REVIEW

Annals of Internal Medicine

# Treatments of Primary Basal Cell Carcinoma of the Skin

## A Systematic Review and Network Meta-analysis

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**Background:** Most interventions for basal cell carcinoma (BCC) have not been compared in head-to-head randomized trials.

**Purpose:** To evaluate the comparative effectiveness and safety of treatments of primary BCC in adults.

**Data Sources:** English-language searches of MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Embase from inception to May 2018; reference lists of guidelines and systematic reviews; and a search of ClinicalTrials.gov in August 2016.

**Study Selection:** Comparative studies of treatments currently used in adults with primary BCC.

**Data Extraction:** One investigator extracted data on recurrence, histologic clearance, clinical clearance, cosmetic outcomes, quality of life, and mortality, and a second reviewer verified extractions. Several investigators evaluated risk of bias for each study.

**Data Synthesis:** Forty randomized trials and 5 nonrandomized studies compared 18 interventions in 9 categories. Relative intervention effects and mean outcome frequencies were estimated using frequentist network meta-analyses. Estimated recurrence rates were similar for excision (3.8% [95% CI, 1.5% to 9.5%]), Mohs surgery (3.8% [CI, 0.7% to 18.2%]), curettage and diathermy (6.9% [CI, 0.9% to 36.6%]), and external-beam radiation (3.5% [CI, 0.7% to 16.8%]). Recurrence rates were higher for cryotherapy (22.3% [CI, 10.2% to 42.0%]), curettage and cryotherapy (19.9% [CI, 4.6% to 56.1%]), 5-fluorouracil (18.8% [CI, 10.1% to 32.5%]), imiquimod (14.1% [CI, 5.4% to 32.4%]), and photodynamic therapy using methyl-aminolevulinic acid (18.8% [CI, 10.1% to 32.5%]) or aminolevulinic acid (16.6% [CI, 7.5% to 32.8%]). The proportion of patients reporting good or better cosmetic outcomes was better for photodynamic therapy using methyl-aminolevulinic acid (93.8% [CI, 79.2% to 98.3%]) or aminolevulinic acid (95.8% [CI, 84.2% to 99.0%]) than for excision (77.8% [CI, 44.8% to 93.8%]) or cryotherapy (51.1% [CI, 15.8% to 85.4%]). Data on quality of life and mortality were too sparse for quantitative synthesis.

**Limitation:** Data are sparse, and effect estimates are imprecise and informed by indirect comparisons.

**Conclusion:** Surgical treatments and external-beam radiation have low recurrence rates for the treatment of low-risk BCC, but substantial uncertainty exists about their comparative effectiveness versus other treatments. Gaps remain regarding high-risk BCC subtypes and important outcomes, including costs.

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Basal cell carcinoma (BCC) is the most common cancer in the United States, with an annual incidence approaching 2 million cases (1). Most cases are not aggressive, but the tumors and their treatment can cause disfigurement or disability, which can adversely affect quality of life (2). The Surgeon General's recent call to action to prevent skin cancer at the population level emphasizes the public health importance of dealing with BCC (3).

Choosing a management strategy for an individual patient with a specific type of BCC from among the many available interventions is complex. Considerations include patient factors (such as age, frailty, immunosuppression, and personal preference), tumor factors (such as histologic subtype, size, and location), and the availability and cost of health care resources.

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The lack of clarity about the comparative efficacy and safety of the available options overall and in specific circumstances further complicates treatment decision making for both physicians and patients. Surgical removal is widely considered the gold standard and is therefore the most common treatment. However, despite several dozen randomized controlled trials (RCTs) and nonrandomized comparative studies (NRCSs), the relative performance of various surgical techniques and other therapeutic options is unclear. Payers are faced with increased use of costly therapies, such as brachytherapy, without clear evidence about relative benefits to justify increased costs (4). The purpose of this systematic review and network meta-analysis is to evaluate the comparative effectiveness and safety of treatments of primary BCC.

## Methods

This article updates and summarizes the findings on BCC from a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) on treatments of BCC and cutaneous squamous cell carcinoma (4). We followed the approach outlined in the AHRQ Methods Guide for Effectiveness and Comparative

Effectiveness Reviews (5). The protocol was developed with input from stakeholders (providers, researchers, payers, patients, and funders) and was prospectively registered with PROSPERO (CRD42016043353).

### Data Sources and Searches

We searched PubMed, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Embase up to 8 May 2018 to identify eligible studies (the full report [4] gives search strategies, search terms, and search and selection figures). We queried ClinicalTrials.gov (most recently in August 2016) to identify ongoing or completed yet unpublished trials. We limited searches to English-language publications and supplemented them with suggestions from stakeholders and by perusing reference lists of eligible articles and of pertinent systematic reviews and guidelines.

### Study Selection

We screened titles, abstracts, and full texts of eligible studies in duplicate. The population of interest was adult patients with primary BCC. Patient subgroups were specified in the protocol and were defined by tumor location (such as face, hands, trunk, or extremities) and histologic subtype (such as superficial or nodular BCC). We excluded subpopulations with rare genetic disorders associated with increased BCC risk (for example, basal cell nevus syndrome). With input from stakeholders, we identified 22 eligible interventions, which we organized into 9 categories (Table 1). Outcomes of interest included tumor recurrence and lack of histologic tumor clearance (proxies for failure to cure), cosmetic appearance (patient- or observer-reported), quality of life, mortality, and costs.

We evaluated RCTs and comparative NRCSs. We included NRCSs only if they took steps to control for patient- or lesion-level confounders. We excluded studies that had fewer than 5 lesions per treatment group.

### Data Extraction and Risk-of-Bias Assessment

One reviewer extracted information from eligible studies, and a second reviewer verified the extraction. Any disagreements were resolved by discussion among the team. Data extractions were done on and are publicly accessible through the Systematic Review Data Repository (http://srdr.ahrq.gov) (6). We recorded information on country of origin; population (mean age; sex distribution; and lesion histology, size, and location); interventions; outcomes (at the longest follow-up and at the follow-up closest to but not longer than 2 years); funding source; and attributes of study design, conduct, and analysis addressed in the Cochrane Risk of Bias Tool (7). For RCTs, at least 2 reviewers critically examined sources of bias and their likely effect and finalized their assessments in discussions with the whole team. We examined the effect of missing data by calculating mathematical bounds for effect estimates (8). This was accomplished by examining extreme scenarios in which all missing observations in one group had the outcome of interest and all missing observations in another group did not. For lack of histologic clearance, input from a pathologist informed our assessments of whether each treatment can be successfully masked. For each observational study, we used the Newcastle-Ottawa Scale (9) to guide our deliberations about sources and risk of bias.

***Table 1.*** Intervention Categories and Specific Interventions

| |
|---|
| Surgical excision without intraoperative evaluation of the margins |
| Surgical excision with intraoperative evaluation of the margins |
| Mohs micrographic surgery |
| Surgery with examination of frozen sections |
| Interventions that destroy the lesion via temperature gradients |
| Cryotherapy |
| Diathermy/electrodesiccation |
| Curettage of the lesion plus diathermy (cauterization) of margins |
| Curettage of the lesion plus cryotherapy |
| Carbon dioxide laser therapy |
| Interventions that destroy the lesion with ionizing radiation |
| External-beam radiation with photons (x-rays or $\gamma$ rays), electrons ($\beta$ rays), or positively charged particles (e.g., protons and helium nuclei/$\alpha$ rays) at orthovoltage or megavoltage energies or using in-office radiation machines |
| Brachytherapy with superficial application or interstitial application (plesiotherapy) of radiation sources (usually emitting $\beta$ or $\alpha$ rays) |
| Photodynamic interventions |
| ALA + blue light |
| MAL + red light |
| Other |
| Medical interventions |
| 5-FU |
| Imiquimod |
| IFN (IFN-$\alpha$2a/b or IFN-$\beta$) |
| Ingenol mebutate |
| Other |
| Shave removal |
| Curettage without diathermy |
| Sham or no treatment |
| Placebo or sham treatment |
| No treatment (watchful waiting) |

5-FU = 5-fluorouracil; ALA = aminolevulinic acid; IFN = interferon; MAL = methyl-aminolevulinic acid.

### Data Synthesis, Analysis, and Assessments of Strength of Evidence

We summarized all studies qualitatively and described important features of the population (including tumor characteristics), design, intervention, outcomes, and results. In each outcome, the evidence comprises 1 or more connected networks of 2 or more treatments. For each connected network in each outcome, we did frequentist (maximum likelihood) pairwise and network meta-analyses with mixed-effects (random intercepts and fixed intervention slopes) or full random-effects (random intercepts and slopes) multilevel models within the generalized linear and latent mixed-model framework. The network meta-analysis approach models the proportion of events in each trial group and thus can estimate not only the mean treatment effects (odds ratios) between treatments but also the mean proportion of events with each treatment using all of the available data. In Part G of the Supplement (available at Annals.org), we describe the models and their estimation and provide access to the data and code.

We assessed consistency qualitatively and deemed direct and indirect effects to be in agreement when

they were in the same direction and the CI of one included the point estimate of the other. We also used a "node-split" approach to assess for consistency quantitatively (10).

In main analyses, we included data from the longest follow-up for each outcome in each trial. We excluded trials that compared versions of the same intervention (for example, different imiquimod treatment schedules). When data were available, we did subgroup analyses by lesion histologic subtype, location, and size (not shown) (4). The unit of analysis was the patient. A minority of studies reported results about lesions (where individual patients had several lesions), which were included as if each lesion belonged to a different patient. We did not correct for clustering of lesions by patient because the requisite estimates of intraclass correlation coefficients were not available.

In sensitivity analyses, we included only trial data on outcomes closest to 1 year within the window of 0 to 2 years, and we fitted network meta-analysis models in the Bayesian framework (not shown). Network meta-analyses of intervention categories were congruent with the main analyses that focused on specific interventions (not shown). All analyses were done in R, version 3.4.4, using the igraph, lme4, metafor, and gemtc packages (11–15). We report 95% CIs with no corrections to control for type I error.

We summarized analyses as key findings and assessed the overall strength of evidence in terms of the risk of bias of the associated evidence base and the directness, precision, and consistency of the evidence, following the AHRQ methods guidance.

### Role of the Funding Source

This report is based on research conducted by the Brown Evidence-based Practice Center under contract to the AHRQ. The funder's role was limited to ensuring adherence to administrative requirements, including timelines and fidelity to the written protocol. The AHRQ was not involved in the design, conduct, or interpretation of the analyses.

## RESULTS

The literature searches returned 16 154 citations, of which 519 were retrieved and screened in full text. Forty RCTs and 5 NRCSs were eligible (**Supplement Figure** and **Supplement Tables 1** and **2**, available at Annals.org). The randomized evidence base is sparse (Part B of the **Supplement**). Across all outcomes, the RCTs examined 18 interventions and provided data on 34 head-to-head comparisons, out of 153 possible comparisons. Of the 34 comparisons, 33 were informed by at most 3 trials.

The evidence graphs in **Figures 1** to **4** depict the head-to-head comparisons in RCTs for recurrence, lack of histologic clearance, and cosmetic outcomes assessed by patients and observers, respectively. They have the same layout to show the partial coverage of the evidence base per outcome. For all outcomes, the evidence base comprises between 2 and 4 connected networks. No comparisons are made between treatments that belong to unconnected networks, and each connected network is sparse. For example, in **Figure 1**, the largest connected network for recurrence comprises 14 treatments. Of these, 4 were compared with only 1 other treatment and 5 with only 2. Treatments that were compared with the most other treatments were surgical excision ($n$ = 7) and photodynamic therapy (PDT) using methyl-aminolevulinic acid ($n$ = 6). For lack of histologic clearance, aside from PDT using methyl-aminolevulinic acid (compared with 6 other treatments), all treatments were compared with at most 3 other treatments (6 treatments were compared with only 1 other treatment) (**Figure 2**).

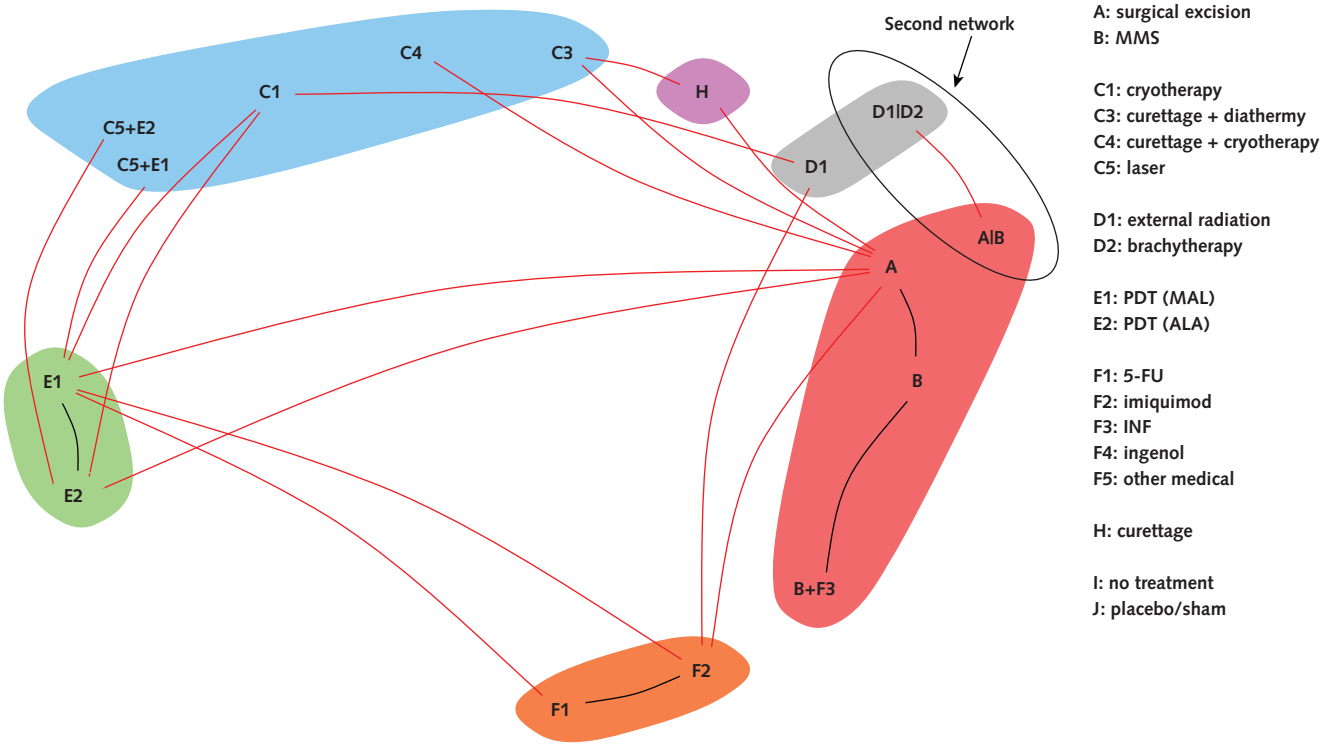
The NRCSs examined 5 comparisons among 6 interventions. Of 40 RCTs, 36 compared 2 treatments, 3 compared 3, and 1 compared 4. The RCTs enrolled a median of 42 patients per group (interquartile range, 16 to 75 patients). The networks were sparse, and statistical analyses for inconsistency between direct and indirect effect estimates were underpowered. However, we found few if any indications of inconsistency in the networks (**Supplement**); thus, we report results only from network meta-analyses.

No RCT or NRCS focused on patients who were immunocompromised or had limited life expectancy. Most lesions in the included studies were histologically low-risk cases of superficial or nodular BCC, which are the most common subtypes (16). The median percentage of women was 39%, and the median average age was 66 years. Mean lesion areas ranged from 30 to 310 $mm^2$ and mean lesion diameters from 5 to 13 mm. Head and neck BCC comprised at most 10% of lesions in 8 trials and at least 90% in 12. The NRCSs enrolled a case mix of lesions representative of those seen in clinical practice. All studies included older adults (range of mean ages, 63 to 66 years) who were mostly men and had mean lesion diameters between 8 and 15 mm.

### Risk-of-Bias Assessment

Most RCTs had attrition rates less than 20% ($n$ = 29), had no gross imbalances in patient and lesion attributes at baseline ($n$ = 24), and clearly described the allocation sequence generation ($n$ = 23) and concealment of treatment allocation ($n$ = 22) (Part B of the **Supplement**). At least 12 trials reported that outcome assessments by patients, providers, or other outcome assessors were masked. Most individual study findings had low or moderate risk of confounding, selection, or measurement biases, with likely minimal effect on our results. We judged risk of bias to be at most moderate in 35 trials and high in 4. For 1 RCT reported only as an abstract, no conclusions could be drawn about risk of bias. Four NRCSs were deemed to be at moderate and 1 at high risk of bias (17), primarily because of concerns about residual confounding. This was because studies did not use causally explicit analyses but instead simple regression adjustments; did not control for clinical variables, such as tumor size, location, or histology; or used imperfect proxies of clinical variables without accounting for measurement error. The ClinicalTrials.gov

***Figure 1.*** Evidence graph for BCC recurrence.




The evidence graph comprises nodes, depicting specific interventions, and edges (links between nodes). An edge exists when the specific interventions represented by the nodes it connects have been compared head-to-head in ≥1 trial. Shaded regions around sets of nodes represent intervention categories. For example, nodes E1 (PDT with MAL) and E2 (PDT with ALA) belong to the same intervention category of PDTs. A connected network is the largest subset of nodes that are linked together with edges. This evidence graph comprises 2 connected networks: A smaller one (identified as "second network") that includes the nodes A|B and D1|D2, and a larger one (the "first network," but not labeled as such) that includes all other nodes. "·|·" means "exclusive or" (i.e., "A|B" means "either surgical excision [A] or MMS [B]"). "·+·" means "combined with" (i.e., "C5+E1" means "laser [C5] combined with PDT using MAL [E1]"). 5-FU = 5-fluorouracil; ALA = aminolevulinic acid; BCC = basal cell carcinoma; INF = interferon; MAL = methyl-aminolevulinic acid; MMS = Mohs micrographic surgery; PDT = photodynamic therapy.

search did not identify any additional eligible studies that were unpublished or ongoing.

## Recurrence

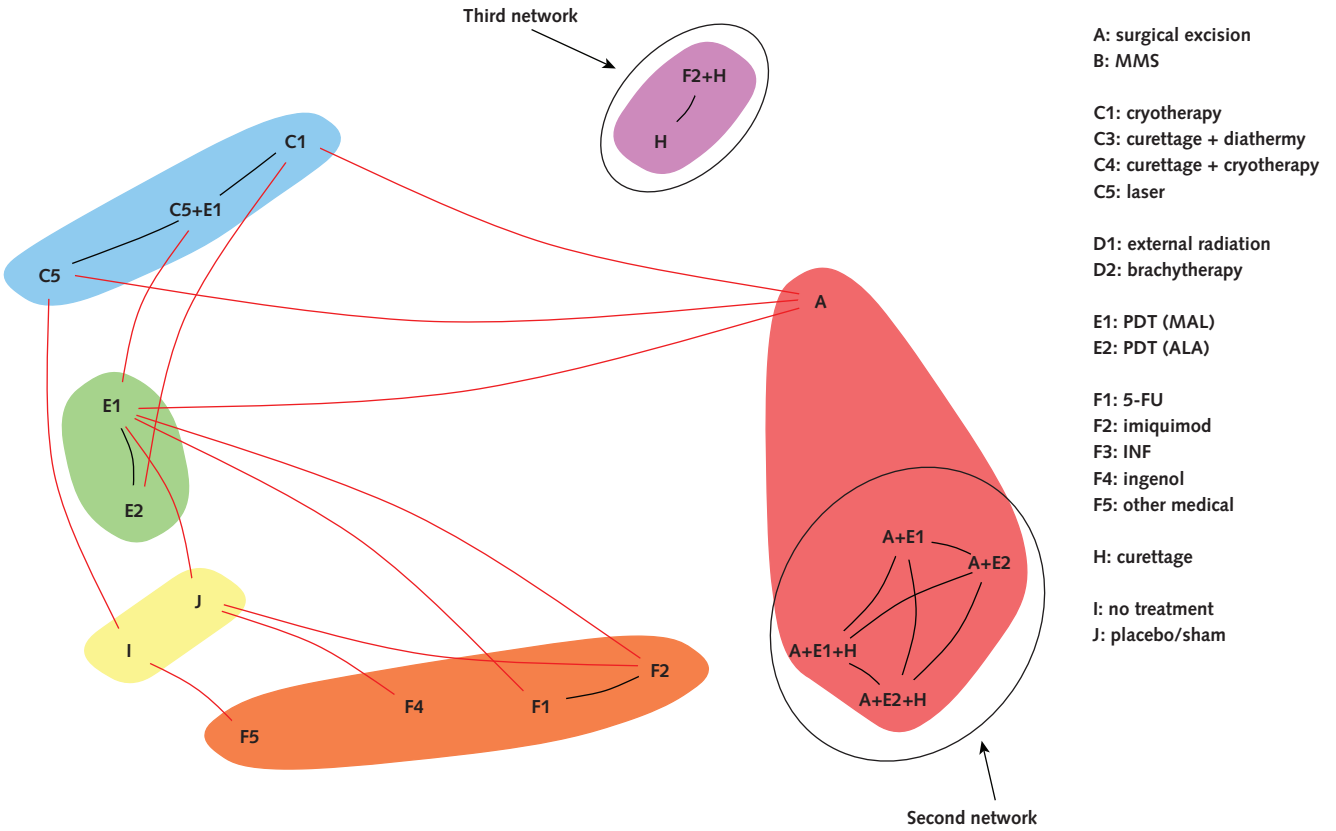
Figure 1 shows a large treatment network of 14 treatments comprising 16 RCTs and 2204 lesions (range per trial, 15 to 394 lesions). Part C of the Supplement lists summary odds ratio estimates for the 91 possible comparisons between the 14 treatments in the larger network. Most estimates are based solely on indirect data and have wide CIs. Taken together, these relative effects suggest that average recurrence rates are similar for excision (3.3% [95% CI, 1.3% to 7.8%]), Mohs surgery (3.8% [CI, 0.7% to 18.9%]), curettage and diathermy (5.9% [CI, 0.7% to 34.9%]), and external-beam radiation (3.2% [CI, 0.6% to 16.1%]) (Table 2). Recurrence rates were higher for cryotherapy (21.0% [CI, 9.0% to 41.4%]), curettage and cryotherapy (17.1% [CI, 3.6% to 53.4%]), 5-fluorouracil (24.7% [CI, 7.1% to 58.4%]), imiquimod (14.1% [CI, 5.4% to 32.4%]), and PDT using methyl-aminolevulinic acid (17.8% [CI, 9.1% to 31.8%]) or aminolevulinic acid (16.9% [CI, 7.4% to 34.4%]). The second network in Figure 1 comprised an RCT ($n$ = 347) that favored surgical treatments over radiation therapies (OR, 0.12 [CI, 0.01 to 0.96]). Results were not materially different when limited 1- to 2-year follow-up or in subgroup analyses by histologic subtype and lesion size or location.

Two NRCSs evaluated recurrence of BCC lesions (17, 18) but were not included in a meta-analysis. The first reported that recurrence was similar across matched surgical and PDT groups at 2 years ($n$ = 74; odds ratio, 0.96 [CI, 0.13 to 7.09]) (18). The second reported that surgical excision had a higher rate of recurrence up to 5 years compared with imiquimod ($n$ = 621; hazard ratio, 2.13 [CI, 1.28 to 3.53]) (17).

## Lack of Histologic Clearance

Figure 2 depicts 3 networks of trials that measured lack of histologic clearance. The largest included 19 RCTs (2613 lesions in total; range per trial, 20 to 692 lesions) comparing 12 treatments. Supplement Table 4 (available at Annals.org) lists the 66 estimates of relative odds ratios from the network meta-analysis, 49 of which are based solely on indirect data. These pairwise comparisons suggest that surgical excision without intraoperative margin evaluation was associated with the lowest estimated rates of lack of histologic clearance (1.7% [CI, 0.3% to 9.9%]). Estimated rates were higher, although imprecisely estimated with overlapping CIs,

***Figure 2.*** Evidence graph for lack of BCC histologic clearance.




Layout is the same as in **Figure 1**. This evidence graph comprises 3 connected networks. The first is the largest group of nodes and is not labeled explicitly. The second and third connected networks are labeled explicitly. 5-FU = 5-fluorouracil; ALA = aminolevulinic acid; BCC = basal cell carcinoma; INF = interferon; MAL = methyl-aminolevulinic acid; MMS = Mohs micrographic surgery; PDT = photodynamic therapy.

for cryotherapy (11.7% [CI, 3.1% to 35.3%]), PDT using methyl-aminolevulinic acid (14.5% [CI, 5.4% to 33.6%]) or aminolevulinic acid (11.0% [CI, 2.1% to 41.4%]), topical 5-fluorouracil (5.5% [CI, 0.5% to 38.8%]), and imiquimod (28.6% [CI, 14.6% to 48.6%]) (**Table 2**).

The second largest network in **Figure 2** comprised a 4-group trial ($n$ = 43) that compared combinations of surgical excision plus PDT using methyl-aminolevulinic acid or aminolevulinic acid versus curettage and found no evidence of a difference. However, the CIs were broad and could not exclude large effects (for example, odds ratios as extreme as 3 for any comparison). The third network comprised 1 RCT comparing imiquimod plus curettage versus imiquimod ($n$ = 20; odds ratio, 0.17 [CI, 0.01 to 1.88]).

We identified 3 adjusted NRCSs reporting lack of histologic clearance in BCC lesions. One reported nonstatistically significant differences between imiquimod and placebo (19). The second favored BCC surface preparation with a carbon dioxide laser over no preparation before PDT using aminolevulinic acid ($n$ = 56; odds ratio, 0.23 [CI, 0.07 to 0.75]) (20). The third favored treating versus not treating lesions with a pulse dye laser 2 weeks before surgical excision ($n$ = 41; odds ratio, 0.06 [CI, 0.01 to 0.34]) (21).

## Cosmetic Outcomes

Patient-reported cosmetic outcomes were evaluated in 10 RCTs. As shown in **Figure 3**, comparisons in RCTs were sparse and involved 4 treatment networks (results in Part E of the **Supplement**). From analyses of the largest network of 7 trials comparing 5 treatments (739 lesions in total; range per trial, 23 to 169 lesions), patients rated their cosmetic outcomes as good or better significantly more often with PDT using methyl-aminolevulinic acid (93.8% [CI, 79.2% to 98.3%]) or aminolevulinic acid (95.8% [CI, 84.2% to 99.0%]) than with standard excision (77.8% [CI, 44.8% to 93.8%]), cryotherapy (51.1% [CI, 15.8% to 85.4%]), or PDT combined with laser preparation of the lesion (20.0% [CI, 1.9% to 76.6%]) (**Supplement Table 6** [available at Annals.org] and **Table 2**). All other comparisons were not statistically significant and had wide CIs. Each of the other 3 networks comprised a single RCT. In 1, an RCT ($n$ = 27) did not find a difference between external-beam radiation and imiquimod (odds ratio, 0.81 [CI, 0.01 to 43.6]). Another RCT favored surgical excision or Mohs micrographic surgery over external-beam radiation or brachytherapy ($n$ = 244; odds ratio, 2.15 [CI, 1.2 to 3.86]). In the last RCT, 7 of 7 patients rated their out-

come as good or better after methyl-aminolevulinic acid PDT followed by Mohs micrographic surgery and 10 of 10 after Mohs surgery alone.

Observer-reported cosmetic outcomes were evaluated in 11 RCTs and 1 NRCS. The larger network in Figure 4 consists of 10 RCTs that compared 9 treatments (3505 lesions in total; range per trial, 23 to 563 lesions). The effect estimates had substantial imprecision, but good or better cosmetic outcomes were estimated to be more common for methyl-aminolevulinic acid PDT (87.9% [CI, 73.3% to 95.1%]) than for aminolevulinic acid PDT (53.4% [CI, 15.9% to 87.4%]), surgical excision (46.7% [CI, 19.4% to 76.1%]), cryotherapy (60.1% [CI, 23.1% to 88.3%]), topical 5-fluorouracil (57.5% [CI, 13.0% to 92.4%]), or imiquimod (61.0% [CI, 24.8% to 88.1%]) (Part E of the Supplement and Table 2). The smaller network in Figure 4 was a single RCT that favored surgical excision or Mohs micrographic surgery over external-beam radiation or brachytherapy ($n$ = 244; odds ratio, 5.56 [CI, 3.17 to 9.76]).

One NRCS found significantly better cosmetic outcomes as rated by an observer with aminolevulinic acid PDT than with surgical excision in 94 cases of BCC at 12 months after treatment (odds ratio, 10.2 [CI, 4.0 to 26.1]) (18).

### Mortality

Three RCTs reported results on all-cause mortality up to 3 years after treatment for various treatments: methyl-aminolevulinic acid PDT, 5-fluorouracil, and imiquimod (22–24); surgical excision and PDT using methyl-aminolevulinic acid (25, 26); and excision versus Mohs micrographic surgery (27). None of the deaths were attributed to the tumor or the treatment.

### Quality of Life

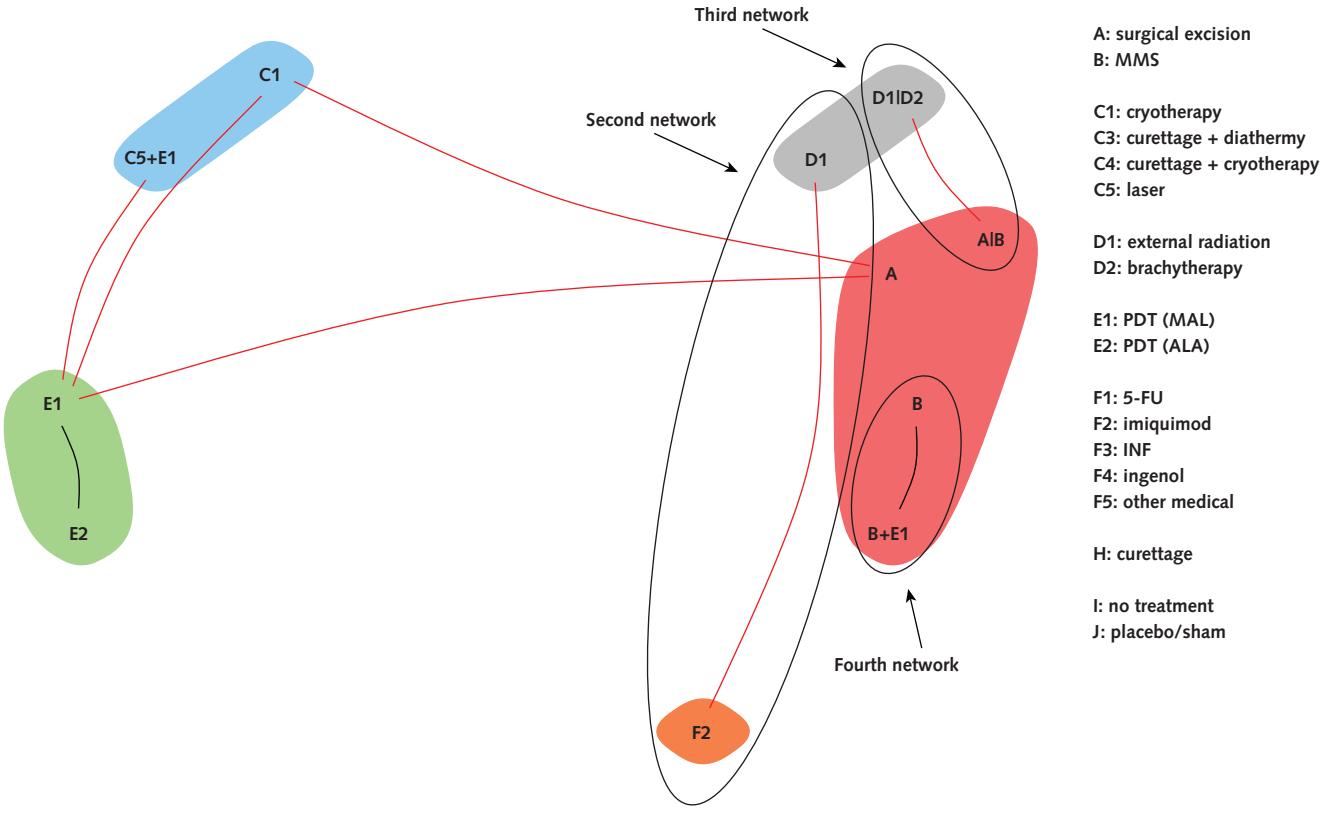
In a single RCT ($n$ = 374) comparing surgical excision with Mohs surgery, patients in both groups had good "health-related quality life" and a "minimum level of anxiety" on the Nottingham Health Profile and the State-Trait Anxiety Inventory at 6 months, with no statistically significant differences ($P$ > 0.07 across 7 variables) (28).

Table 3 summarizes the evidence for all aforementioned outcomes.

## DISCUSSION

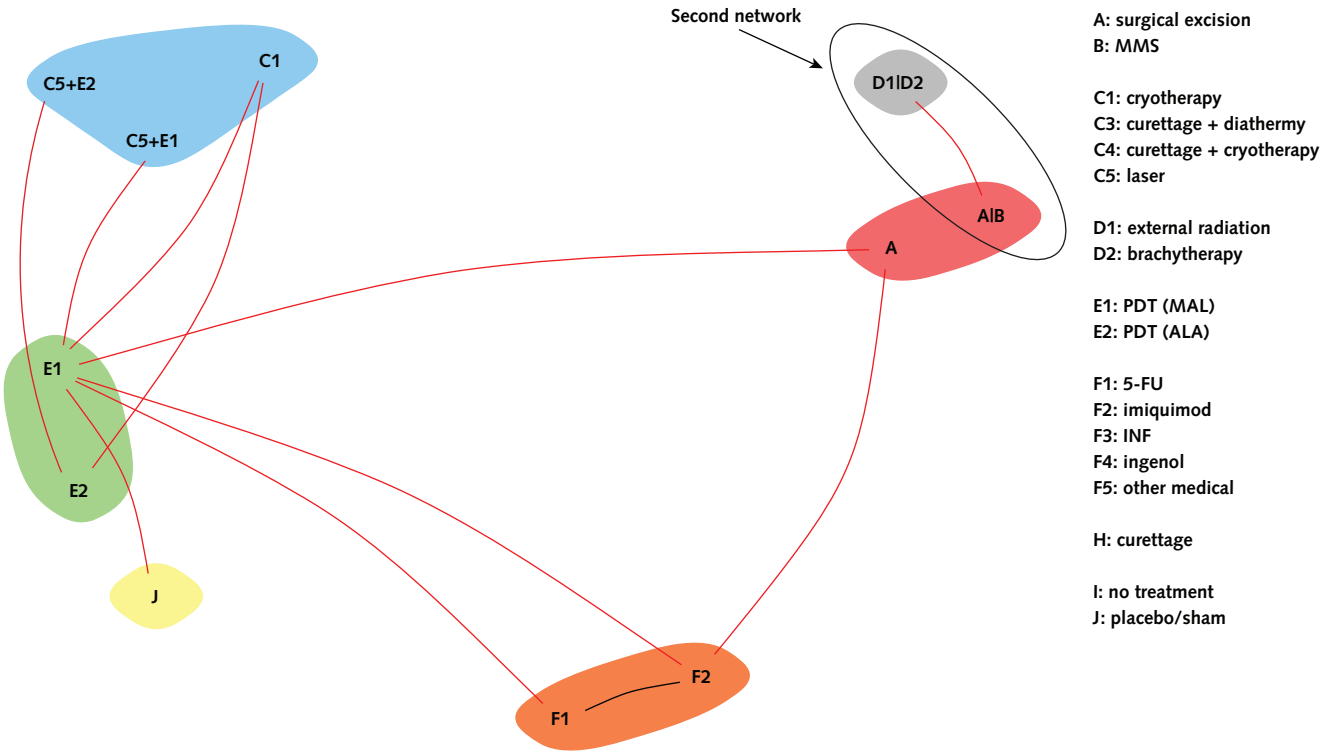
In the existing evidence, which pertains mostly to low-risk histologic subtypes, surgical treatments and external-beam radiation therapy seem to confer better chances of cure for BCC (as approximated by recurrence rates and histologic clearance) than PDT or curet-

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




Layout and naming of connected networks are the same as in Figure 1. 5-FU = 5-fluorouracil; ALA = aminolevulinic acid; BCC = basal cell carcinoma; INF = interferon; MAL = methyl-aminolevulinic acid; MMS = Mohs micrographic surgery; PDT = photodynamic therapy.

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




Layout and naming of connected networks are the same as in **Figure 1**. 5-FU = 5-fluorouracil; ALA = aminolevulinic acid; BCC = basal cell carcinoma; INF = interferon; MAL = methyl-aminolevulinic acid; MMS = Mohs micrographic surgery; PDT = photodynamic therapy.

tage. Curettage and diathermy is associated with a low recurrence rate, but this estimate is imprecise. Recurrence rates with imiquimod were higher in our analysis and inferior to those for excision in a single large RCT; however, recurrence rates were acceptable (29). Therefore, our results support the effectiveness of surgery, external-beam radiation, topical imiquimod, and curettage and diathermy for low-risk BCC. Despite substantial uncertainty in estimates of their relative effectiveness, our results are reassuring, in that these treatments are among the most commonly used in clinical practice.

We provide a comprehensive update to previously published systematic reviews on the treatment of BCC (30, 31), and ours is the first analysis to our knowledge to compare more than 1 intervention simultaneously. Our work complements recent guidelines from the American Academy of Dermatology that call out the paucity of comparative effectiveness evidence for this very common type of cancer (32). For example, the guidelines recommend curettage and diathermy for low-risk BCC not located on the head and neck on the basis of expert opinion alone.

Some comparisons in our analysis are of limited practical utility for clinicians. Radiation therapy is rarely used in routine clinical practice to treat low-risk BCC; it is generally reserved for patients with high-risk or recurrent disease or contraindications to surgery because of its expense, suboptimal cosmetic outcomes in the long term, and complications. Although portable radiation machines are being increasingly used to treat low-risk lesions in the office setting (4), comparisons of radiation treatment with topical drugs are not relevant for most clinical scenarios.

Morbidity and mortality associated with low-risk BCC are generally low, so outcomes other than cure, such as cosmesis, are important. Management of BCC is amenable to shared decision making, in which patients' educated and considered values inform treatment decisions. For example, patients who value cosmetic outcomes may favor PDT despite its higher recurrence rates. Other patients may not favor radiation therapy, which is effective but increases the risk for poorer cosmetic outcomes and, perhaps, of secondary tumors in the long term. Despite sparse evidence on the curative effect of topical medications, such as 5-fluorouracil and imiquimod, some patients may value the convenience of applying them at home compared with the hassle of surgery or many hospital visits to receive external-beam radiation therapy. Access to treatments will also affect clinical decision making. Specialty care is not available in all communities. Primary care physicians can do basic surgical procedures and prescribe topical medications but do not have access to specialized treatments, such as Mohs micrographic surgery, radiotherapy, and PDT. Decision analysis for decision making about personal and public health, cost-effectiveness analysis for public or organizational

*Table 2.* Mean Outcome Rates for Specific Interventions for BCC

| Intervention | Mean Outcome Rate (95% CI), % |
|---|---|
| **Figure 1: Recurrence** | |
| First network | |
| Surgical excision | 3.3 (1.3–7.8) |
| MMS | 3.8 (0.7–18.9) |
| MMS + IFN | 4.6 (0.2–56.2) |
| Cryotherapy | 21.0 (9.0–41.4) |
| Diathermy + curettage | 5.9 (0.7–34.9) |
| Cryotherapy + curettage | 17.1 (3.6–53.4) |
| Laser + PDT (MAL) | 12.0 (1.8–49.6) |
| Laser + PDT (ALA) | 25.9 (5.1–69.6) |
| External-beam radiation | 3.2 (0.6–16.1) |
| PDT (MAL) | 17.8 (9.1–31.8) |
| PDT (ALA) | 16.9 (7.3–34.4) |
| 5-FU | 24.7 (7.1–58.4) |
| Imiquimod | 14.1 (5.4–32.4) |
| Curettage | 15.4 (2.6–55.3) |
| Second network | |
| Surgical excision or MMS | 0.6 (0.1–4.0) |
| External-beam radiation or brachytherapy | 4.6 (2.3–9.0) |
| **Figure 2: Lack of histologic clearance** | |
| First network | |
| Surgical excision | 1.7 (0.3–9.9) |
| Cryotherapy | 11.7 (3.1–35.3) |
| Laser | 33.7 (10.9–67.9) |
| Laser + PDT (MAL) | 37.5 (4.7–87.9) |
| PDT (MAL) | 14.5 (5.4–33.6) |
| PDT (ALA) | 11.0 (2.1–41.4) |
| 5-FU | 5.5 (0.5–38.8) |
| Imiquimod | 28.6 (14.6–48.6) |
| Ingenol | 77.1 (23.7–97.3) |
| Other medical interventions | 78.1 (23.9–97.6) |
| No treatment | 81.8 (48.3–95.6) |
| Placebo | 86.3 (72.1–93.9) |
| Second network | |
| Surgery + PDT (MAL) | 36.4 (14.3–66.1) |
| Surgery + PDT (MAL) + curettage | 20.0 (5.0–54.1) |
| Surgery + PDT (ALA) | 36.4 (14.3–66.1) |
| Surgery + PDT (ALA) + curettage | 18.2 (4.6–50.7) |
| Third network | |
| Imiquimod + curettage | 10.0 (1.4–46.7) |
| Curettage | 40.0 (15.8–70.3) |
| **Figure 3: Patient-reported good or better cosmetic outcomes** | |
| First network | |
| Surgical excision | 77.8 (44.8–93.8) |
| Cryotherapy | 51.1 (15.8–85.4) |
| Laser + PDT (MAL) | 20.0 (1.9–76.6) |
| PDT (MAL) | 93.8 (79.2–98.3) |
| PDT (ALA) | 95.8 (84.2–99.0) |
| Second network | |
| External-beam radiation | 96.2 (59.7–99.8) |
| Imiquimod | 96.9 (65.0–99.8) |
| Third network | |
| Surgical excision or MMS | 80.9 (73.3–86.8) |
| External-beam radiation or brachytherapy | 66.4 (57.2–74.5) |
| Fourth network | |
| MMS | 95.5 (55.2–99.7) |
| MMS + PDT (MAL) | 93.8 (46.1–99.6) |
| **Figure 4: Observer-reported good or better cosmetic outcomes** | |
| First network | |
| Surgical excision | 46.7 (19.4–76.1) |
| Cryotherapy | 60.1 (23.1–88.3) |
| Laser + PDT (MAL) | 93.5 (63.5–99.2) |
| Laser + PDT (ALA) | 5.9 (0.5–45.9) |
| PDT (MAL) | 87.9 (73.3–95.1) |
| PDT (ALA) | 53.4 (15.9–87.4) |
| 5-FU | 57.5 (13.0–92.4) |
| Imiquimod | 61.0 (24.8–88.1) |
| Placebo/sham | 93.3 (41.5–99.6) |
| Second network | |
| Surgical excision or MMS | 78.6 (70.8–84.8) |
| External-beam radiation or brachytherapy | 39.8 (31.2–49.1) |

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

policymaking, and value-of-information analysis for identifying research priorities are important future directions.

This analysis and the associated evidence base have several limitations. First, the RCTs included patients and lesions that are typically encountered in clinical practice but did not extensively analyze how patient-level factors may modify treatment effects (4). This hinders the extrapolation of findings to finer patient subgroups (for example, superficial BCC of the H zone of the face) or to individual persons.

Second, our analyses are based on sparse data. For example, only 16 RCTs and 2204 lesions informed comparisons about BCC recurrence among the network of 14 treatments. Almost all comparisons for all outcomes were based on at most 3 trials. Most treatments were compared with at most 3 other treatments. Only 20 patients with BCC in 1 trial were treated with curettage despite its common use in clinical practice (33). The relative dearth of randomized and nonrandomized data adds to concerns about the generalizability of our results. Comparative evidence is needed for commonly used treatment modalities, such as curettage with diathermy, standard excision (including differing excision margins), Mohs surgery, PDT, and topical medical therapies. Further, as external-beam radiation therapy becomes increasingly available in the office setting, trials comparing that technique specifically with commonly used modalities are necessary. As of this writing, the American Academy of Dermatology discourages superficial radiotherapy and electronic brachytherapy for most BCC because of the lack of comparative evidence (34, 35).

Third, evidence is scant on the treatment of more aggressive primary BCC subtypes, including infiltrative and sclerosing patterns. These are more likely to recur and are considered indications for Mohs surgery (with some exceptions) (36). Similarly, no RCT information

*Table 3.* Summary Statements for BCC Lesions, by Intervention Category and Strength of the Relevant Evidence

| Selected Summary Statements | ROB (Evidence Base) | Consistency | Precision | Directness | Overall Rating per Conclusion Statement | Comments* |
|---|---|---|---|---|---|---|
| **Recurrence** | | | | | | |
| 1. Surgical interventions and external-beam radiation were associated with lower recurrence rates than interventions that destroy lesions with heat or cold and PDT<br>2. Curettage may have higher recurrence rates than surgical interventions or radiation<br>3. Recurrence rates did not differ between imiquimod and surgical interventions<br>4. [Data on the comparison of curettage and interventions that destroy lesions with heat or cold or PDT are imprecise] | 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<br>2: Low<br>3: Low<br>4: [Insufficient] | 1: Statistically significant differences<br>2–4: Statistically nonsignificant differences<br>See Part C of the Supplement (available at Annals.org ) |
| **Histologic clearance** | | | | | | |
| 1. Surgical interventions were associated with better histologic clearance outcomes than interventions that destroy lesions with heat or cold, PDT, drugs, and placebo<br>2. Interventions that destroy lesions with heat or cold, PDT, and drugs had better histologic outcomes than placebo<br>3. [Data on the relative comparisons of nonsurgical active interventions are imprecise] | Moderate | Possibly consistent (no robust indications of inconsistency) | Varies by comparison from precise to imprecise | Mix of direct and indirect data | 1: High<br>2: Moderate to high<br>3: [Insufficient] | 1, 2: Statistically significant differences<br>3: Statistically nonsignificant differences<br>See Part D of the Supplement |
| **Patient-reported cosmetic outcomes** | | | | | | |
| 1. PDT was associated with better cosmetic outcomes than other intervention categories<br>2. [Data on relative comparisons among nonsurgical active intervention categories are imprecise] | 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<br>2: Insufficient | 1: Statistically significant differences<br>2: Statistically nonsignificant differences<br>See Part E of the Supplement |
| **Observer-reported cosmetic outcomes** | | | | | | |
| 1. PDT was associated with significantly better cosmetic outcomes than surgery<br>2. [There is no evidence that PDT may be associated with better cosmetic outcomes than nonsurgical active intervention categories (but not statistically significantly)]<br>3. [Data on relative comparisons among heat/cold, radiation, and drugs are imprecise] | 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<br>2: [Insufficient]<br>3: [Insufficient] | 1: Statistically significant differences<br>2, 3: Statistically nonsignificant differences<br>See Part F of the Supplement |
| **Other outcomes** | | | | | | |
| [Evidence on quality of life and mortality is reported in a minority of studies, and its strength is not rated] | [Not rated] | [Not rated] | [Not rated] | [Not rated] | [Not rated] | – |

BCC = basal cell carcinoma; PDT = photodynamic therapy; ROB = risk of bias.
* Per statement. Based on relative effects tables.

exists on subpopulations of patients who have limited life expectancy, are frail, or are immunocompromised (for example, have chronic lymphocytic leukemia and other types of cancer, have immunodeficiency disorders, or receive immunomodulating or immunosuppressive treatments). Active nonintervention has been posited as a potential management strategy for patients with limited life expectancy, but no trials have evaluated it (37).

Finally, BCC outcomes and their definitions should be standardized, ideally as a core outcome set, such as that being developed by the IMPROVED (Measurement of Priority Outcome Variables in Dermatologic Surgery) group (38). In our opinion, trials should measure lesion

recurrence, standardize and measure adverse events and cosmetic outcomes, and include information on costs and health care resource use.

Better monitoring of population trends in BCC would help prioritize research on the most consequential groups of patients and types of cancer. Such monitoring can be done by the SEER (Surveillance, Epidemiology, and End Results) program, which currently ignores these types of cancer; less expensive sentinel registries; the Centers for Disease Control and Prevention; or large health organizations. Although the large number of these tumors makes surveillance logistically difficult and costly, advances in health information technology and big data analytics should make it more feasible (39).

On the basis of sparse evidence and with substantial imprecision, surgery and external-beam radiation have lower recurrence rates than other modalities for the treatment of BCC. In order for clinicians, patients, and payers to make informed decisions about treating BCC, new RCT or high-quality NRCS evidence is needed.

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