41	OR 0.04 (0.02, 0.07)
24332516 Bath-Hextall	(F) excision	face (33), trunk (39), neck (9), arm (7), leg (9), other (3)	1/98	OR 0.58 (0.05, 6.47)
24332516 Bath-Hextall	(A,B) Imiquimod	face (37), trunk (38), neck (6), arm (6), leg (10), other (3)	2/114	OR 0.58 (0.05, 6.47)
24903544 Haak	(C) AFXL MAL PDT	nose (56), forehead (19), cheek (13), oral area (6), periorbital area (6)	0/16	OR 0.61 (0.1, 3.56)
24903544 Haak	(E) MAL PDT	nose (37), forehead (31), cheek (6), oral area (13), periorbital area (13)	2/16	OR 0.61 (0.1, 3.56)
26551044 Choi	(C) Er:YAG ablative fractional laser-primed MAL- PDT	NR	6/21	OR 0.61 (0.1, 3.56)
26551044 Choi	(E) MAL-PDT	NR	17/21	OR 0.61 (0.1, 3.56)
298425 Allen	(D) cryotherapy	NR	1/15	OR 3.41 (0.13, 90.49)
298425 Allen	(C) radiotherapy	NR	0/16	OR 3.41 (0.13, 90.49)
9218740 Avril	(D) surgery	nose (53), cheek, pre- and retroauricular areas (21), eyelids, internal and external eye angles (19), forehead, temple, between eyebrows 36 (21), chin, cutaneous superior lip 10 (6), ear (3)	0/174	OR 0.14 (0.01, 2.72)
9218740 Avril	(A,B) radiotherapy	nose (28), cheek, pre- and retroauricular areas (24), eyelids, internal and external eye angles (20), forehead, temple, between eyebrows (17), chin, cutaneous superior lip (7), ear (3)	3/173	OR 0.14 (0.01, 2.72)

Table I-4. Recurrence, SCCIS

Study	Arm	Lesion Location	n/N	Result
12653747 Salim	(E) PDT	extremities (100)	6/33	OR 0.21 (0.07, 0.64)
12653747 Salim	(F) 5-FU	face (12), extremities (88)	17/33	OR 0.21 (0.07, 0.64)
16785375 Morton	(C) Cryotherapy or Fluorouracil	NR	19/97	OR 1.21 (0.61, 2.4)
16785375 Morton	(C) Cryotherapy or Fluorouracil	NR	19/97	OR 0.24 (0.03, 1.84)
16785375 Morton	(E) MAL PDT	face/scalp (23), extremities (65), trunk/neck (12)	15/103	OR 0.17 (0.02, 1.3)
16785375 Morton	(E) MAL PDT	face/scalp (23), extremities (65), trunk/neck (12)	15/103	OR 1.21 (0.61, 2.4)
16785375 Morton	(I,J) PDT placebo	face/scalp (25), extremities (67), trunk/neck (8)	2/4	OR 0.24 (0.03, 1.84)
16785375 Morton	(I,J) PDT placebo	face/scalp (25), extremities (67), trunk/neck (8)	2/4	OR 0.17 (0.02, 1.3)
24102369 Ko	(C) Er:YAG AFL PDT	extremities (100)	1/19	OR 1.21 (0.61, 2.4)
24102369 Ko	(E) MAL-PDT	extremities (100)	1/19	OR 1.21 (0.61, 2.4)
8977678 Morton	(C) cryotherapy	hands (5), face (15), legs (80)	2/20	OR 1.21 (0.61, 2.4)
8977678 Morton	(E) photodynamic	hands (5), face (10), legs (85)	0/20	OR 1.21 (0.61, 2.4)

Table I-5. Lack of histological clearance, SCCIS

Study	Arm	Lesion Location	n/N	Result
16713457 Patel	(F) imiquimod 5%	NR	12-Mar	OR 0.01 (0, 0.24)
16713457 Patel	(I,J) vehicle	NR	16/16	OR 0.01 (0, 0.24)

Table I-6. Lack of clinial clearance, SCCIS

Author	Arm	Lesion Location	n/N	Result
12653747 Salim	(E) PDT	extremities (100)	4/33	OR 0.28 (0.08, 0.98)
12653747 Salim	(F) 5-FU	face (12), extremities (88)	11/33	OR 0.28 (0.08, 0.98)
16713457 Patel	(F) imiquimod 5%	NR	3/12	OR 0.01 (0, 0.24)
16713457 Patel	(I,J) vehicle	NR	16/16	OR 0.01 (0, 0.24)
16785375 Morton	(C) Cryotherapy or Fluorouracil	NR	17/114	OR 0.94 (0.46, 1.94)
16785375 Morton	(C) Cryotherapy or Fluorouracil	NR	17/114	OR 0.05 (0.01, 0.16)
16785375 Morton	(E) MAL PDT	face/scalp (23), extremities (65), trunk/neck (12)	8/111	OR 0.02 (0.01, 0.08)
16785375 Morton	(E) MAL PDT	face/scalp (23), extremities (65), trunk/neck (12)	8/111	OR 0.94 (0.46, 1.94)
16785375 Morton	(I,J) PDT placebo	face/scalp (25), extremities (67), trunk/neck (8)	15/19	OR 0.05 (0.01, 0.16)
16785375 Morton	(I,J) PDT placebo	face/scalp (25), extremities (67), trunk/neck (8)	15/19	OR 0.02 (0.01, 0.08)
24102369 Ko	(C) Er:YAG AFL PDT	extremities (100)	4/32	OR 0.94 (0.46, 1.94)
24102369 Ko	(E) MAL-PDT	extremities (100)	13/26	OR 0.94 (0.46, 1.94)
8977678 Morton	(C) cryotherapy	hands (5), face (15), legs (80)	0/20	OR 0.94 (0.46, 1.94)
8977678 Morton	(E) photodynamic	hands (5), face (10), legs (85)	0/20	OR 0.94 (0.46, 1.94)