Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies

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Abstract

Objectives To assess the effects of treatments for non-metastatic invasive squamous cell carcinoma (SCC) of the skin using evidence from observational studies, given the paucity of evidence from randomised controlled trials.

Design Systematic review of observational studies.

Data sources Medline, Embase, to December 2012.

Review methods Observational studies of interventions for primary, non-metastatic, invasive, SCC of the skin that reported recurrence during follow-up, quality of life, initial response to treatment, adverse events, cosmetic appearance, or death from disease. Studies were excluded if data for primary cutaneous SCC was not separable from other data. Data were extracted independently by two reviewers. Meta-analysis was performed where appropriate using a random effects model to estimate the pooled proportion of an event with 95% confidence intervals.

Results 118 publications were included, covering seven treatment modalities. Pooled estimates of recurrence of SCCs were lowest after cryotherapy (0.8% (95% confidence interval 0.1% to 2%)) and curettage and electrodesiccation (1.7% (0.5% to 3.4%)), but most treated SCCs were small, low risk lesions. After Mohs micrographic surgery, the pooled estimate of local recurrence during variable follow-up periods from 10 studies was 3.0% (2.2% to 3.9%), which was non-significantly lower than the pooled average local recurrence of 5.4% (2.5% to 9.1%) after standard surgical excision (12 studies), and 6.4% (3.0% to 11.0%) after external radiotherapy (7 studies). After an apparently successful initial response of SCCs to photodynamic therapy, pooled average recurrence of 26.4% (12.3% to 43.7%; 8 studies) was significantly higher than other treatments. Evidence was limited for laser treatment (1 study) and for topical and systemic treatments (mostly single case reports or small non-comparative series with limited follow-up).

Conclusions Many observational studies have looked at different treatment modalities for SCC, but the evidence base for the effectiveness of these interventions is poor. Comparison of outcomes after different treatments should be interpreted cautiously owing to biases inherent in the types of study included, and lack of direct comparisons to enable the estimation of relative treatment effect. Further evidence is needed to develop a prognostic model and stratify individuals at high risk of developing SCC, to improve the evidence base for this common cancer and to optimise clinical management.

Protocol registration International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42011001450.

Introduction

Cutaneous squamous cell carcinoma (SCC), the second most common type of non-melanoma skin cancer after basal cell carcinoma, arises most commonly in sun exposed areas of the body from keratinocytes in the epidermis. Invasive SCC, characterised histologically by the spread of malignant cells into the dermis, could arise de novo or from the transformation of precursor lesions such as actinic keratoses and Bowen’s disease. The tumour could present clinically as a smooth or
hyperkeratotic enlarging plaque, nodule, or ulcer and could be associated with pain, pruritus, or bleeding when traumatised. Induration, the limits of which might not be sharply defined, can spread beyond the extent of a clinically apparent tumour. Invasive SCC can recur and metastasise to regional lymph nodes or distant organs and, if left untreated or inadequately treated, can cause extensive local tissue destruction.

Worldwide, the incidence of SCC has been increasing since the 1960s. More than 80% of non-melanoma skin cancers occur in people aged 60 years and older, and with an increasingly ageing population, the workload of non-melanoma skin cancers for dermatologists in the United Kingdom has been predicted to increase by 50% by 2030. Additionally, solid organ transplant recipients are at particular risk of developing SCC. In one cohort study of more than 1000 ethnically diverse, solid organ transplant recipients followed prospectively over a 22 year period, this group showed a 153-fold excess risk for developing SCC and dying from it compared with the general population.

The aims of treatment of SCC are to completely remove or destroy the tumour and to minimise functional and cosmetic impairment. Stratification of patients based on the American Joint Committee on Cancer’s staging system, which takes into account tumour features associated with a worse prognosis (tumour diameter >2 cm; tumour depth >2 mm; Clarks’ level ≥IV; location on the ear, lip, and sites not exposed to the sun, presence of perineural invasion, and poorly differentiated or undifferentiated histology), together with the nodal and metastatic status of the patient, can be used as a guide to treatment. Current UK guidelines for primary SCC recommend surgical excision, including Mohs micrographic surgery if appropriate, as the mainstay of treatment, but emphasise the need to be aware of the factors that could influence success when choosing treatment modality. However, in general, SCC treatment has not been thoroughly or rigorously studied. Our recent Cochrane systematic review of the treatment of primary non-metastatic SCC found only one randomised controlled trial that compared recurrence between groups receiving either adjuvant 13-cis retinoic acid and interferon alpha after initial surgery, or no adjuvant treatment. However, we found no randomised controlled trials that assessed the effectiveness of different interventions used commonly in clinical practice in the UK.

This review looks at studies other than randomised controlled trials to assess the effectiveness of common treatment modalities used in everyday practice for SCC. This review aimed to provide an overview of the current evidence base, highlight areas in which the evidence base requires strengthening, and stimulate future research in the field.

Methods

The systematic review was conducted according to the MOOSE guidance for meta-analysis of observational studies. Details of the protocol for this systematic review are registered on PROSPERO (www.metaxis.com/prospero/full_doc.asp?RecordID=1450; web appendix 1).

Search strategies

We searched Medline (from 1948) and Embase (from 1980) up to December 2012 for relevant studies using search criteria for observational studies based on Scottish Intercollegiate Guideline Network filters (web appendix 2). We checked the bibliographies of included studies and recent review articles for additional articles that were relevant. Owing to the large number of studies and limited accuracy of translation, only studies published in English were retrieved.

Inclusion and exclusion criteria

We included all studies, other than randomised controlled trials, reporting one of the following items:

- Surgical excision
- Mohs micrographic surgery
- Radiotherapy (external radiotherapy, brachytherapy, and adjuvant radiotherapy)
- Laser irradiation
- Photodynamic therapy
- Cryotherapy
- Curettage and electrodesiccation
- Topical treatments (fluorouracil and imiquimod)
- Other chemotherapy used to treat previously untreated invasive squamous cell carcinoma of the skin, which was non-metastatic at presentation.

Based on our previous Cochrane systematic review, the main outcomes of interest were recurrence of SCC during follow-up from one month to 10 years after treatment, and quality of life. Secondary outcomes were initial response to treatment, cosmetic appearance, or death due to disease. We excluded studies for which we were unable to extract data for primary non-metastatic SCC. These included studies containing data for mixed populations of SCC and basal cell carcinoma, previously treated and untreated SCCs, or primary and metastatic SCCs. Studies in which separate data were not reported for different treatment modalities were also excluded. Owing to the large number of studies, studies reporting outcomes after surgical excision and Mohs micrographic surgery were only included if there were 20 or more eligible participants, unless they were restricted to a specific anatomical location, such as periorbital or auricular sites.

Study selection and data extraction

Three review authors (LL, FB-H, JL-B) independently checked the titles and abstracts of studies that potentially met the inclusion criteria. Studies that clearly did not refer to treatment of SCC of the skin were excluded. The full text was obtained for those studies that potentially fulfilled the inclusion criteria or for which the scope was unclear. Any disagreements were resolved through discussion between the authors. Data were extracted independently by two reviewers (LL, and JB or AA) and entered onto a standardised, pre-piloted data extraction form for assessment of study quality and evidence synthesis. A third author (JL-B or FB-H) resolved any discrepancies.

Quality of reporting and risk of bias

We evaluated the relative reporting quality of each study using a self developed tool based on criteria suggested by Joerg Albrecht for reporting case series and case reports (web appendix 3). Case series and open label studies were scored for the number of reporting quality items present and arbitrarily rated as being of poor (score 0-3), intermediate (4-7), or good quality (8-10). For those studies in which pharmaceutical preparations were an integral part of the treatment modality, we also recorded the declaration of sponsorship by a pharmaceutical manufacturer.
Data analysis

For each study, we calculated raw proportions using the number of events divided by the total number of people in the study. Variances of the raw proportions were stabilised using the Freeman-Tukey variant of the arcsine square root transformation. We did pooled analyses on the transformed quantity using a random effect model, to allow for heterogeneity resulting from inherent biases within the studies. Analyses were conducted using StatsDirect version 2. We were not able to directly allow for differences in length of follow-up using time to an event as an outcome measure, owing to lack of such data in the papers. However, we performed a subgroup analysis where possible, comparing the outcomes in studies that gave the mean follow-up as less than two years, between two and five years, and greater than five years.

To examine the effect of removing studies with greatest potential for risk of bias, we conducted a sensitivity analysis where possible by repeating the analysis with data from selected papers meeting at least three of the following criteria: 50 or more SCCs reported, mean follow-up greater than three years, recurrence type specified, scoring 8-10 on our reporting quality assessment. Adverse events and cosmetic appearance outcomes were described qualitatively.

Results

The searches identified 3826 publications after removal of duplicates, of which 451 were potentially eligible based on their titles; on review of the abstracts, 161 records were not relevant to the review. Of 290 full text articles assessed for eligibility, 172 were excluded, mainly because of lack of separable primary SCC data, leaving 118 that were included in the review (fig 1). The review included 106 non-comparative studies and 12 single case reports, which were included due to a lack of more robust study designs for particular interventions. Four studies reported outcomes for more than one treatment modality. Web appendix 3 shows full details of the studies, including details of the methodology, types of SCC included, and quality of reporting.

Figure 2 summarises the risk of bias for the studies. Forty eight per cent of studies were evaluated as having collected data retrospectively and 36% prospectively; the remaining studies could not be evaluated with regard to the design owing to the lack of sufficient information reported in the publications. Overall, 41% of studies were assessed as being at high or unclear risk of attrition bias due to analyses not accounting for losses to follow-up. Selection of a specific treatment modality on the basis of tumour or patient characteristics was assessed as presenting a high risk of bias in 54% of the studies, with low risk in 15%. Risk of bias relating to selection could not be assessed in the remaining 31% of included studies because of insufficient reporting in the publications.

Overall, we classified 13% of the case series as being of poor reporting quality, 56% as intermediate quality, and 30% as high quality. Of 24 studies in which topical or systemic treatments were reported, seven (29%) received some form of sponsorship from a pharmaceutical company but did not declare that the sponsor had had no involvement in the design, results and analysis of the study.

Surgical excision

We included 12 studies (1144 patients). Local recurrence during follow-up after surgical excision ranged from 0% to 15% (table 1), with an estimate of overall pooled recurrence of 5.4% (95% confidence interval 2.5% to 9.1%, I²=81%; fig 3). Duration of follow-up varied between the studies. One study had a mean follow-up period of less than two years (16 months), with local recurrence of 1.8% of surgically excised SCCs of the head and neck region. In those studies with mean follow-up between two and five years (736 patients), recurrence ranged from 0% to 13.0%, with a pooled estimate of recurrence of 5.0% (95% confidence interval 2.3% to 8.3%, I²=62%).

One of the 12 surgical excision studies had a minimum follow-up of five years and reported no local recurrences of 86 surgically excised SCCs at various sites. Three studies reported recurrence of 4.8% for eyelid SCCs, 10.5% for trunk and extremity SCCs, and 15.3% for SCCs of the pinna, but did not specify how long patients were followed. SCCs in the ear region were associated with highest recurrence rates. Three studies (n=261) in which SCCs of the pinna were surgically excised gave a pooled average local recurrence of 14.1% (95% confidence interval 10.2% to 18.5%, I²=0%). This recurrence was significantly higher than the lower pooled average of 3.2% (1.5% to 5.5%, I²=57%) for studies (n=916) in which SCCs at other sites were included (fig 4 and 5). We noted a non-significant increase in local recurrence with increasing SCC diameter in one series. There were local recurrences in 12.2% (4.6% to 24.7%) of 49 lesions smaller than 10 mm in diameter, 14.3% (7.8% to 23.2%) of 91 lesions 10-30 mm in diameter, 21.7% (7.4% to 43.7%) of 23 lesions 30-40 mm in diameter, and 42.8% (9.9% to 81.6%) of seven tumours greater than 40 mm in diameter.

Sensitivity analysis of the four papers meeting our criteria for studies at lowest risk of bias had no significant effect on local recurrence (4.2% (95% confidence interval 0.6% to 10.8%), I²=81%). Recurrence in regional lymph nodes after surgical excision of SCC was reported in eight series (comprising of 786 patients), ranging from 0% to 9.7%, with pooled average recurrence of 4.4% (2.4% to 6.9%, I²=50%; fig 6). Sensitivity analysis in which only the three papers considered at lowest risk of bias were included had no significant effect on regional recurrence (4.6% (1.3% to 10.0%), I²=72%).

One study (108 patients) had a mean duration of follow-up of less than two years, with 0.1% recurrence (95% confidence interval 0% to 5.1%). In four studies, specified mean follow-up duration was between two and five years, with a pooled average recurrence of 3.6% (1.9 to 5.9, I²=11%). None of the studies had a mean follow-up longer than five years, and in three papers, follow-up duration was either not specified or given as a broad range.

In those series that only included treatment of SCCs located around the ear, the pooled average regional recurrence was 7.7% (95% confidence interval 4.8% to 11.2%, I²=0%). This proportion was significantly greater than the pooled average regional recurrence of 2.9% (1.4% to 5.0%, I²=27%) for the five remaining studies that included other head and neck locations (figs 7 and 8). We found two studies that reported distant metastases after surgical excision. Of 211 patients with SCCs at various sites who were followed up for at least a year, only one developed distant metastasis. There were no distant metastases in any of 35 patients with periorcular SCC during a mean follow-up period of 31.1 months.

In four articles (comprising 146 patients), recurrence was reported but not defined as being local, regional, or distant. Two of these studies had mean follow-up periods greater than five years, with pooled average recurrence of 5.4% (95% confidence interval 0.7% to 27.6%). There were no reported recurrences...
in the study in which mean follow-up was less than five years. The fourth study included 13 patients with stage I or II SCC of the external ear, with a relatively high recurrence of 61.5% (31.6% to 86.1%) during follow-up ranging from six months to 20 years.31 From analysis of eight studies comprising 485 patients with primary SCC, deaths attributable to disease ranged from 0% to 8.1% during follow-up, with a pooled average of 4.1% (95% confidence interval 1.7% to 7.6%, I²=58%; fig 9).14 16 17 20 23 29 Three studies with a follow-up period specified as between two and five years,14 16 23 had a significantly lower pooled average of 0.8% (0.1% to 2.5%, I²=0%) than the two studies with follow-up of more than five years from which the pooled average percentage of patients dying from their disease was 8.6% (4.7% to 13.6%).17 29 In three papers, duration of follow-up was not specified or was given as a range only.20 22 27 No deaths were reported in either of the two included studies in which SCCs of the eyelid were surgically excised.16 21 Incompleteness of surgical excision was reported in 11 studies (comprising 2343 excisions). Overall, the pooled average estimate of incomplete excisions was 8.8% (95% confidence interval 5.4% to 13.0%, I²=89%; table 2, fig 10).14 17 19 20 26 28 32 36 Definitions of incomplete excision within the studies were not consistent. These were based on the presence of tumour cells at the surgical margin,26 32 34 35 the presence of residual tumour at or within 1 mm of the lateral or deep margins of the excised specimen,24 tumour within one microscopic high-power field (0.5 mm),13 and the presence of tumour at or “close to” the margin of the resected specimen.36 Excision margins used varied. One prospective study used margins of 2 mm to more than 10 mm,14 with 6.2% of tumours being incompletely excised (4.2% to 8.8%). In another prospective series with no SCCs incompletely excised, excision margins were based on the clinical diagnosis and surgeon’s preference.25 The other studies assessing incomplete excision were retrospective reviews. Retrospective reviews that specified the excision margin used margins between 3 mm and 6 mm,19 20 28 32 36 The highest percentage of incompletely excised tumours was observed after excision of periorbital lesions with a 5 mm margin, with 25% being incompletely excised (15.3% to 37.0%).13 None of the included studies reported SCC specific quality of life, cosmetic appearance, and adverse event data.

**Mohs micrographic surgery**

Sixteen studies reported outcomes after Mohs micrographic surgery. In a seminal series of papers, Mohs reported cure rates at five years for previously untreated SCCs of the trunk and extremities (95.7%);4 of the ear (96.6%);5 of the face, scalp, and neck (97.8%);6 of the eyelid (98.5%);7 and of the nose (98.8%).7 A pooled cure rate at five years for the 2133 SCCs at all sites was 97.4% (95% confidence interval 96.2% to 98.3%, I²=48%).

Ten studies reported local recurrence,14 40-45 ranging from 0% (95% confidence interval 0% to 36.9%) in one small study including eight periorbital SCCs,45 to 5.7% (1.9% to 12.9%) in a study of auricular SCCs.47 For the 10 studies (comprising 1572 participants), the pooled average local recurrence was 3.0% (2.2% to 3.9%, I²=40%; table 3, fig 11). Sensitivity analysis including only the six studies meeting the prespecified criteria had no significant effect on local recurrence (2.7%; 1.9% to 3.7%, I²=40%).40 41 43-45 48 In one study with specified mean follow-up of less than two years, recurrence was 3.5% (95% confidence interval 1.3% to 7.5%). This proportion did not differ significantly from the average recurrence of 2.8% (2.0% to 3.9%, I²=0%) in seven studies with mean follow-up of between two and five years,40 41 43-45 47 and 3.1% (1.4% to 5.4%) in the two studies with mean follow-up greater than five years.44 48 Six studies reported recurrence in the regional lymph nodes after treatment with Mohs micrographic surgery.40 41 43-45 49 On pooled analysis (comprising 1162 patients), the average regional recurrence was 4.2% (95% confidence interval 2.5% to 6.6%, I²=56%; fig 12). There was no significant effect on regional recurrence in the sensitivity analysis, which included only the four studies meeting the criteria,34 43 44 45 with average recurrence of 3.2% (1.9% to 5.0%, I²=29%).

Five studies,14 40 41 43 45 specified mean follow-up between two and five years, with a pooled regional recurrence of 3.4% (95% confidence interval 1.8% to 5.3%, I²=34%). None of the studies had mean follow-up greater than five years. One study reported no distant metastases during at least five years’ follow-up in 229 patients treated with Mohs micrographic surgery.44 In a case series of 87 auricular SCCs, no distant metastases were reported during a mean follow-up period of 34.6 months.50 One smaller series of 48 SCCs treated by Mohs micrographic surgery observed one patient with distant metastasis during a mean follow-up of 3.4 years.51 Another series including eight patients with periorcular SCC also noted one patient with metastases to the lung.52 Although the authors presumed that this patient had subclinical spread of tumour before treatment with Mohs micrographic surgery, because there was no evidence of local recurrence.

Five studies (766 patients) did not define recurrence as being local, regional, or distant.51 53 54 55 56 These five studies had a pooled average unspecified recurrence of 4.7% (95% confidence interval 0.7% to 11.7%, I²=81%; fig 13). The highest proportion of unspecified recurrences was seen in a small series of 16 external ear SCCs during follow-up of between six months to 20 years, in which 31.2% of tumours recurred (11.7% to 58.7%).31 Three studies (735 patients) specified mean duration of follow-up as being between two and five years.55-57 For these studies, the average unspecified recurrence was 2.2% (95% confidence interval 0.3% to 5.4%, I²=61%). The remaining studies51 56 did not specify the mean duration of follow-up.

Four studies with mean follow-up of between two and five years reported deaths attributable to SCC,40 41 43 47 with an average of 1.1% (95% confidence interval 0.2% to 2.6%, I²=49%) of the 941 eligible patients dying from disease on pooled analysis (fig 14). One of the included studies reported a relatively high proportion of deaths compared to the other studies. It was a small series of eight patients with periorcular SCCs, one of whom developed regional metastases and lung metastases without evidence of local recurrence, indicating that the tumour had spread subclinically before treatment.50 None of the included studies reported separate SCC data for quality of life, cosmetic outcomes, or adverse events.

**External radiotherapy**

We found 14, mostly retrospective, studies in which a total of 1018 primary SCCs were treated with external radiotherapy.15 19 20 27 54-64 Seven studies (comprising 761 patients) reported local recurrence after external radiotherapy, with pooled average local recurrence of 6.4% (95% confidence interval 3.0% to 11.0%, I²=76%; table 4); fig 15).15 20 30 35 37-39 Three studies
were included in the sensitivity analysis, with no significant effect on local recurrence (7.3%, 2.1% to 15.4%, I²=87%). The four studies with a mean follow-up period between two and five years, had a pooled average recurrence of 6.1% (95% confidence interval 2.2 to 11.7, I²=85%). None of the studies had mean follow-up greater than five years, and three studies did not specify duration of follow-up or gave it as a broad range.

In one study, location in the ear and scalp region was found to be significantly associated with relapse of tumour compared with other sites (P=0.025). Age and tumour size were also significantly correlated with risk of relapse in this study (P=0.012 and P<0.0001, respectively). There was a trend towards better outcome with well-differentiated tumours, although this finding was not significant (P=0.1). Two studies (with 155 patients in total) only assessed nasal SCCs, with a pooled average local recurrence of 5.6% (95% confidence interval 2.6% to 9.7%). In another two small studies (19 patients) that only included SCCs of the pinna, the pooled average local recurrence was 20.3% (0.0% to 64.6%). Although the wide confidence intervals suggested that this recurrence was not significantly different from recurrence of nasal SCCs.

Regional lymph node failure was also reported in three studies (comprising 272 patients in total), giving an average regional recurrence of 2.6% on pooled analysis (95% confidence interval 0.04% to 8.9%, I²=70%; fig 16). In both larger studies—which included patients with SCCs of the nose and at various sites, respectively—the mean duration of follow-up was between two and five years. In the third study, there were only two eligible patients with SCC of the pinna, one of whom developed metastasis. Excluding this study from the analysis had no effect on the outcome.

One study reported locoregional recurrence after either local radiotherapy alone, or after local radiotherapy plus radiotherapy to first echelon lymph nodes. Overall recurrence in the 37 SCCs treated with local radiotherapy alone was 30.0% (95% confidence interval 15.9% to 47.0%). Recurrence ranged from 14.3% (0.3% to 57.9%) for the seven T2 tumours to 29.2% (12.6% to 51.1%) for the 24 T3 tumours, to 50% (11.8% to 88.2%) for the six T4 tumours. However, with wide overlapping confidence intervals, statistical significance cannot be inferred from these differences. Of five T4 tumours treated with local radiotherapy plus nodal radiotherapy, there was one recurrence (20%, 0.5% to 71.6%).

Recurrence was not defined as local, regional, or distant in another six studies. Pooled data from 220 treated SCCs from the studies gave an average recurrence of 4.8% (95% confidence interval 0.6% to 12.8%, I²=70%; fig 17). Two of the studies had a mean duration of follow-up of less than two years with pooled recurrence of 27.2% (2.0% to 89%). However, the number of patients was very small (n=5), and in one study only T4 tumours were treated, with recurrence in two of three patients. Average recurrence in the two studies with specified mean duration of follow-up of between two and five years was 6.1% (44 patients, 0% to 22.6%). There were no studies in which the mean follow-up period was greater than five years, with unspecified mean follow-up duration on the remaining two studies.

We found five studies including 191 patients that reported deaths as a result of SCC, with an average of 9.1% of patients dying from their disease on pooled analysis (95% confidence interval 1.4% to 22.8%, I²=79%; fig 18). The greatest proportion of deaths was observed in a study of advanced T4
tumours in which two of three patients with eligible SCCs died (66%, 9.4% to 99.1%), during a mean follow-up period of 14 months. For studies with mean duration of follow-up between two and five years, the average recurrence was 4.8% (119 patients, 1.6% to 9.8%). None of the studies had mean duration of follow-up greater than five years.

SCC specific data for cosmetic appearance and adverse events were not available from any of the included studies.

### Brachytherapy

Six studies (comprising 88 SCCs) reported recurrence after brachytherapy (table 5; fig 19), giving a pooled average local recurrence of 5.2% (95% confidence interval 1.6% to 10.5%, I²=0%). Of these studies, four were prospective reports (35 SCCs23 67 68 69) and two were retrospective (53 SCCs),65 66 with varying follow-up periods from an average of 9.6 months up to a median of 55 months. Four studies had no recurrences during follow-up.69 70 In the largest study, a retrospective review in which 48 SCCs at various sites were treated with a superficial radon mould, there were two local recurrences of hand and scalp SCCs at 10 and six months, respectively.70 The other reported SCC recurrence occurred 23 months after high dose rate brachytherapy with an 125I surface mould, and was a 4 cm tumour located on the frontal area.71 None of these studies included regional or distant metastases after treatment.

One study reported that four (8.5%) of 48 SCCs treated with a radon mould persisted after initial treatment and required treatment by other methods to ablate the lesions. The study authors attributed their high failure rate to the inclusion of tumours with a high volume, or with a thickness greater than 4 mm, which had been inappropriately treated by brachytherapy.

None of the included studies reported on deaths attributable to disease. Furthermore, SCC specific data for cosmetic appearance and adverse events were not available from any of the included studies.

### Adjuvant radiotherapy

We included nine studies which used adjuvant radiotherapy with surgery to treat previously untreated SCCs that were non-metastatic at presentation. Tables 6 and 7 show details of these studies and pooled outcome data.

Adjuvant radiotherapy was administered for perineural invasion in five retrospective studies (comprising 22 patients).42 71 73 74 75 In one of these studies,71 local recurrence occurred in two of six patients with asymptomatic perineural invasion in nerve branches of 0.4 mm diameter. All excised SCCs had clear surgical margins of at least 3 mm. One of these patients also had regional metastasis, and the other had distant metastasis after treatment. Metastasis to the skull after one year of treatment was reported in one patient with symptomatic perineural invasion, affecting the supraorbital nerve in a further series.71 In the other three studies, two included patients with asymptomatic perineural invasion in unnamed nerves42 72 and one involved named cranial nerves.71 None of these three studies reported recurrence after treatment during follow-up ranging 10.4-104.8 months.

Four studies (47 patients) reported outcomes after adjuvant radiotherapy for SCCs other than with perineural invasion. These included patients with pinna SCCs,73 trunk and extremity SCCs,74 75 and aggressive SCCs after a cardiothoracic transplant.76 The basis on which patients were selected to receive adjuvant radiotherapy as opposed to surgical monotherapy was not clearly identified in any of the studies. Three of the included
studies were retrospective,\textsuperscript{21,77,78} and the other a prospective assessment of adjuvant radiotherapy to draining lymph nodes in patients with trunk and extremity SCCs (50% of which developed in an area of erythema ab igne).\textsuperscript{79} Adjuvant radiotherapy was administered to the draining regional lymph nodes in both studies of trunk and extremity SCCs.\textsuperscript{76,77} The irradiation field was not specified in the other studies.\textsuperscript{20,70} Three of the four studies reported recurrence after treatment during follow-up ranging from less than one year to more than three years. In the prospective study, three (12%) of 26 patients developed local recurrence six to 12 months after treatment, with regional recurrence developing in one patient. No distant metastases were reported during follow-up of up to 12 months.\textsuperscript{78} Local recurrence was also reported in two of six patients who developed SCC after cardiohcaoric transplantation, one of whom also developed regional recurrence. Another patient in this series also had a systemic relapse, despite local control of their SCC.\textsuperscript{78}

One study reported two deaths (of four eligible patients) attributable to SCC at six and 11 months after treatment for perineural invasion involving named cranial nerves. Both patients had intracranial disease extending through a peripheral foramen but had refused an intracranial operation.\textsuperscript{71} No deaths attributable to SCC after adjuvant radiotherapy for perineural invasion were reported in any of the remaining three studies (16 patients).\textsuperscript{71,73,74}

Three studies (comprising 21 patients) investigated adjuvant radiotherapy of other SCCs and had data on patient deaths. One study reported the deaths of three of six patients who had SCCs after undergoing a cardiohcaoric transplantation between eight months and 54 months after diagnosis.\textsuperscript{70} No deaths were reported in the other studies.\textsuperscript{20,70} which included patients with SCCs of the trunk and extremities, and of the pinna. Table 7 presents pooled data.

In one study, initial failure of wide local excision and adjuvant radiotherapy to control disease locally was reported in one patient (of six),\textsuperscript{70} who died 15 months after treatment. Mild erythema, dry and moist desquamation, and alopecia of hair bearing areas in the irradiated field after adjuvant radiotherapy were the most commonly reported adverse events in included studies.\textsuperscript{71,72,74} Single adverse events recorded were wound infection and serious otitis media,\textsuperscript{71} self limiting mucositis, radiation dermatitis and residual mild xerostomia,\textsuperscript{71} and reactive lymphoedema of the leg.\textsuperscript{76}

**Curettage and electrodesiccation**

| Table 8 | shows details of the included studies. Only one small retrospective study of 15 patients with SCC of the pinna described local and regional recurrence separately after treatment by curettage and electrodesiccation.\textsuperscript{80} Of the 15 patients included, three had local recurrence (20%), of whom one (7%) developed regional disease and two died as a result of their disease.

Seven studies (comprising 1131 patients) which included SCCs from various sites, reported on recurrence after curettage and electrodesiccation but did not specify the nature of the recurrence.\textsuperscript{81,82,70,79,83} On pooled analysis, average recurrence was 1.7% (95% confidence interval 0.6% to 3.4%, \(I^2=59\%\); fig 20). We did not perform a sensitivity analysis as none of the studies met the criteria for this.

For the two studies\textsuperscript{80,81} with specified mean follow-up periods between two and five years, the pooled recurrence was 4.5% (109 patients, 95% confidence interval 1.4% to 9.0%). Just one study\textsuperscript{80} had a mean follow-up of more than 5 years, with recurrence in one of 29 patients (3.4%; 0% to 17.8%). The remaining studies did not specify mean duration of follow-up. Most of the treated SCCs in these series were small, with a total of 91% having a diameter less than 2 cm in the studies in which data about diameter was provided.\textsuperscript{70,82,83} Increased lesion size as a significant prognostic feature was observed in one study; recurrence in the 17 SCCs larger than 2 cm was 11.8% (95% confidence interval 1.4% to 36.4%) compared with 0.4% (0.0% to 2.1%) in the 264 SCCs smaller than 2 cm.\textsuperscript{80} One study separated results according to the number of treatment cycles used with no recurrences after either two or three cycles.\textsuperscript{80} Two studies specified the number of cycles of electrodesiccation as either double or triple,\textsuperscript{80} but this information was not reported for the remaining studies.

Cosmetic outcome was reported in just one of the included studies (41 patients),\textsuperscript{81} and rated as ‘good’ in 29% of SCCs, ‘satisfactory’ in 54% or ‘poor’ in 17%, although no definition of each of these terms was provided and it was unclear how soon after treatment the assessment of cosmesis was made. None of the included studies reported adverse event data.

**Cryotherapy**

There were eight studies (comprising 273 patients) that described recurrence after cryotherapy.\textsuperscript{81,82} Only one study reported recurrence after cryotherapy\textsuperscript{80} in one of the 34 included patients with SCCs at any site who were treated with a double freeze-thaw cycle using liquid nitrogen. Data from the 273 patients in the eight studies gave a pooled average recurrence of 0.8% (95% confidence interval 0.1% to 2.2%, \(I^2=0\%\); fig 21). Table 9\textsuperscript{81} contains details of prognostic features of the SCCs included. Sensitivity analysis was not conducted because only one study met our prespecified criteria,\textsuperscript{80} with no reported recurrences (53 patients; 0% to 6.7%).

In five studies,\textsuperscript{81,83,84,85,86} the mean duration of follow-up was between two and five years, with a pooled average recurrence of 0.4% (221 patients; 95% confidence interval 0% to 1.7%, \(I^2=0\%\); fig 21). None had a mean follow-up of greater than five years, and for three studies,\textsuperscript{81,83,86} follow-up was given as a range only. An overall cure rate of 97% was reported after either a single or double freeze-thaw cycle with liquid nitrogen in a retrospective series of 563 SCCs at any site that were treated over a 23 year period.\textsuperscript{81} Because the authors did not define “cure,” this rate could include lesions that failed to respond to the initial treatment in addition to those which recurred. The duration of follow-up was not specified.

Failure to respond to initial treatment was reported in one (3%) of 34 patients in one prospective series.\textsuperscript{80} A double freeze-thaw cycle was used to treat the original SCC, a 5 mm lesion on the scalp, which showed little clinical response despite a second course of cryotherapy two months after the initial treatment.

None of the studies that reported cosmetic appearance and adverse events separated results for SCCs and basal cell carcinomas, but presented results for non-melanoma skin cancers as a whole.

**Photodynamic therapy**

There were 14 small prospective studies (comprising 297 patients) that evaluated the response of SCCs to photodynamic therapy (table 10).\textsuperscript{82,102} Three studies separated SCCs according to level or depth of invasion,\textsuperscript{92,95,96} and one was a non-randomised two-arm comparison of topical photodynamic therapy either with or without a 5% glycolic acid penetration enhancer.\textsuperscript{90} On pooled analysis, an average of 72.0% of treated
lesions appeared to respond completely to treatment (95% confidence interval 61.5% to 81.4%, 12:71%; fig 22). Five studies specified that histological assessment of at least some of the treated areas was done to confirm apparent clinical response.33 97 102 104 105

In eight of the included studies, SCCs that had apparently completely responded to photodynamic therapy initially were observed for recurrence.96 98 106 Pooled recurrence data from these studies (119 SCCs) gave an odds of recurrence of 26.4% (95% confidence interval 12.3% to 43.7%, 12:72%; fig 23). Table 11 summarises the results. Mean duration of follow-up ranged from six months (at which time the trial was abandoned due to recurrence in more than 50% of lesions)97 to 38 months.94

One study evaluated cosmetic appearance on a scale of 1 to 4 (excellent to poor) at three months and 24 months after treatment,98 with high agreement between patient and investigator scores for both time points. At three months, 4% of 46 treated microinvasive (Clark level II) and invasive (Clark level III/IV) SCCs were assessed as having "excellent" cosmetic appearance, 48% as assessed as "good," 44% assessed as "fair," and 4% assessed as "poor." By 24 months, of 31 assessable treated lesions, 10% were rated as having poor cosmetic appearance, 48% as fair, 36% as good, and 6% as excellent.

Tumour thickness, depth of dermal penetration, and the degree of cell atypia were found by the authors to be univariate predictors of outcome (Kruskal-Wallis test P<0.01). One smaller study also evaluated cosmetic appearance on a scale of 1 (very good) to 4 (poor). Five treated lesions (56% of nine patients) were assessed as having a very good appearance, three (33%) assessed as good, and one (11%) assessed as fair.100 None was deemed to have poor appearance in this study. Two further studies described cosmetic results as "very satisfactory"107 or "very good" with no scar formation and only transient residual hypopigmentation or hyperpigmentation.94

Separate SCC data for adverse events were not available from the included studies.

Data for laser therapy, imiquimod, 5-fluorouracil, interferon, retinoids, and chemotherapy are presented in web appendix 4.

Discussion

This is the first systematic review to our knowledge that assesses the effectiveness of all treatment modalities for primary non-metastatic SCC, giving an overview of current evidence from non-randomised studies.

Caution needs to be exercised when comparing outcomes after different treatment modalities, owing to the limitations of the included studies. Surgery with a predefined excision margin is the treatment of choice for most cutaneous SCCs, with Mohs micrographic surgery being recommended for SCCs considered to be higher risk or in cosmetically sensitive areas. Our pooled analysis suggests lower rates of local recurrence and deaths attributable to disease after Mohs micrographic surgery, despite the fact that tumours treated by this method are likely to be at higher risk—although there have been no randomised controlled trials to directly compare the two treatments. However, in our pooled analysis, regional recurrence was of a similar magnitude for both treatment modalities, which suggested subclinical spread of some higher risk tumours treated with Mohs micrographic surgery to regional lymph nodes at the time of treatment. Overlapping confidence intervals for average effect estimates for the different treatments suggested that apparent differences between treatments might not be significant. This finding accords with those of Chren and colleagues.96 In their large prospective cohort study of all primary non-melanoma skin cancers, they reported no significant difference in hazard of recurrence between surgically excised tumours and those treated with Mohs micrographic surgery.

In our pooled analysis of external radiotherapy, average local recurrence was slightly higher than that seen after conventional surgical excision, although the differences were probably not significant owing to overlapping confidence intervals. Average regional recurrence was lower than local recurrence, although these data were generated from just two studies.94 104 Other studies did not specify whether reported recurrences were local or regional failures, thus the true significance of this is unclear. The lower rates of local recurrence from the studies using brachytherapy could indicate the more superficial, lower risk nature of the included SCCs treated by this method. However, patient numbers were generally small and follow-up was limited (only a few months in some studies) and could be inadequate to detect later recurrences. The greater rates of recurrence, metastasis, and death from disease observed with adjuvant radiotherapy after surgical excision accords with other studies.107 However, numbers of patients in included studies were small and for SCCs that did not have perineural invasion, the reasons justifying the use of adjuvant radiotherapy was not always clear. The results could therefore reflect the selection of those SCCs with a particular poor prognosis, and the identification of prognostic factors that could benefit from adjuvant radiotherapy remains an area of uncertainty and one in which prospective studies are needed.

Lowest recurrence rates were observed after cryotherapy and after electrodesiccation and curettage, but most SCCs included in these analyses were small and considered to be low risk lesions. However, the evidence is poor to advocate their use in lesions considered at higher risk of recurrence and recurrent SCCs.

Based on our results, the use of photodynamic therapy to treat invasive SCCs cannot be advocated. Few studies confirmed histological clearance in apparently completely responsive SCCs, and in those that attempted to do so, residual tumour remained in several biopsies. Furthermore, more than a quarter of those tumours that had seemed to completely respond to photodynamic therapy initially recurred during follow-up. Not all patients with SCC are amenable to surgical treatment or radiotherapy, and some are susceptible to multiple SCCs as a result of a genetic or immune predisposition. Such groups pose particular therapeutic challenges, and there is a growing need for effective topical or systemic agents that could be used in such groups. The current evidence for these agents to treat primary SCCs is largely anecdotal, based on single case reports or very small numbers of eligible patients in open label trials with limited follow-up and generally lacking recurrence data, but is an interesting area for further development as new insights into the pathogenesis and targeted therapies emerge.

Although we included quality of life as one of our outcomes, none of the included studies in this review measured this. Patient reported outcome measures (PROMs) have great potential to improve the quality of health services by providing validated evidence of health from the patient’s perspective. Two recent systematic reviews94 107 of these measures in skin cancer showed that there have been limited evaluations of patient reported outcome measures that were specifically designed for patients with non-melanoma skin cancers. Furthermore, the questionnaires developed so far have not been perfect for assessing the quality of life in these particular patients. Nevertheless, the incorporation of patient reported outcomes will undoubtedly be important in the development of future...
clinical trials comparing treatments for SCC. These outcomes should also be able to capture quality of life issues that are important to patients with SCCs, including detailed assessment of cosmetic and functional outcomes at specific time points.

**Strengths and limitations of this systematic review**

Although we tried to be as thorough as possible in our literature search, it is inevitable that we failed to find relevant studies. Observational studies, and especially case series, are more difficult to identify from searching literature databases than randomised controlled trials. Observational studies are usually not identifiable from the title and are less consistently indexed according to study design in bibliographic databases; there is undoubtedly also an element of publication bias with these types of studies.

We did not review treatments of recurrent SCCs and tumours known to be metastatic at presentation. Many studies were excluded because they included previously treated relapsed tumours without separation of data from non-recurrent tumours. Such recurrent tumours could have different features to those that have not been treated previously—which makes them more likely to recur or be resistant to treatment.

Similarly, we did not specifically search for studies relating solely to the management of SCC in solid organ transplant recipients, although some of the studies did include such patients. Cutaneous SCC is an important cause of morbidity in this group of patients, and is associated with the likelihood of multiple tumours and a potentially more aggressive clinical course.108 This topic is therefore perhaps suitable for separate consideration and beyond the scope of this more general review.

We found that mean follow-up periods were generally poorly reported and few studies reported mean follow-up of more than five years; therefore, assessment of recurrence according to duration of follow-up was limited in our review. When possible, we did subgroup analyses to compare outcomes in those studies with mean follow-up periods of less than two years, between two and five years, and greater than five years. Our main finding on subgroup analysis was that the proportion of deaths attributable to SCC was significantly greater for studies with a mean follow-up longer than five years after conventional surgical excision compared with studies with a shorter follow-up. Between 70% and 90% of recurrences and metastases occur within the first two years after treatment,49 111 112 and 95% within five years.112 113 Therefore, the results from our analysis probably represent the true recurrence up to five years of follow-up.

**Bias and quality of reporting**

Validated tools for assessing the risk of bias in non-randomised studies are limited, making the evaluation of study quality less objective than for randomised controlled trials. Owing to the lack of evidence in the literature specifically reviewing the assessment of case series, we have based our evaluation on a modified assessment tool on risk of bias from the Cochrane Collaboration,114 together with suggestions drawn up by Albrect14 for improving the quality of case series. Albrect’s suggestions are based on a few published articles115-117 and Albrect’s own experience of systematic reviews of case series and reports.118

Most of the included studies were of limited methodological quality and prone to bias (fig 2), with variable patient mixes in terms of prognostic factors, overall disease severity, and duration of follow-up. Recruitment bias with selection of particular treatment modalities based on tumour or patient characteristics is a serious consideration for case series and was positively identified or was an unclear risk in 85% of the studies in this review. Therefore, we could not directly compare the effectiveness of different treatments. In 41% of studies, losses to follow-up were either incompletely reported or not mentioned, making it difficult to assess the risk of attrition bias.

**Stratification of risk**

A limited number of studies stratified outcomes according to particular prognostic indicators, although it was not possible to stratify results from data provided by most studies. SCC location in the ear was a poor prognostic feature, supported by our pooled analysis of data from studies that considered ear and other locations. We did not do a pooled analysis of other features considered high risk, owing to different reporting methods in the studies. Increased risk of recurrence with tumours greater than 2 cm was noted in some studies.24 25 49 However, this finding was not supported by Mourouzis and colleagues26 with 60% of metastases originating in SCCs smaller than 2 cm, nor by Dzubow and colleagues,46 who found a trend towards significance with tumours larger than 5 cm in diameter. Several studies showed the importance of SCC depth as a risk factor for recurrence. Mourouzis and colleagues did not observe any metastases in SCCs less than 2 mm in depth,26 in accordance with Brantsch and coauthors,45 who reported a significantly increased risk of metastases for SCCs greater than 2 mm thick. Griffiths and colleagues77 also reported a significant difference in thickness between SCCs in patients who died of their disease and those who did not. Poor differentiation was noted to be an adverse prognostic feature in two of the included studies.26 49 with the presence of perineural invasion being significantly associated with a worse outcome in one of the series.29 There are currently no accurate prognostic models to stratify patients with SCC and to help guide clinical decisions, leading to a lack of uniformity in the management of the tumour. In 2010, the American Joint Committee on Cancer updated the staging system for SCC, incorporating high risk features into the tumour (T) classification.119 Although the update was an improvement on the previous classification, it was not without criticism.120-122 Alternative staging systems have been proposed in an attempt to stratify the large group of heterogeneous T2 tumours according to their prognostic features.13 123 Although further validation work is required, these systems could be useful tools when designing future clinical trials.
Summary: surgical excision of SCCs

12 studies, mostly retrospective case series, of limited quality and with varying follow-up periods
Local recurrence varied owing to different time points assessed
Local recurrence average 5.4% (95% confidence interval 2.5% to 9.1%; 12 studies, n=1144)
Regional recurrence average estimate 4.4% (2.4% to 6.9%; eight studies, n=786)
Ear location significantly associated with local and regional recurrence
Unspecified recurrence average 5.4% (0.7% to 27.6%; two studies, n=113)
Death from disease average 4.1% (1.7% to 7.6%; eight studies, n=485)
Increased proportion of deaths attributable to disease in studies with follow-up longer than five years compared with follow-up between two and five years (8.6% (4.7% to 13.6%; two studies, n=149) vs 0.8% (0.1% to 2.5%; three studies, n=223))
Incomplete excision average 8.8% (5.4% to 13.0%; 11 studies, n=2343)

Summary: Mohs micrographic surgery of SCCs

16 case series, prospective and retrospective
Local recurrence average 3.0% (95% confidence interval 2.2% to 3.9%; 10 studies, n=1572)
Regional recurrence average 4.2% (2.3% to 6.6%; six studies, n=1162)
Unspecified recurrence average 4.7% (0.7% to 11.7%; five studies, n=766)
Death from disease average 1.1% (0.2% to 2.6%; four studies, n=941)

Summary: external radiotherapy of SCCs

One prospective series and 13 retrospective series
Variation between studies for radiation source and length of follow-up
Local recurrence average 6.4% (95% confidence interval 3.0% to 11.0%; seven studies, n=761)
Regional recurrence average 2.6% (0.04% to 8.9%; three studies, n=272)
Unspecified recurrence average 4.8% (0.6% to 12.8%; six studies, n=220)
Death from disease average 9.1% (1.4% to 22.8%; five studies, n=191)

Summary: brachytherapy of SCCs

Four prospective studies and two retrospective studies
Variable methods of application and radiation and generally short follow-up periods
Generally small numbers of patients
Local recurrence average 5.2% (95% confidence interval 1.6% to 10.5%; six studies, n=68)
No regional or distant metastases or deaths attributable to disease reported

Summary: adjuvant radiotherapy of SCCs

Adjuvant radiotherapy for SCCs with perineural invasion (five small retrospective studies)
Local recurrence average 18.2% (95% confidence interval 3.8% to 39.8%; five studies, n=22)
Regional recurrence average 8.3% (1.1% to 21.4%; five studies, n=22)
Distant metastasis average 11.5% (2.4% to 26.1%; five studies, n=22)
Death from disease average 11.1% (0.4% to 33.1%; four studies, n=20)

Adjuvant radiotherapy for other SCCs (one prospective and three retrospective small studies)
Local recurrence average 11.1% (2.4% to 25.0%; four studies, n=47)
Regional recurrence average 8.5% (2.5% to 17.6%; four studies, n=47)
Distant metastasis average 3.2% (0.1% to 10.4%; four studies, n=47)
Death from disease average 13.9% (0.05% to 50.2%; three studies, n=21)

The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166:1069-80.
Summary: curettage and electrodesiccation of SCCs
Eight retrospective series of variable follow-up periods
Treated SCCs mostly less than 2 cm in diameter
Unspecified recurrence average 1.7% (95% confidence interval 0.5% to 3.4%; seven studies, n=1131)
20% recurrence after electrodesiccation and curettage of pinna SCC (one study, n=20)
Lesions more than 2 cm in size had significantly greater average recurrence than those smaller than 2 cm (11.8% (1.4% to 36.4%, 17 SCCs) vs 4.0% (0% to 2.1%, 284 SCCs; one study))

Summary: cryotherapy of SCCs
Six prospective series and three retrospective series with variable follow-up periods
Mostly low risk lesions less than 2 cm in diameter
Recurrence average 0.8% (95% confidence interval 0.1% to 2.2%; eight studies, n=273)

Summary: photodynamic therapy of SCCs
Fourteen small prospective case series
Histological confirmation of apparent initial clinical response sought in five of 14 studies
Follow-up for recurrence in eight of 14 studies
Apparent initial complete response average 72.0% (95% confidence interval 61.5% to 81.4%; 14 studies, n=297)
Recurrence after apparent initial complete response average 26.4% (12.3% to 43.7%; eight studies, n=119)

What is already known on this topic
Squamous cell carcinoma (SCC) of the skin is the second most common type of skin cancer, with the potential to recur, metastasise, and lead to death
Surgical excision (by conventional or Mohs micrographic surgery) is currently the preferred treatment for SCC, but no randomised controlled trials have directly compared different treatment modalities for the cancer

What this study adds
This systematic review compares all treatment types for non-metastatic cutaneous SCC to include evidence from observational studies
Accurate comparisons of estimates of treatment effects were not possible from the current evidence, and the significance of apparent differences between treatments should be interpreted cautiously
The current evidence base for SCC treatments is extremely limited, and there is a need for well designed comparative studies to help stratify patients and optimise their clinical management

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The current evidence base for SCC treatments is extremely limited, and there is a need for well designed comparative studies to help stratify patients and optimise their clinical management.
### Table 1 | Recurrence and death after surgical excision

| Study and No of patients | Site          | Follow-up          | Local recurrence | Regional recurrence | Distant metastases | Unspecified recurrence | Patient died of disease | Prognostic features* |
|--------------------------|---------------|--------------------|------------------|--------------------|--------------------|------------------------|------------------------|----------------------|
| Ang 2004 (n=50)          | Various       | Mean 71.1          | —                | —                  | 0.00 (0.00 to 0.07)| —                      | No data                | Mean diameter 19.7 mm (range 4-60) |
| Baker 2001 (n=227)       | Head and neck | 2 years minimum    | 0.04 (0.02 to 0.07) | 0.03 (0.01 to 0.06) | —                  | 0.00 (0.00 to 0.03) | No data                | Perineural invasion (8%), orbital invasion (6%) |
| Donaldson 2002 (n=35)    | Eyelids       | 31.1 months        | 0.00 (0.00 to 0.10) | 0.00 (0.00 to 0.1) | —                  | 0.00 (0.00 to 0.1) | Diameter <2 cm (62%), >2 cm (38%); median duration 52 weeks |
| Fitzpatrick 1985 (n=21)  | Eyelids       | Not specified      | 0.05 (0.00 to 0.24) | —                  | 0.14 (0.07 to 0.25) | 0.08 (0.03 to 0.18) | Depth ≤4 mm (62%), 4-8 mm (26%), >8 mm (12%); differentiation grades 1 (30%), II (60%), III (10%) |
| Friedman 1984 (n=63)     | Trunk and extremities | Non-recurrent group: mean 7.5 years; recurrent group: minimum 5 years | — | — | 0.05 (0.00 to 0.03) | — | Diameter <2 cm (60%), >2 cm (20%) |
| Griffiths 2002 (n=86)    | All           | Minimum 5 years    | 0.00 (0.00 to 0.04) | —                  | —                  | 0.08 (0.03 to 0.16) | Depth ≤4 mm (62%), 4-8 mm (26%), >8 mm (12%); differentiation grades 1 (30%), II (60%), III (10%) |
| Knox 1967 (n=211)        | Various       | >1 year            | —                | —                  | 0.00 (0.00 to 0.03) | —                      | No data                | Diameter <2 cm (60%), >2 cm (20%) |
| Mourozis 2009 (n=194)    | Head and neck | 30-60 months       | —                | 0.05 (0.02 to 0.09) | —                  | —                      | No data                | Diameter <2 cm (60%), >2 cm (20%) |
| Nemet 2006 (n=58)        | Periocular    | Mean 33 months     | 0.06 (0.02 to 0.14) | —                  | —                  | —                      | Differentiation: well (86.8%), moderate (13.2%) |
| Pless 1976 (n=176)       | External ear  | Not specified      | 0.15 (0.10 to 0.22) | 0.06 (0.03 to 0.11) | —                  | —                      | Diameter <1 mm to >40 mm |
| Rank 1973 (n=288)        | All           | 2 years            | 0.01 (0.00 to 0.04) | —                  | —                  | —                      | Not specified |
| Reiffer 1986 (n=12)      | Eyelid        | Mean 3 years       | 0.08 (0.00 to 0.38) | 0.00 (0.00 to 0.26) | —                  | 0.00 (0.26 to 2.64) | Surface area <1 cm (58%), >1 cm (42%) |
| Shiffman 1975 (n=31)     | Pinna         | <1 year to >3 years| 0.06 (0.01 to 0.21) | 0.10 (0.02 to 0.26) | —                  | 0.03 (0.00 to 0.17) | Diameter <2 cm (59.6%), 2-4 cm (33.8%), >4 cm (3.2%); histology grade: well/moderately differentiated (78.2%), poorly differentiated (21.8%); perineural invasion (2.3%); perivascular invasion (0.5%) |
| Shiu 1980 (n=38)         | Trunk and extremities | Not specified     | 0.10 (0.03 to 0.25) | —                  | —                  | 0.06 (0.01 to 0.18) | 10.5% of stage I SCCs were high grade; included tumours secondary to radiation exposure, chronic dermatitis in ulcers, and osteomyelitis |
| Thomas 1994 (n=54)       | Pinna         | <1 year to >3 years| 0.13 (0.05 to 0.25) | 0.09 (0.03 to 0.20) | —                  | 0.04 (0.00 to 0.15) | Stages I (52%), II (37%), III (0%); IV (11%); differentiation: well (68.5%), moderate (9.3%), poor (7.4%) |
| Van der Eerden 2010 (n=108) | Head and neck | Mean 16 months     | 0.02 (0.00 to 0.06) | 0.01 (0.00 to 0.05) | —                  | —                      | No data                |
| Werlinger 2002 (n=20)    | Various       | Mean 4.1 years     | —                | —                  | 0.00 (0.00 to 0.17) | —                      | Diameter 7.9 mm (SD 3.7), <5 mm (14.1%), 5-10 mm (69.4%), >10 mm (16.4%); 5.2% of all tumours displayed aggressive growth pattern |

*Prognostic features: Mean diameter 19.7 mm (range 4-60); Perineural invasion (8%), orbital invasion (6%); Diameter <2 cm (62%), >2 cm (38%); median duration 52 weeks; Depth ≤4 mm (62%), 4-8 mm (26%), >8 mm (12%); differentiation grades 1 (30%), II (60%), III (10%); Diameter <2 cm (60%), >2 cm (20%); Diameter <1 mm to >40 mm; Surface area <1 cm (58%), >1 cm (42%); Diameter <2 cm (59.6%), 2-4 cm (33.8%), >4 cm (3.2%); histology grade: well/moderately differentiated (78.2%), poorly differentiated (21.8%); perineural invasion (2.3%); perivascular invasion (0.5%); 10.5% of stage I SCCs were high grade; included tumours secondary to radiation exposure, chronic dermatitis in ulcers, and osteomyelitis; Stages I (52%), II (37%), III (0%); IV (11%); differentiation: well (68.5%), moderate (9.3%), poor (7.4%); Diameter 7.9 mm (SD 3.7), <5 mm (14.1%), 5-10 mm (69.4%), >10 mm (16.4%); 5.2% of all tumours displayed aggressive growth pattern.
Table 1 (continued)

| Study and No of patients | Site          | Follow-up | Proportion with outcome (95% CI) | Prognostic features* |
|--------------------------|---------------|-----------|----------------------------------|----------------------|
|                          |               |           | Local recurrence | Regional recurrence | Distant metastases | Unspecified recurrence | Patient died of disease | Stages 0 (5%), I (37.5%), II (32.5%), III (5%), IV (10%); unknown (10%) |
| Yoon 1992 (n=13)         | External ear  | 6 months to 20 years | —          | —                   | —                   | 0.62 (0.32 to 0.86)  | —                   | —                   |

SD=standard deviation.

*Percentages indicate proportion of patients in study.
| Study and No of excisions | Site                  | Proportion (95% CI) incompletely excised | Prognostic features* | Excision margin                  |
|--------------------------|-----------------------|------------------------------------------|----------------------|----------------------------------|
| Ang 2004 (n=63)          | All                   | 0.16 (0.08 to 0.27)                      | Mean diameter 19.7 mm | Retrospective; 4-6 mm margin     |
| Baker 2001 (n=227)       | Head and neck         | 0.07 (0.04 to 0.11)                      | No data              | Retrospective; margin not specified |
| Bogdanov-Berezovsky 2005 (n=369) | All                   | 0.07 (0.04 to 0.10)                      | Completely excised: diameter 1.1 cm, depth 0.6 cm; differentiation: well (84.6%), moderate (13.6%), poor (5.6%); Incompletely excised: diameter 0.9 cm, depth 0.4 cm; differentiation: well (72.2%), moderate (22.2%), poor (5.6%). | Retrospective; 3-6 mm margin |
| Bovill 2009 (n=676)       | All                   | 0.18 (0.15 to 0.21)                      | Re-excision cohort: mean diameter 17.2 mm, mean thickness 6.02 mm; differentiation: well (43%), moderate (42%), poor (15%), perineural invasion (3.6%) | Retrospective; margin not specified |
| Griffiths 2002 (n=93)    | All                   | 0.04 (0.01 to 0.11)                      | Median thickness 3.1 mm; mean diameter 13 mm (surviving patients) v 20 mm (patients who died of disease); immunocompromised (3.2%) | Retrospective; mean margin 7.2 mm (surviving patients) v 6.3 mm (patients who died of disease) |
| Mourouzis 2009 (n=218)   | Head and neck         | 0.12 (0.08 to 0.17)                      | Diameter <2 cm (63%), >2 cm (33.8%), >4 cm (3.2%); differentiation: well (78.2%), poor (21.8%); perineural invasion (2.9%), perivascular invasion (0.5%) | Retrospective; 5 mm margin |
| Nemet 2006 (n=68)        | Periocular            | 0.25 (0.15 to 0.37)                      | Differentiation: well (86.8%), moderate (13.2%) | Retrospective; 5 mm margin |
| Pua 2009 (n=69)          | All                   | 0.00 (0.00 to 0.05)                      | Diameter <1 cm to 2 cm | Retrospective; 4 mm ("wider" for larger tumours) |
| Tan 2007 (n=480)         | All                   | 0.06 (0.04 to 0.09)                      | Diameter <1 cm (52.3%), >2 cm (40.8%), >4 cm (33%) | Prospective; margin 2 mm to >10 mm |
| Thomas 1994 (n=54)       | Pinna                 | 0.11 (0.04 to 0.23)                      | Stages I (52%), II (37%), III (0%), IV (11%); differentiation: well (68.5%), moderate (9.3%), poor (7.4%) | Retrospective; wedge excision to complex surgical procedure |
| Thomas 2003 (n=26)       | All                   | 0.00 (0.00 to 0.13)                      | Average diameter 16.9 mm, diameter >10 mm (26%); differentiation: well (57.8%), moderate (38.5%), poor (3.8%) | Prospective; margin based on diagnosis and surgeon’s preference |

*Percentages indicate proportion of excisions in study.
### Table 3 | Recurrence and death from disease after Mohs micrographic surgery

| Study and No of patients | Site           | Follow-up              | Local recurrence | Regional recurrence | Distant metastases | Unspecified recurrence | Patient died of disease | Prognostic features*                                                                 |
|-------------------------|---------------|------------------------|------------------|---------------------|-------------------|-----------------------|------------------------|-------------------------------------------------------------------------------------|
| Anderson 1982 (n=8)     | Eyelid       | Average 36 months      | 0.00 (0.00 to 0.37) | 0.12 (0.00 to 0.53) | —                 | —                     | 0.12 (0.00 to 0.53)     | No details                                                            |
| Brantsch 2008 (n=615)   | All          | Mean 43 months         | 0.03 (0.02 to 0.04) | 0.04 (0.03 to 0.06) | —                 | —                     | 0.01 (0.01 to 0.03)     | Median diameter 15 mm, mean thickness 3 mm; differentiation: good (53%), moderate (22%), poor (25%); desmoplasia (8%); immunosuppression (5%) |
| Cherpelis 2002 (n=186)  | Various      | 6 months to 10 years   | —                 | 0.08 (0.04 to 0.12) | —                 | —                     | —                      | Diameter >20 mm (20%); Clark level V (28%); poorly differentiated (9.5%); perineural invasion (4%) |
| Dzubow 1982 (n=171)     | All          | Mean 18.6 months       | 0.04 (0.01 to 0.07) | —                   | —                 | —                     | —                      | Diameter 1-9 mm (18.7%), 10-49 mm (68.7%), >50 mm (12.6%)                  |
| Leibovitch 2005 (n=229) | All          | 5 years                | 0.03 (0.01 to 0.06) | —                   | 0.00 (0.00 to 0.02) | —                     | —                      | Diameter 0-9 mm (57%), 1-9 mm (38%), 2-9 mm (5%) perineural invasion (4.3%)  |
| Malhotra 2004 (n=56)    | Periocular    | Mean 77.3 months       | —                 | —                   | —                 | —                     | 0.01 (0.00 to 0.02)     | — data                                                               |
| Mohs 1976 (n=615)       | Various       | Up to 5 years          | —                 | —                   | —                 | —                     | 0.01 (0.00 to 0.02)     | — data                                                               |
| Pugliano-Mauro 2010 (n=231) | “High risk” | Mean 3.9 years       | 0.01 (0.00 to 0.04) | 0.02 (0.00 to 0.04) | —                 | —                     | 0.00 (0.00 to 0.02)     | "High risk": diameter average 1.5 cm (standard deviation 0.7); immunosuppression (20%) |
| Silapunt 2005 (n=87)    | Auricle      | 2 years                | 0.06 (0.02 to 0.13) | —                   | 0.00 (0.00 to 0.04) | —                     | 0.00 (0.00 to 0.04)     | Average surface area 3.04 cm²                                        |
| Skaria 2010 (n=54)      | Not specified | Mean 59.6 months       | —                 | —                   | —                 | 0.02 (0.00 to 0.10)   | —                      | — data                                                               |
| Thomas 2007 (n=66)      | Various       | Mean 45 months         | —                 | —                   | —                 | 0.04 (0.01 to 0.13)   | —                      | Mean size 3.9 cm²                                                       |
| Tomsick 1984 (n=15)     | Fingers       | 5 months to 7 years    | —                 | —                   | —                 | 0.00 (0.00 to 0.22)   | —                      | 3 patients with SCC in area of chronic radiodermatitis                |
| Turner 2000 (n=48)      | All           | Mean 3.4 years         | 0.02 (0.00 to 0.11) | 0.04 (0.01 to 0.14) | 0.02 (0.00 to 0.11) | —                     | —                      | Median diameter 15 mm (range 3-40); median depth 2 mm (range 0.4-25); differentiation: grades 1 (57.2%), 2 (44.2%), 3 (14%), 4 (4.6%); vascular invasion (16%) |
| Van der Eerden 2010 (n=74) | Head and neck  | Mean 24 months         | 0.03 (0.00 to 0.09) | 0.01 (0.00 to 0.07) | —                 | —                     | —                      | — data                                                               |
| Vuyk 2001 (n=53)        | Head and neck | Mean 33 months         | 0.02 (0.00 to 0.10) | —                   | —                 | —                     | —                      | Poorly to well differentiated                                        |
| Yoon 1992 (n=16)        | External ear  | 6 months to 20 years   | —                 | —                   | —                 | 0.31 (0.11 to 0.59)   | —                      | Stages 0-IV (only data for stage I-II included)                          |

*Percentages indicate proportion of patients in study.*
Table 4. Recurrence and deaths after external radiotherapy

| Study and No of patients | Site* | Radiotherapy dose | Follow-up | Prognostic features* |
|--------------------------|-------|-------------------|-----------|---------------------|
| Abbatucci 1989 (n=179)  | Face  | Superficial, 0.5-1 cm peripheral margin, 1 mm deep margin. Most doses 30.6 Gy, 3 fractions, 14 days | Minimum 2 years | — — — Diameter <1.6 cm to ≥4 cm |
| Barysch 2012 (n=177)    | All (head and neck 87%) | Superficial, beryllium windowed, soft x rays | Mean 4.9 years (SD 4.7, 95% CI 4.2 to 5.6) | 0.14 (0.10 to 0.20) 0.01 (0.00 to 0.03) — — Mean area 3.5 cm²; differentiation: good (66.7%), moderate (22.4%), poor (10.9%) |
| Grosch 1979 (n=5)       | Head and hand | 6-10 meV electron beam, total dose 4000-6000 rads, 10-20 fractions, 14-28 days | Mean 15 months (range 6-33) | — — 0.00 (0.00 to 0.52) — No data |
| Holmes 1982 (n=67)      | Various | Short distance cobalt unit, 5000-5500 cGy, 10-15 fractions, 2-3 weeks | 2-8 years | — — 0.00 (0.00 to 0.05) 0.00 (0.00 to 0.05) No data |
| Honeycutt 1973 (n=18)   | Various | X rays, total dose 4500 rads, 9 or 15 fractions | 4 years (range 4-8) | — — 0.00 (0.00 to 0.18) — Diameter <2 cm (39%), >2 cm (61%) |
| Hunter 1982 (n=26)      | Pinna  | 10 meV electron beam, total dose 4500-5500 cGy, B-15 daily fractions | Average 44 months (range 12-136) | — — 0.11 (0.02 to 0.30) 0.08 (0.01 to 0.23) Mean duration 26 months (range 1-136) |
| Knox 1987 (n=101)       | All    | Total dose 4000-5000 rads, 500 or 1000 rads every other day, ≤10 fractions | >1 year | — — 0.02 (0.00 to 0.07) — Diameter <2 cm (79%), >2 cm (21%) |
| Kwan 2004 (n=37)        | Various | Orthovolt x rays, electrons, megavoltage photons, or combination of electrons and photons; Total dose <4000 cGy to >6000 cGy, 5-25 fractions | Median 42 months (range 1.4-97.1) | 0.30 (0.16 to 0.47) (locoregional recurrence) — — — Tumour stages T2 (19%), T3 (65%), T4 (16%) |
| Matthiesen 2011 (n=3)   | Cheek and forehead | 3D conformal radiotherapy with 6 mV photons or intensity modulated radiotherapy with 6 mV photons; Total dose 7425-7960 cGy, 33-35 fractions | Mean 14.3 months (range 4-36) | — — 0.67 (0.09 to 0.99) 0.67 (0.09 to 0.99) All tumour stage 4; volumes 126 cm³, 175 cm³, 341 cm³; bone involvement in 1 tumour |
| Podd 1992 (n=17)        | Lower leg | Photon based; dose not specified | Not specified | 0.06 (0.00 to 0.29) — — — No data |
| Rank 1973 (n=231)       | Not specified | No details | No details | 2 years | 0.03 (0.01 to 0.06) — — — No data |
| Shiftman 1975 (n=2)     | Pinna  | No details | <1 year to >3 years | 0.5 (0.01 to 0.99) 0.5 (0.01 to 0.99) — 0.5 (0.01 to 0.99) 1 SCC 2-4 cm (no data for second SCC) |
| Sist 1964 (n=62)        | Nose   | Roentgen therapy 4000-8000 rads in 300-500 rads fractions over ≥26 days | ≥6 months to 144 months | 0.03 (0.00 to 0.11) — — — Diameter <0.5 cm (33.9%), 0.5-1 cm (56.4%), 1.5-2.5 cm (4.8%), >2.5 cm (4.8%) |
| Tsao 2002 (n=93)        | Nose   | Orthovoltage (81%); electrons (14%); megavoltage x rays (4%); high energy photons (1%) | Median 2.9 years (0.2–10.4) | 0.06 (0.02 to 0.14) 0.02 (0.00 to 0.08) — 0.03 (0.01 to 0.09) Turnour stages T1 (64%), T2 (11.7%), T3 (0%), T4 (7.4%); stage not evaluable (17%); 5 immunosuppressed patients |

SD=standard deviation; 3D=three dimensional.

*Percentages indicate proportion of patients in study.
| Study and No of SCCs | Site | Brachytherapy modality and dose | Follow-up | Proportion with local recurrence (95% CI) | Prognostic features* | Study design |
|---------------------|------|--------------------------------|-----------|------------------------------------------|----------------------|-------------|
| Allan 1998 (n=3)    | Pinna| High dose rate microselectron 192Ir plane or mould; 42.5-45 Gy, 8 fractions | Minimum 18 months | 0.00 (0.00 to 0.71) | Confined to skin of pinna | Prospective |
| Ashby 1989 (n=48)   | Any (33% head and neck) | Radon mould, 35-40 Gy; overall treatment time 6 days 20 h | 45.3 months (1-146) | 0.04 (0.01 to 0.14) | Median tumour volume 1099 mm³ (16-6300 mm³); differentiation: well (84%), moderate (16%) | Retrospective |
| Guix 2000 (n=18)    | Facial | High dose rate custom made 192Ir surface mould, 60-65 Gy, 33-36 fractions (<4 cm diameter) or boosted to 75-80 Gy after 3 week pause (>4 cm diameter) | Minimum 12 months | 0.06 (0.00 to 0.27) | Diameter (all SCCs) <2 cm (23.5%), 2-5 cm (73.5%), 5-8 cm (3%); perineural invasion (5.6%); lymphatic invasion (14.7%) | Prospective |
| Lee 1997 (n=3)      | Scalp, neck, face | ¹⁹²Ir impregnated patch for total 30 min to 1 h, 50 Gy | 8-20 months | 0.00 (0.00 to 0.71) | Selected superficial tumours only | Prospective |
| Rio 2005 (n=5)      | Facial | Interstitial brachytherapy with 192Ir wires, average dose 50-65 Gy, mean implantation time 79 h | Median 55 months (range 6-132) | 0.00 (0.00 to 0.52) | Lip carcinomas excluded | Retrospective |
| Svodoba 1995        | Any   | High dose rate 192Ir afterloaded moulds, 12-50 Gy, 1-15 fractions | Average 9.6 months (range 5-22) | 0.00 (0.00 to 0.28) | Area <0.5 to >6.1 cm² | Prospective |

*Percentages indicate proportion of SCCs in study.
| Study and No of SCCs | Reasons for adjuvant radiotherapy | Surgical treatment | Site of adjuvant radiotherapy | Dose of adjuvant radiotherapy | Follow-up |
|---------------------|----------------------------------|--------------------|------------------------------|-----------------------------|-----------|
| Barrett 1993 (n=3)  | Head and neck perineural invasion (asymptomatic) | Surgical excision or Mohs micrographic surgery | Not specified | Mean 51.7 Gy, 18-22 fractions | Mean 28.3 months (range 18-37) |
| Cottel 1982 (n=2)  | Head and neck perineural invasion, both symptomatic (infraorbital and supraorbital nerves); patients with the “most difficult cases” selected for adjuvant radiotherapy | Mohs micrographic surgery | Primary site and course of involved cranial nerve | 4600-5000 rads (200 rads/day over 4.5-6 weeks) | Mean 30 months (range 24-36) for adjuvant radiotherapy |
| DeAmbrosis 2010 (n=6) | Head and neck perineural invasion, nerve diameter 0.15-0.4 mm (all asymptomatic) but indications for radiotherapy inconsistent | Excision | Not specified | Not specified | Mean 104.8 months (range 44-218) |
| Geist 2008 (n=7)  | Head and neck perineural invasion (all incidental) | Mohs micrographic surgery | Tumour bed and first echelon lymphatics and course of involved nerve | Mean dose 57.9 Gy (range 52-66), 20-33 fractions | Mean 10.4 months (range 4-20) |
| Khan 1999 (n=26)  | No specific reasons. Prospective cohort with SCC diameter >2 cm | Excision | Elective irradiation of draining lymph nodes | Total dose 45 Gy, 20 fractions | Up to 12 months |
| Lilesio 1990 (n=11) | Unclear | Amputation or wide local excision | Regional lymph nodes | 4500 rads, 20 fractions, 4 weeks | Mean 37 months (range 24-86) |
| Osguthorpe 1997 (n=4) | Head and neck perineural invasion; supraorbital, infraorbital, and buccal nerves; regional lymphatic or perivascular spread; neural spread on multiple nerves from primary tumour site; extension through bony foramen, needing extended resection | Mohs micrographic surgery with or without intracranial clearance | Not specified | Mean 56.2 Gy (range 50-65) | 49.5 months (range 6-99) |
| Shiffman 1975 (n=4) | Not specified | Surgery | Not specified | Not specified | <1 year to >3 years |
| Veness 1999 (n=6)  | Patients undergoing cardiothoracic transplantation who developed “aggressive cutaneous malignancies,” but not specified how patients were selected to have adjuvant radiotherapy | Wide local excision | Not specified | Mean dose 52 Gy | Mean 25.8 months (range 8-54) |
Table 7 | Pooled estimates of SCC specific outcomes after adjuvant radiotherapy

|                                  | Proportion (95% CI) of patients, %, No of patients |
|----------------------------------|-----------------------------------------------|
|                                  | Local recurrence | Regional recurrence | Distant metastases | Patient died from disease |
| Adjuvant radiotherapy for perineural invasion | 18.2% (3.8% to 39.8%), 37%, n=22 | 8.3% (1.1% to 21.4%), 0%, n=22 | 11.5 (2.4% to 26.1%), 1%, n=22 | 11.1% (0.4% to 33.1%), 45%, n=20 |
| Adjuvant radiotherapy for other types of SCC | 11.1% (2.4% to 25.0%), 35%, n=47 | 8.5% (2.5% to 17.6%), 0%, n=47 | 3.2% (0.1% to 10.4%), 9%, n=47 | 13.9% (0.05% to 50.2%), 74%, n=21 |
Table 8 | Recurrence of SCCs after curettage and electrodesiccation

| Study and No of patients | Site | Follow-up | Proportion (95% CI) with recurrence | Prognostic features* | Study design |
|--------------------------|------|-----------|-------------------------------------|----------------------|-------------|
| Knox 1967 (n=545)        | Various | >1 year | 0.00 (0.00 to 0.01) | Diameter <2 cm (91%), >2 cm (9%) | Retrospective |
| Honeycutt 1973 (n=281)   | Various | 4-8 years | 0.01 (0.00 to 0.03) | Diameter <2 cm (94%), >2 cm (6%) | Retrospective |
| Reschly 2010 (n=120)     | Exposed body surface excluding lip and ear | 13-33 months | Triple cycle: 0.00 (0.00 to 0.03); double cycle: 0.00 (0.00 to 0.23) | Diameter <2 cm | Retrospective |
| Shiffman 1975 (n=15)     | Pinna | <1 to >3 years | Local recurrence: 0.20; regional recurrence 0.07 | Diameter <2 cm (59.6%), 2-4 cm (28.8%), >4 cm (3.8%); invasion of cartilage (21.1%) | Retrospective |
| Tromovitch 1965 (n=29)   | Not specified | Average 6.8 years (minimum 5 years) | 0.03 (0.00 to 0.18) | No data | Retrospective |
| Werlinger 2002 (n=56)    | Various | Mean 4.1 years | 0.04 (0.00 to 0.12) | No separate data on electrodesiccation | Retrospective |
| Whiting 1978 (n=47)      | No data | 6-12 months, then “thereafter as necessary” | 0.04 (0.01 to 0.14) | No data | Retrospective |
| Williamson 1964 (n=53)   | Various | 5 years | 0.04 (0.00 to 0.13) | Diameter: <2 cm (60.4%), >2 cm (39.6%) | Retrospective |

*Percentages indicate proportion of patients in study.
### Table 9 | Recurrence of SCCs after cryotherapy studies

| Study and No of SCCs | Site                          | Follow-up          | Proportion (95% CI) of SCCs with recurrence | Prognostic features* | Study design |
|---------------------|-------------------------------|--------------------|---------------------------------------------|----------------------|-------------|
| Fontana 1975 (n=7)  | Unspecified                   | 32 months to 5 years | 0.00 (0.00 to 0.41)                         | No data              | Retrospective |
| Fraunfelder 1980 (n=21) | Periocular                    | Average 21.6 months | 0.00 (0.00 to 0.16)                         | Diameter <10 mm (71%), ≥11 mm (29%) | Prospective |
| Graham 1990 (n=563) | All                           | Unspecified        | 97.3% (*"cure"†*)                          | Diameter <5 mm (25%), 6-12 mm (56.4%), 13-24 mm (15.5%), >24 mm (3.1%) | Retrospective |
| Holt 1988 (n=34)    | All                           | Range 6 months to 5.5 years | 0.03 (0.00 to 0.15)                         | Diameter ≥2 cm (14.7%); indeterminate margins, tethering, deeply invasive, and SCCs of external ear involving underlying cartilage excluded | Prospective |
| Graham 1990 (n=563) | All                           | Unspecified        | 97.3% (*"cure"†*)                          | No data              | Retrospective |
| Holt 1988 (n=34)    | All                           | Range 6 months to 5.5 years | 0.03 (0.00 to 0.15)                         | Diameter ≥2 cm (14.7%); indeterminate margins, tethering, deeply invasive, and SCCs of external ear involving underlying cartilage excluded | Prospective |
| Kuflik 1986 (n=5)   | Arms and hands                | Range 12 months to 6 years | 0.00 (0.00 to 0.52)                         | Diameter; all 2-5 cm | Prospective |
| Kuflik 2004 (n=134) | All                           | 5 years            | 0.00 (0.00 to 0.03)                         | Diameter 3-5 mm; *"Only cases amenable to cryotherapy were treated" | Retrospective |
| Lindemalm-Lundstam 2009 (n=53) | Face and scalp                  | Mean 42 months | 0.00 (0.00 to 0.07)                         | Mean diameter 8 mm (range 1-76); lesions in area circumscribed by upper lip and nasolabial folds excluded | Prospective |
| Nordin 2002 (n=13)  | External ear                  | ≤10 years (8 of 13 followed for at least 5 years) | 0.00 (0.00 to 0.25)                         | Mean diameter 18 mm (range 5-70) | Prospective |
| Peikert 2011 (n=6)  | Below neck                    | 5 years            | 0.00 (0.00 to 0.46)                         | Diameter; all <2 cm; no invasion beyond papillary dermis; spindle cell and poorly differentiated SCCs excluded | Prospective |

*Percentages indicate proportion of SCCs in study.
†"Cure" not defined.
### Table 10 Photodynamic therapy regimens

| Study and No of SCCs | Photosensitiser or occlusion | Light source, irradiance, dose | Treatment regimen | Prognostic features* |
|----------------------|------------------------------|-------------------------------|-------------------|---------------------|
| Baptista 2006 (n=4)  | Topical 20% ALA, 4-6 h       | 630 nm for 1000 s at 100 mW/cm²; total dose 100 J/cm² | Up to 5 treatments | No data |
| Calzavara-Pinton 1995 (n=18) | Topical 20% ALA, 6-8 h | 630 nm for 10-15 min until slight pain or burning stopped at 100 mW/cm²; total dose 60-80 J/cm² | Every other day until area eroded without clinically evident tumour, or stopped when no further improvement after 2 further treatments | Diameter: superficial SCCs median 18 mm (range 12-45); nodular median 15 mm (range 5-25) |
| Calzavara-Pinton 2008 (n=71) | Topical 160 mg/g MAL, 3 h | 635±18 nm at 37 J/cm³ at irradiance of 86 mW/cm² | 2 treatments, 7 days apart | Mean diameter 20 mm (range 15-30); depth: Clark levels II (56%), III/IV (44%) |
| Fink-Puchs 1998 (n=35) | Topical 20% ALA oil in water, 4 h | Either unfiltered full spectrum visible light or filtered light of >515 nm or >570 nm or >610 nm, for 5-30 min; median total light dose 61 J/cm² | 1 treatment | Diameter 1.6-6 cm; depth confined to papillary dermis |
| Fritsch 1998 (n=36) | Topical 20% ALA, 4-6 h | Incoherent light source 570-750 nm for 20 min; 80 mW/cm² for superficial SCCs up to 150 mW/cm² for nodular and exulcerated SCCs; total dose 96-180 J/cm² | Maximum 3 treatments (1 month apart) | Diameter 0.5-3.1 cm; 28 SCCs described as “superficial”† |
| Haddad 2004 (n=43) | Topical 20% ALA, 16 h | Non-laser light at 580-720 nm and 1250-1600 nm for 10 min at 100 J/cm² | 1-3 treatments | Mean diameter 1.4±0.6 cm (range 1-3) |
| Harth 1998 (n=5) | Modified topical 20% ALA plus 2% EDTA and 2% DMSO, 12 h | Red light (585-720 nm) at 150 mW/cm² and near infrared (1.25-1.6 mm) at 50 mW/cm² for 10-15 min | 1-3 treatments | “Superficial” |
| Kennedy 1990 (n=8) | Topical 20% ALA, 3-6 h | Filtered light >600 nm at 150-300 mW/cm² for 3.5-30 min; total dose 15-150 mW/cm² | Treatment repeated weekly for 2 elevated SCCs | 6 early invasive SCCs; 2 elevated SCCs |
| Lui 1995 (n=2) | Topical 20% ALA, 3 h | Red light at 19-44 mW/cm²; total dose 100 J/cm² | 1 treatment | Diameter >5 mm |
| Wolf 1993 (n=6) | Topical 20% ALA oil in water, 4-8 h | Unfiltered light at 100 mW/cm² for 15 min or red light at 100 mW/cm² for 30 min; total dose 90 J/cm² | No of treatments not specified | Diameter 1-6 cm; depth: all early invasive |
| Ziolkowski 2004 (n=23) | Group 1: topical 20% ALA plus 5% DMSO and 5% EDTA, 4 h occlusion; group 2: topical 20% ALA plus 5% DMSO, 5% EDTA, and glycolic acid, 4 h occlusion | 650 nm >30 nm light at 100 mW/cm²; total dose 85-87.6 J/cm² | Up to 3 sessions of treatment | Group 1 diameter 2-7 mm, group 2 diameter 2-9 mm |
| Feyh 1990 (n=5) | Systemic haematoporphyrin derivative 2 before photodynamic therapy; dose not specified | 630 nm laser light at 100 mw/cm²; dose 100 J/cm² | — | All tumour stage T1 |
| Kübler 1999 (n=9) | mTHPC at 0.15mg/kg, intravenous, 96 h before photodynamic therapy | 652 nm red light at 100 mW/cm²; total dose 20 J/cm² | — | No data |
| Pennington 1988 (n=32) | Systemic haematoporphyrin derivative as 5 mg/kg intravenous bolus, 3 days before photodynamic therapy | 630 nm coherent light at 30 J/cm³ | — | Estimated maximal thickness <1 cm |

*ALA=aminolevulinic acid; MAL=methylaminolevulinate; EDTA=ethylenediaminetetraacetic acid; DMSO=dimethyl sulfoxide; mTHPC=meta-tetrahydroxyphenylchlorin. *Percentages indicate proportion of SCCs in study. †“Superficial” not defined.
| Study               | System of photosensitising | No of SCCs | Initial assessment after treatment | Proportion (95% CI) with apparent complete response | Proportion (95% CI) of SCCs with recurrence after apparent complete response | Duration of follow-up | Comments |
|---------------------|-----------------------------|------------|------------------------------------|-----------------------------------------------------|----------------------------------------------------------------|-----------------------|----------|
| Baptista 2006       | Topical photosensitisier    | 4          | 1 month                            | 0.25 (0.01 to 0.80)                                  | 0.00 (0.00 to 0.96), n=1                                          | Median 38 months      | —        |
| Calzavara-Pinton 1995 | Topical photosensitisier    | 6 nodular, 12 superficial | 1 month                            | 0.5 (0.12 to 0.88), 0.83 (0.52 to 0.98)              | 0.50 (0.01 to 0.99), n=2; 0.00 (0.00 to 0.71), n=3                  | 29 months (24-36)     | Residual tumour in 1 of 2 biopsied apparently responsive nodular SCCs, and in 1 of 8 biopsied responsive superficial SCCs |
| Calzavara-Pinton 2008 | Topical photosensitisier    | 40 microinvasive, 31 invasive | 3 months                           | 0.6 (0.64 to 0.91), 0.45 (0.27 to 0.64)              | 0.28 (0.14 to 0.47), n=32; 0.43 (0.18 to 0.71), n=14                | ≤24 months            | —        |
| Fink-Puches 1998    | Topical photosensitiser     | 35         | 2-4 weeks                          | 0.54 (0.37 to 0.71)                                  | 0.69 (0.41 to 0.89), n=16                                        | Median 6 months (range 3-47) | —        |
| Fritsch 1998        | Topical photosensitiser     | 36         | Not specified                      | 0.75 (0.58 to 0.88)                                  | —                                                             | —                     | —        |
| Haddad 2004         | Topical photosensitiser     | 43         | 21 days                            | 0.74 (0.59 to 0.86)                                  | —                                                             | —                     | —        |
| Harth 1998          | Topical photosensitiser     | 5          | Not specified                      | 0.8 (0.28 to 0.99)                                   | —                                                             | —                     | —        |
| Kennedy 1990        | Topical photosensitiser     | 2 "elevated," 6 "early invasive" | 2-3 months                          | 0.00 (0.00 to 0.94), 1.0 (0.54 to 1.0)                | —                                                             | —                     | —        |
| Lui 1995            | Topical photosensitiser     | 2          | 3 months                           | 0.00 (0.00 to 0.84)                                  | —                                                             | —                     | —        |
| Wolf 1993           | Topical photosensitiser     | 6          | 4 and/or 8 weeks                   | 0.83 (0.36 to 1.0)                                   | 0.00 (0.00 to 0.52), n=5                                         | 7 months (range 3-12) | —        |
| Ziokolowski 2004    | Topical photosensitiser     | 11 (no glycolic acid), 12 (plus glycolic acid) | Not specified                      | 0.64 (0.31 to 0.89), 1.0 (0.74 to 1.0)                | "Complete response" at 12 months                                 | "Complete response" defined as no clinically visible or 5-ALA fluorescence detectable tumour after 12 months of observation |
| Feyh 1990           | Systemic photosensitiser    | 5          | 2 months                           | 1.0 (0.48 to 1.0)                                   | 0.00 (0.00 to 0.52), n=5                                         | Maximum 14 months     | —        |
| Kubler 1999         | Systemic photosensitiser    | 9          | 3 months                           | 1.0 (0.66 to 1.0)                                   | 0.00 (0.00 to 0.34), n=9                                         | Mean 20 months (range 8-24) | —        |
| Pennington 1988     | Systemic photosensitiser    | 32         | 6 weeks                            | 0.81 (0.64 to 0.93)                                  | 0.5 (0.32 to 0.68), n=32                                         | 6 months              | Authors found no correlation between recurrence and presence of residual tumour on histology at initial assessment, and abandoned trial in view of results |
Figures

**Fig 1** PRISMA flowchart of studies. BCC=basal cell carcinoma

**Fig 2** Risk of bias assessment of included studies. Percentage indicates proportion of studies
Fig 3 Local recurrence of SCCs after surgical excision
Fig 4 Local recurrence of SCCs in ear locations after surgical excision
**Fig 5** Local recurrence of SCCs in non-ear locations after surgical excision
**Fig 6** Regional recurrence of SCCs after surgical excision
Fig 7 Regional recurrence of SCCs in ear locations after surgical excision
Fig 8 Regional recurrence of SCCs in non-ear locations after surgical excision
**Fig 9** Deaths attributable to disease after surgical excision
Fig 10  Incomplete excision of SCCs after surgical excision
Fig 11 Local recurrence of SCCs after Mohs micrographic surgery
Fig 12 Regional recurrence of SCCs after Mohs micrographic surgery
Unspecified recurrence of SCCs after Mohs micrographic surgery

**Fig13** Proportion meta-analysis plot [random effects]

| Study      | Proportion (95% CI) |
|------------|---------------------|
| Mohs 1978  | 0.0081 (0.0026, 0.0139) |
| Tommick 1984 | 0.0000 (0.0000, 0.2180) |
| Yoon 1992  | 0.3125 (0.1102, 0.5856) |
| Thomas 2007 | 0.0455 (0.0095, 0.1271) |
| Skaria 2010 | 0.0185 (0.0005, 0.0989) |
| combined   | 0.0470 (0.0077, 0.1173) |
Proportion meta-analysis plot [random effects]

| Study            | Proportion (95% CI)            |
|------------------|-------------------------------|
| Anderson 1982    | 0.0000 (0.0000, 0.0415)       |
| Silapunt 2009    | 0.0146 (0.0067, 0.0276)       |
| Brantsch 2009    | 0.0043 (0.0001, 0.0239)       |
| Pagliaro-Mauro 2010 | 0.0108 (0.0022, 0.0258)   |
| combined         |                               |

**Fig 14** Deaths attributable to disease after Mohs micrographic surgery
Fig 15 Local recurrence of SCCs after external radiotherapy
Fig 16 Regional recurrence of SCCs after external radiotherapy

Proportion meta-analysis plot [random effects]

Study   Proportion (95% CI)

Shiffman 1975   0.5000 (0.0126, 0.9874)

Tsao 2005   0.0215 (0.0026, 0.0755)

Barysch 20   0.0056 (0.0001, 0.0311)

combined   0.0260 (0.0004, 0.0893)
**Fig 17** Unspecified recurrence of SCCs after external radiotherapy
Fig 18 Deaths attributed to disease after external radiotherapy
Fig 19 Local recurrence of SCCs after brachytherapy
Fig 20  Unspecified recurrence of SCCs after curettage and electrodesication
Fig 21 Unspecified recurrence of SCCs after cryotherapy
Fig 22 Apparent complete response of SCCs after photodynamic therapy. (1) "elevated" SCCs; (2) "early invasive" SCCs; (3) "nodular" SCCs; (4) "superficial" SCCs; (5) no glycolic acid added to photodynamic therapy; (6) photodynamic therapy plus glycolic acid; (7) "invasive" SCCs; (8) "microinvasive" SCCs
Fig 23 Recurrence after apparent complete response of SCCs following photodynamic therapy. (1) "superficial" SCCs; (2) "nodular" SCCs; (3) "microinvasive" SCCs; (4) "invasive" SCCs