



Effective Health Care Program

Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin

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

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.



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?

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

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 (continued)

PICOTS and Description
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
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://sdr.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.

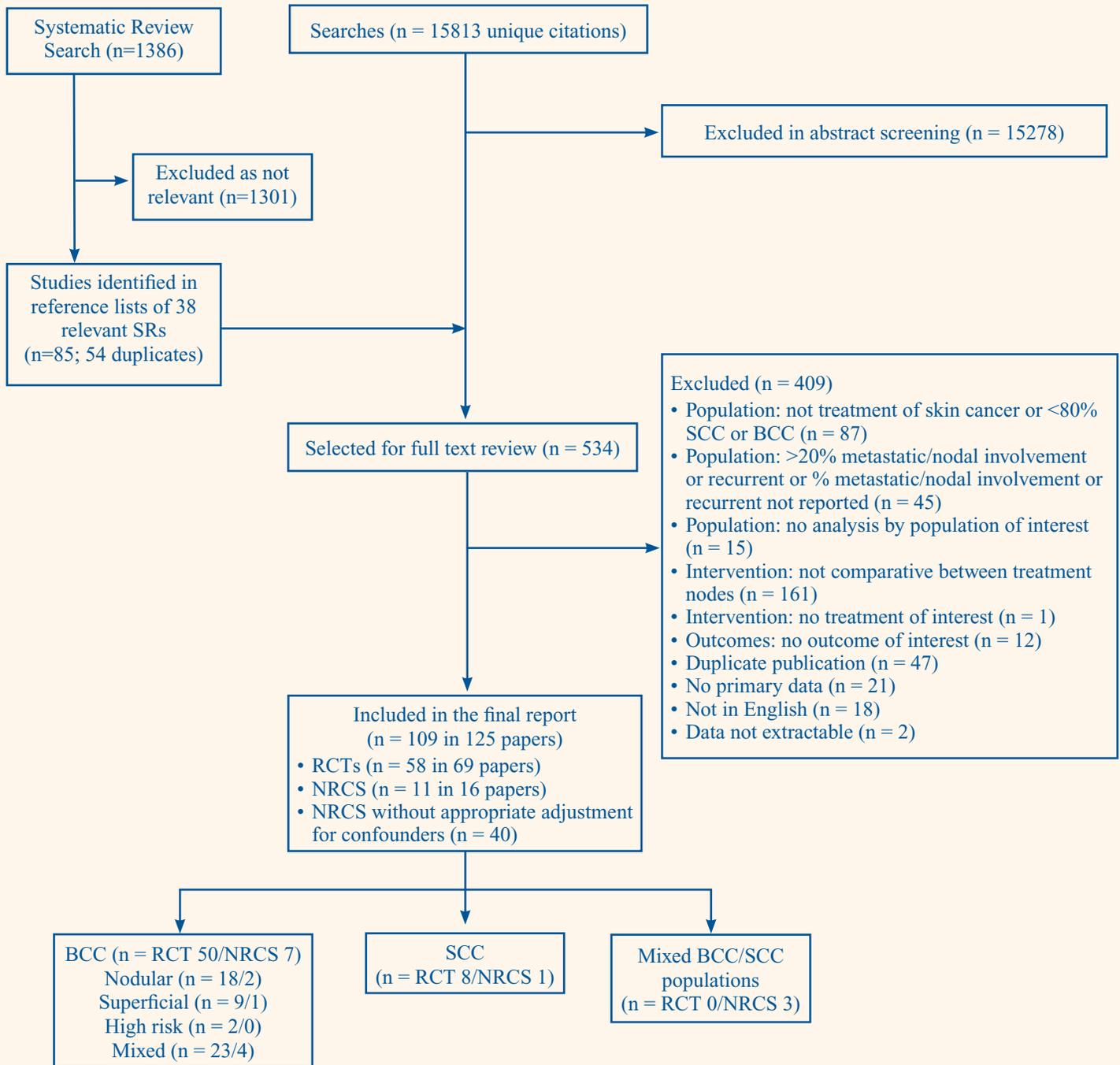
Peer Review

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

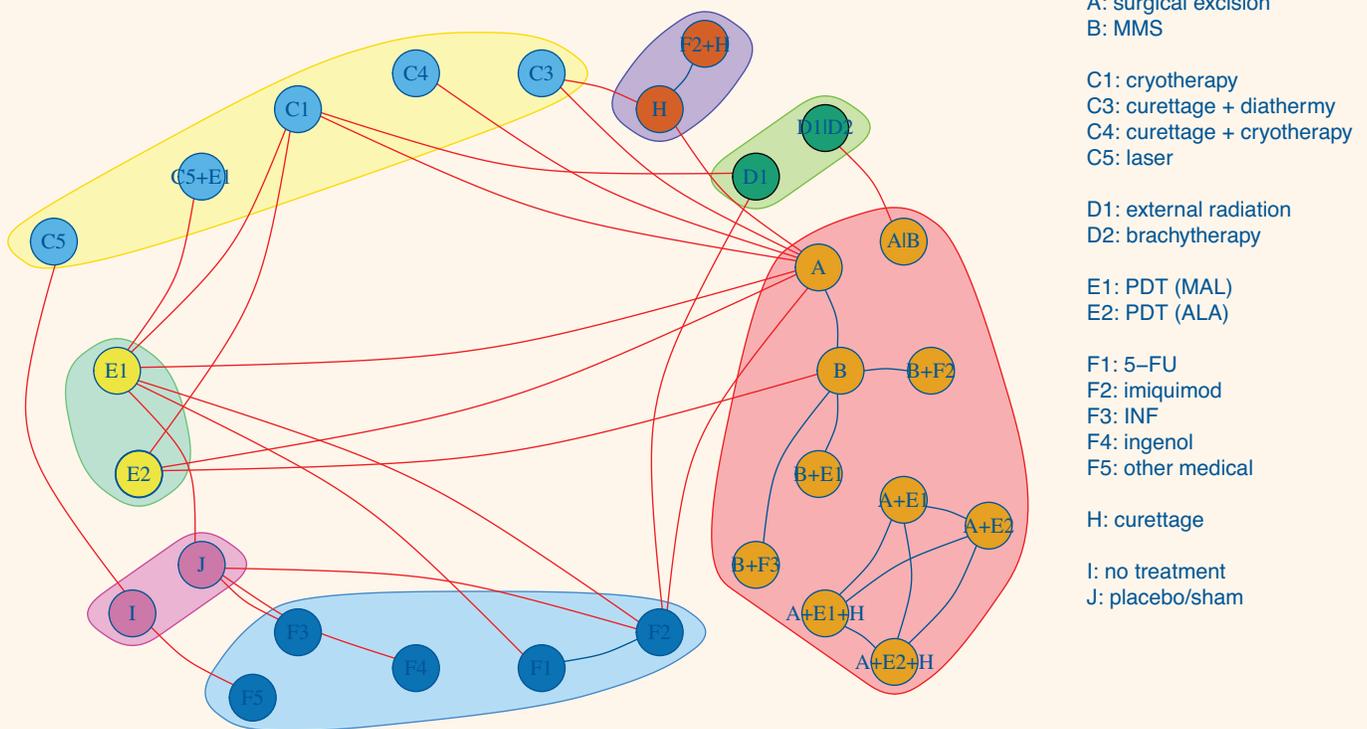
The studies primarily reported on BCC, with a minority reporting results for SCC. Nearly all reported results for recurrence or cure rate outcomes and adverse events, and many reported results for cosmetic outcomes. Few studies reported results using validated instruments for quality of life, mental 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.

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

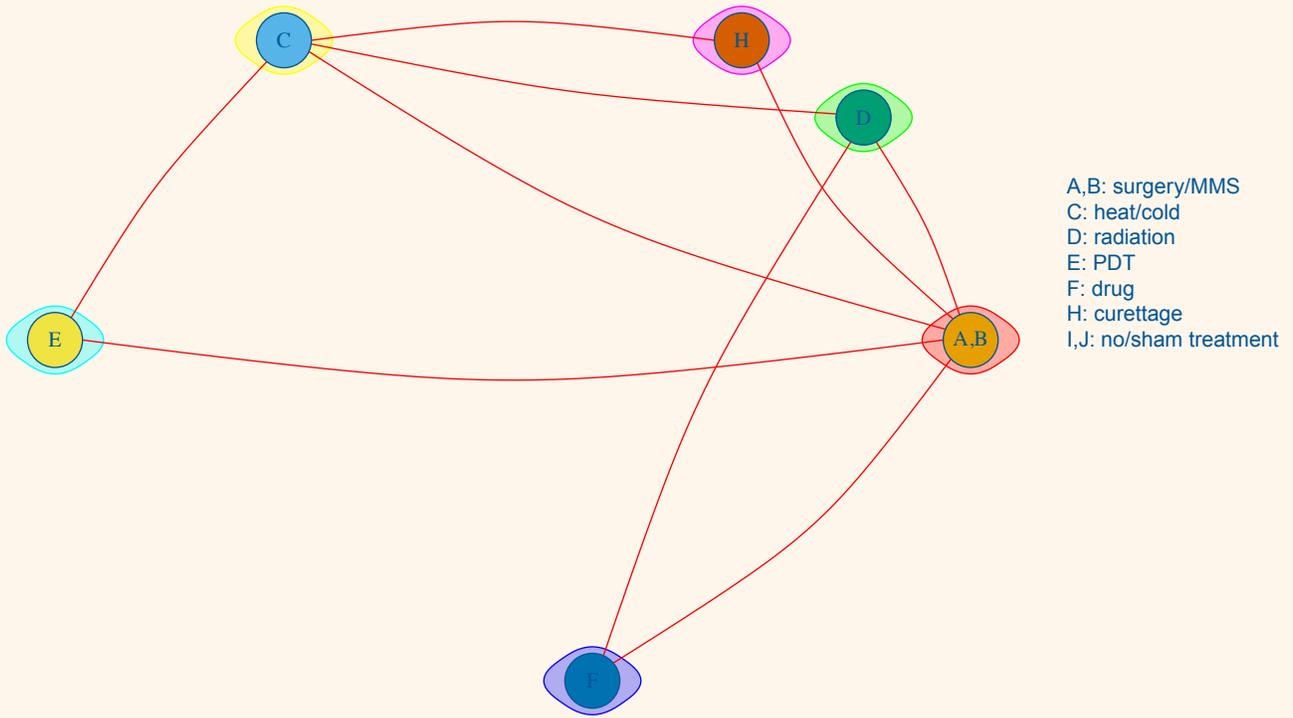


- A: surgical excision
- B: MMS
- C1: cryotherapy
- C3: curettage + diathermy
- C4: curettage + cryotherapy
- C5: laser
- D1: external radiation
- D2: brachytherapy
- E1: PDT (MAL)
- E2: PDT (ALA)
- F1: 5-FU
- F2: imiquimod
- F3: INF
- F4: ingenol
- F5: other medical
- H: curettage
- I: no treatment
- J: placebo/sham

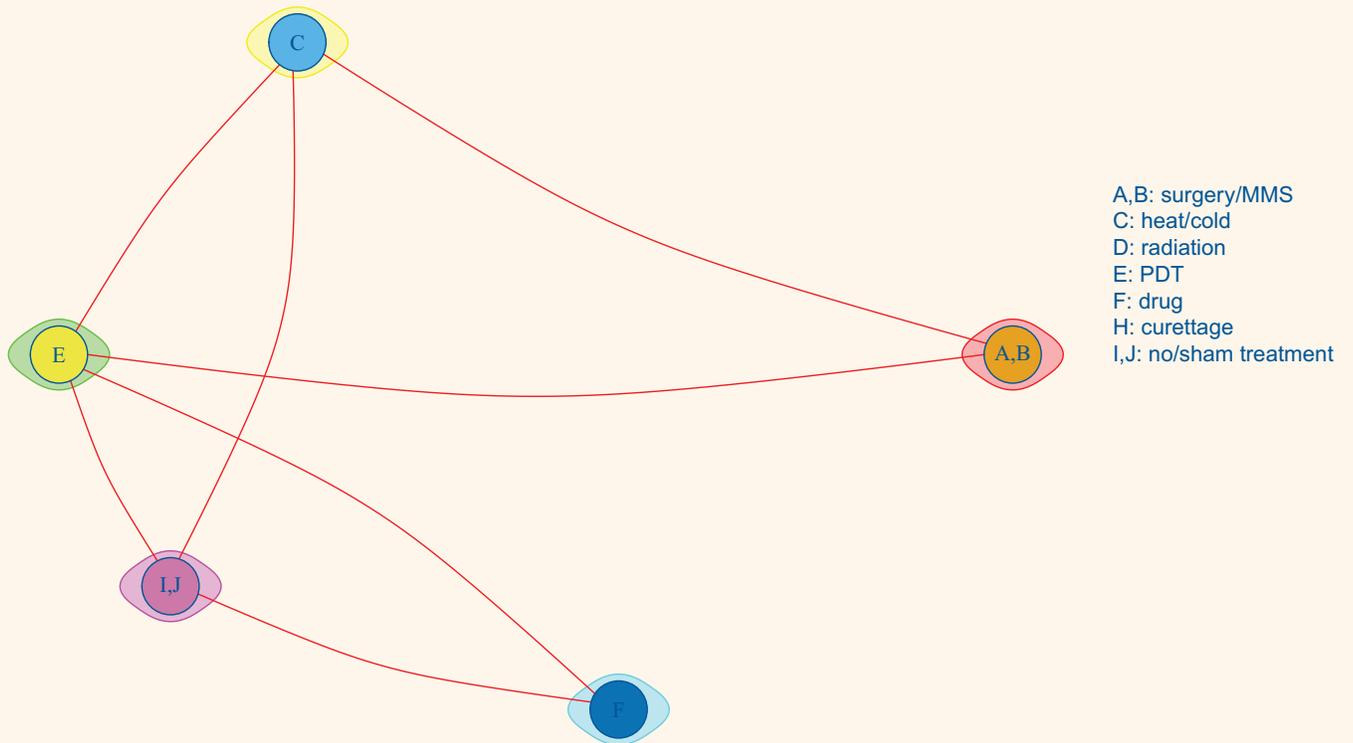
MMS = Mohs micrographic surgery; PDT = photodynamic therapy; ALA = 5-aminolevulinic acid; MAL = methyl aminolevulinate; FU = fluorouracil, INF = interferon

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

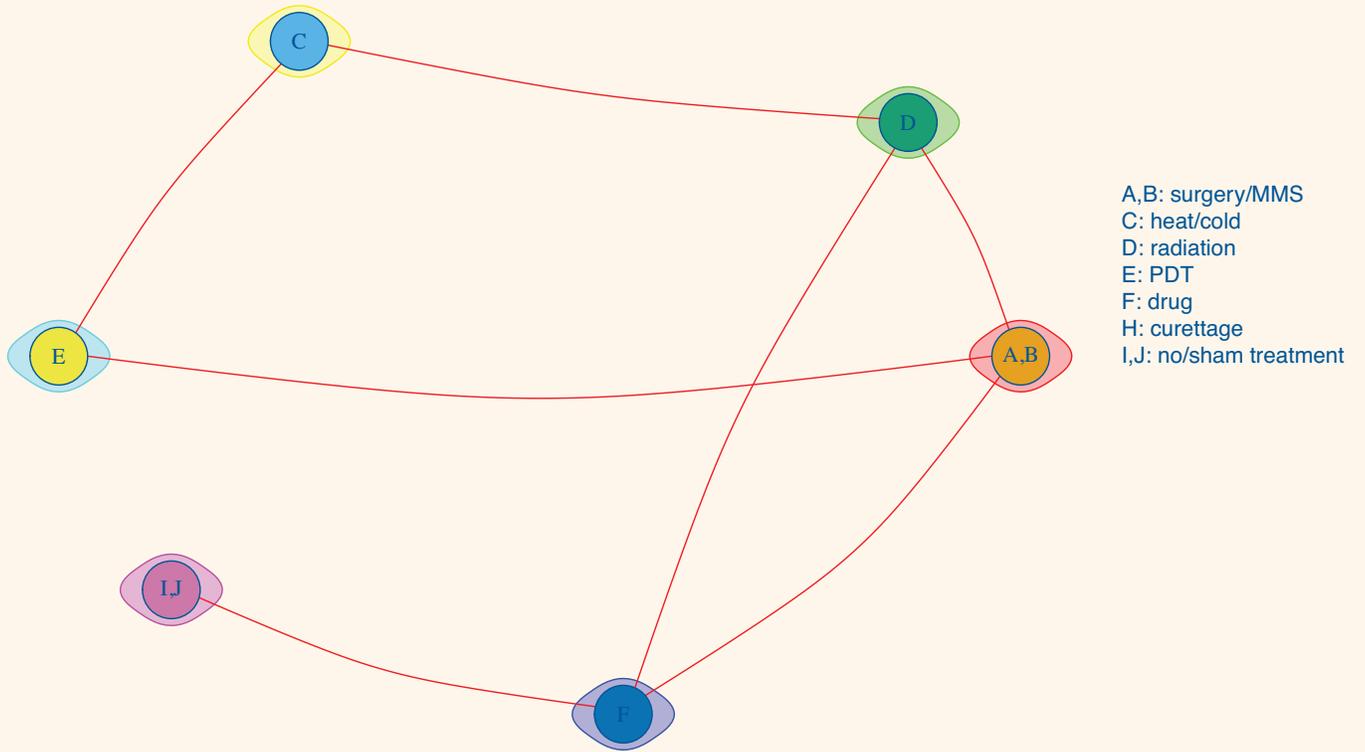
(A) Recurrence



(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: Shaded 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

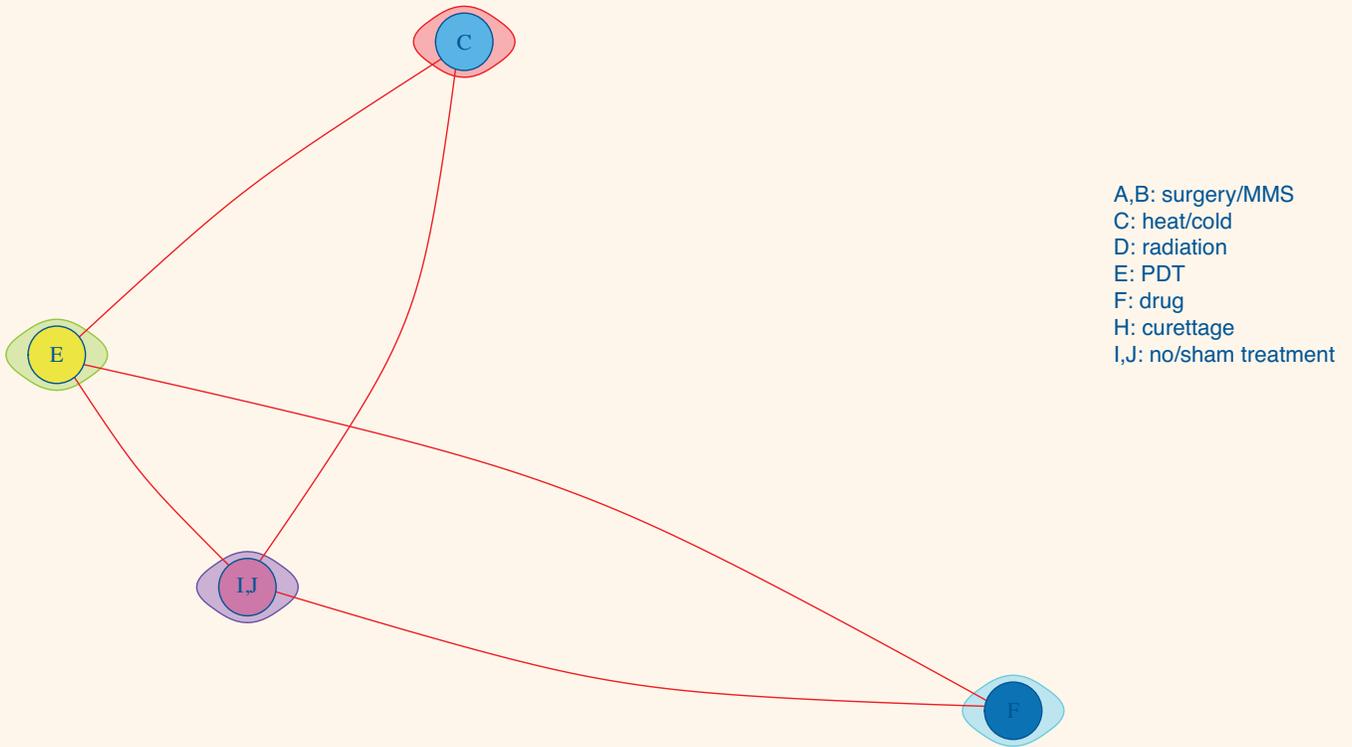
In Table B drugs were most likely to have adverse events leading to discontinuation (4.9%; 95% CI, 2.0 to 20.1); other interventions types had a much smaller percentage (1.2%). The number of adverse events characterized as “serious” by the investigators was smaller than 3.6 percent for all intervention 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.

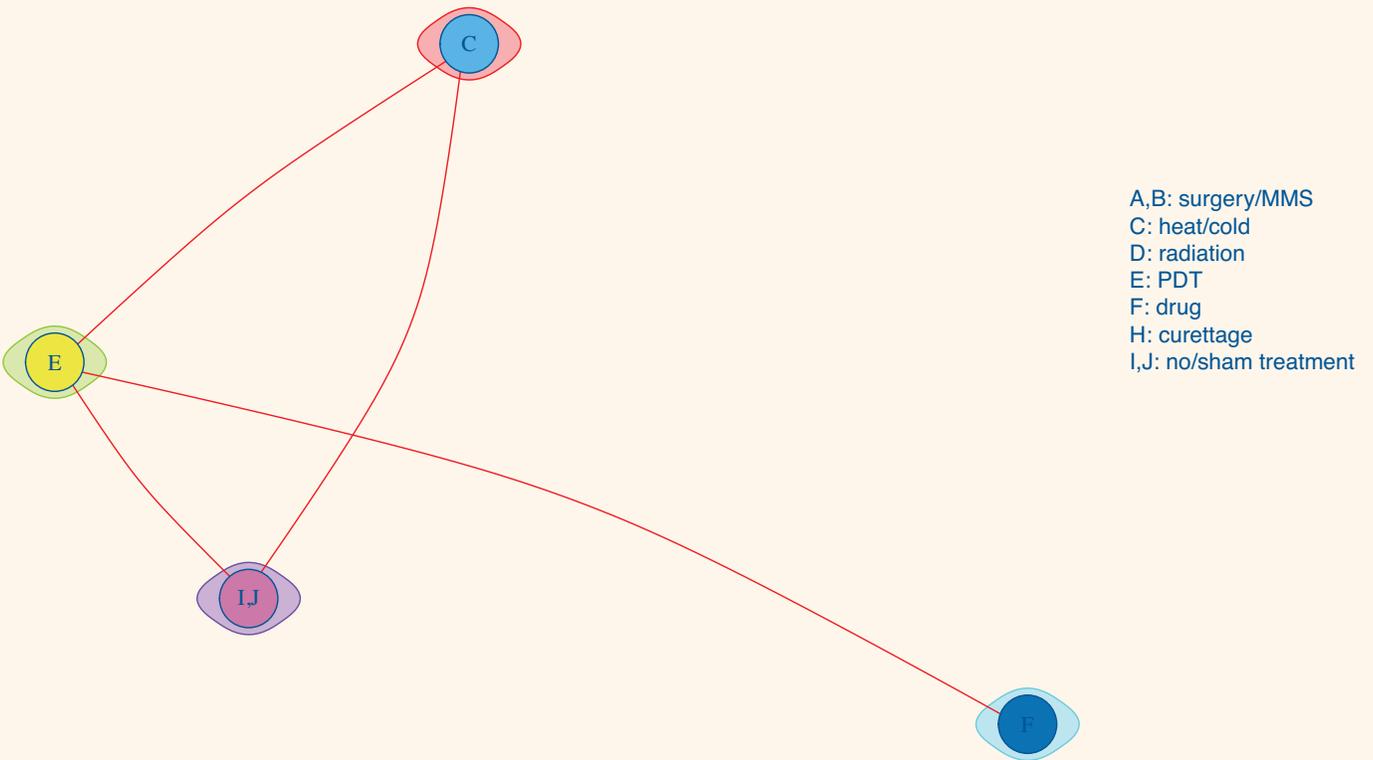
Figure D. Evidence graph depicting compared interventions in RCTs of SCC lesions



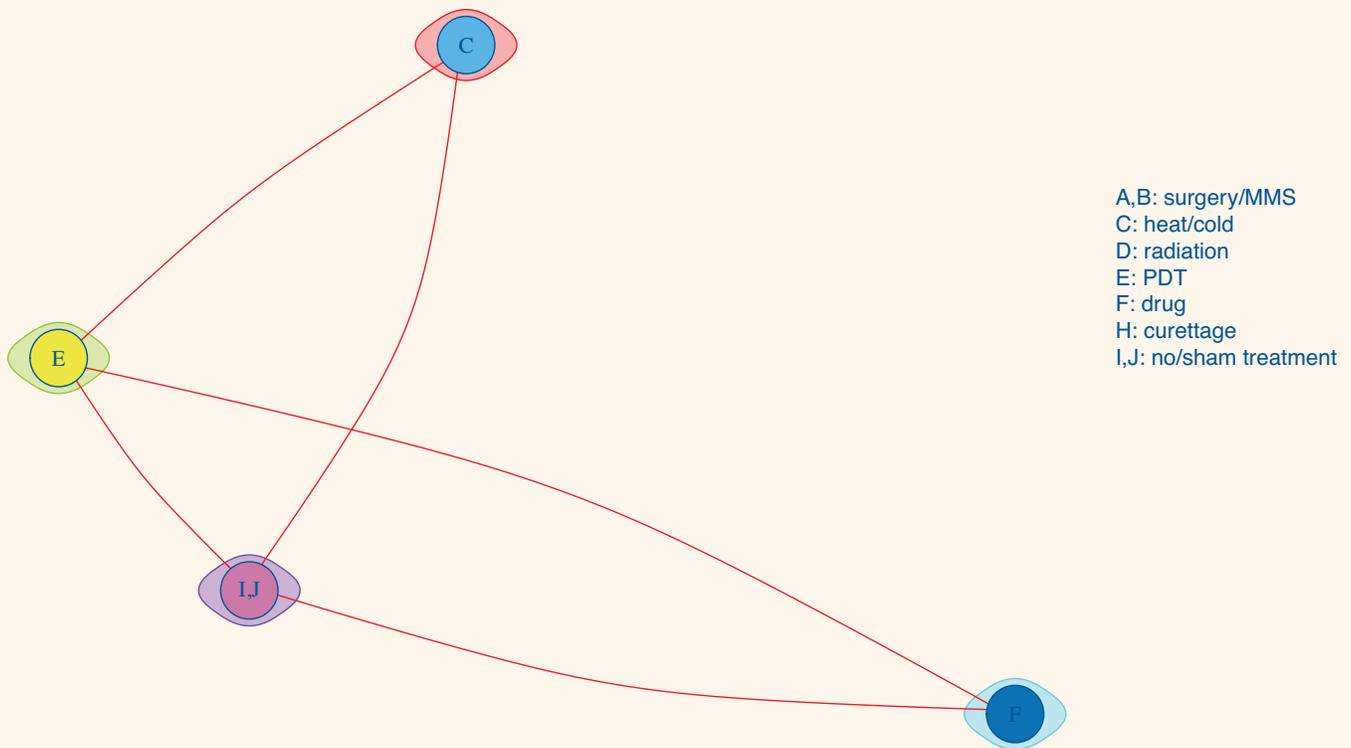
MMS = Mohs micrographic surgery; PDT = photodynamic therapy

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 intervention 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
<p><i>Recurrence, all BCC</i></p> <p>(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)</p> <p>(2) Curettage (H) may have higher recurrence rates than surgical interventions (A,B) or radiation (D)</p> <p>(3) Imiquimod (F) was associated with recurrence rates that were not significantly different than that of surgical interventions (A,B)</p> <p>(4) [Imprecise data on the comparison on curettage and interventions that destroy lesions with heat or cold (C) or PDT (E)]</p>	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	<p>(1) Moderate to High</p> <p>(2) Low</p> <p>(3) Low</p> <p>(4) [Insufficient]</p>	<ul style="list-style-type: none"> • 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)
<p><i>Histologic clearance, all BCC</i></p> <p>(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).</p> <p>(2) Interventions that destroy lesions with heat or cold (C), PDT (E), and drugs (F) have better histological outcomes than placebo (I,J)</p> <p>(3) [Imprecise data on the relative comparisons of nonsurgical active interventions]</p>	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise.	Mix of direct and indirect data	<p>(1) High</p> <p>(2) Moderate to high</p> <p>(3) [Insufficient]</p>	<ul style="list-style-type: none"> • 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 worse 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))

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

Conclusion statement	RoB (evidence-base)	Consistency	Precision	Directness	Overall Rating	Comments
<p><i>Clinical clearance, all BCC</i></p> <p>1) Surgical interventions (A,B) were associated with better clinical clearance outcomes than PDT (E), drugs (F) and placebo (I,J)</p> <p>(2) All active treatments were associated with better clinical clearance outcomes than placebo</p> <p>(3) [Imprecise data on relative comparisons between nonsurgical active treatments]</p>	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]	<ul style="list-style-type: none"> • 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 placebo, 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, nonsignificantly worse than PDT and heat/cold, and significantly worse than surgery (5 RCTs)
<p><i>Patient-reported cosmetic outcomes, all BCC</i></p> <p>(1) PDT is associated with better cosmetic outcomes than other intervention categories</p> <p>(2) [Imprecise data on relative comparisons between nonsurgical active intervention categories]</p>	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	<ul style="list-style-type: none"> • (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)

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

Conclusion statement	RoB (evidence-base)	Consistency	Precision	Directness	Overall Rating	Comments
<p><i>Observer-reported cosmetic outcomes, all BCC</i></p> <p>(1) PDT is associated with significantly better cosmetic outcomes than surgery (A,B)</p> <p>(2) [PDT may be associated with better cosmetic outcomes compared to nonsurgical active intervention categories]</p> <p>(3) [Imprecise data on relative comparisons between heat/cold (C), radiation, and drugs (D)]</p>	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]	<ul style="list-style-type: none"> (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)
<p><i>Adverse effects, all BCC</i></p> <p>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)</p> <p>(2) For the interventions above, on average, 1 in 10 to 1 in 5 patients report experiencing pain after treatment</p>	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	<ul style="list-style-type: none"> 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%)

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

Conclusion statement	RoB (evidence-base)	Consistency	Precision	Directness	Overall Rating	Comments
<i>Other outcomes, all BCC</i> [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]
<i>Other analyses</i> [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
<i>Recurrence, SCCIS</i> (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)
<i>Histologic clearance, SCCIS</i> (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 (1, J)	(1) Low (2) High	[Not rated]	(1) Imprecise (2) Precise	(1) Direct (2) Direct	(1) [Insufficient] (2) Low	[2 RCTs, 50 patients.]

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

Conclusion statement	RoB (evidence-base)	Consistency	Precision	Directness	Overall Rating	Comments
<p><i>Clinical clearance, SCCIS</i></p> <p>(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</p> <p>(2) [Imprecise data on relative comparisons between types of active interventions]</p>	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)
<p><i>Observer-reported cosmetic outcomes, SCCIS</i></p> <p>(1) Cryotherapy plus 5-FU (C1+F1) is associated with better outcomes than PDT (MAL) (E1)</p> <p>(2) [No difference between laser pretreatment of the lesion before PDT versus PDT alone]</p>	Low	Unclear (Consistency cannot be rated)	(1) Precise (2) Imprecise	Mix of direct and indirect data	(1) Moderate (2) [Insufficient]	[2 RCTs, 204 patients.]
<p><i>Adverse effects, SSCIS</i></p> <p>(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)]</p> <p>(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]</p>	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.]

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

Conclusion statement	RoB (evidence-base)	Consistency	Precision	Directness	Overall Rating	Comments
<i>Other outcomes, SCCIS</i>	[Evidence on patient-reported cosmetic outcomes, quality of life, mental health, patient satisfaction, mortality, cost and resource use and reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
<i>Other analyses</i> [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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Full Report

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