RESEARCH

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

OPEN ACCESS

Louise Lansbury *research associate*¹, Fiona Bath-Hextall *reader in evidence based healthcare*^{1,2}, William Perkins *consultant dermatologist*³, Wendy Stanton *librarian*⁴, Jo Leonardi-Bee *associate professor in medical statistics*⁵

¹Centre of Evidence Based Dermatology, University of Nottingham, Nottingham NG7 2NR, UK; ²School of Health Sciences, University of Nottingham, Nottingham, UK; ³Department of Dermatology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK; ⁴Greenfield Medical Library, Nottingham Education Centre, University of Nottingham, UK; ⁵Division of Epidemiology and Public Health, University of Nottingham, Nottingham City Hospital, Nottingham, UK

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 keratosis and Bowen's disease. The tumour could present clinically as a smooth or

Correspondence to: L Lansbury Louise.Lansbury@nottingham.ac.uk

Extra material supplied by the author (see <http://www.bmj.com/content/347/bmj.f6153?tab=related#webextra>)

Web appendix 1: Protocol of systematic review

Web appendix 2: Search strategies

Web appendix 3: Characteristics of included studies

Web appendix 4: Supplementary data on treatments with less robust data

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.¹ 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 2030.² Additionally, solid organ transplant recipients are at particular risk of developing SCC.³⁻⁵ 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.⁶

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.⁷ 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.⁸ However, in general, SCC treatment has not been thoroughly or rigorously studied. Our recent Cochrane systematic review of the treatment of primary non-metastatic SCC⁹ 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.⁹

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.¹⁰ Details of the protocol for this systematic review are registered on PROSPERO (www.metaxis.com/prospetro/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).¹¹ 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).¹² 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.¹³ 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%¹⁴⁻²⁵ (table 1), with an estimate of overall pooled recurrence of 5.4% (95% confidence interval 2.5% to 9.1%, $I^2=81\%$; 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.¹⁸ 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%, $I^2=62\%$).^{14-16 19-21 23 25} 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.¹⁷ Three studies reported recurrence of 4.8% for eyelid SCCs,²⁵ 10.5% for trunk and extremity SCCs,²² and 15.3% for SCCs of the pinna,²⁴ 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%, $I^2=0\%$).^{20 23 24} This recurrence was significantly higher than the lower pooled average of 3.2% (1.5% to 5.5%, $I^2=57\%$) for studies ($n=916$) in which SCCs at other sites were included (figs 4 and 5).^{14-19 21 22 25} 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.²⁴

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%), $I^2=81.4\%$).^{17-19 23} 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%,^{14 16 18 20 21 23 24 26} with pooled average recurrence of 4.4% (2.4% to 6.9%, $I^2=50\%$; 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%), $I^2=72\%$).^{18 23 26}

One study (108 patients)¹⁸ 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,^{14 16 21 26} specified mean follow-up duration was between two and five years, with a pooled average recurrence of 3.6% (1.9 to 5.9, $I^2=11\%$). 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.^{20 23 24}

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%, $I^2=0\%$).^{20 23 24} This proportion was significantly greater than the pooled average regional recurrence of 2.9% (1.4% to 5.0%, $I^2=27\%$) for the five remaining studies that included other head and neck locations (figs 7 and 8).^{14 16 18 21 26}

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.²⁷ There were no distant metastases in any of 35 patients with periocular SCC during a mean follow-up period of 31.1 months.¹⁶

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%).^{28 29} There were no reported recurrences

in the study in which mean follow-up was less than five years.³⁰ 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%, $I^2=58\%$; fig 9).^{14 16 17 20-23 29} Three studies with a follow-up period specified as between two and five years^{14 16 21} had a significantly lower pooled average of 0.8% (0.1% to 2.5%, $I^2=0\%$) 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 23} 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%, $I^2=89\%$; table 2), fig 10).^{14 17 19 23 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,²⁸ tumour within one microscopic high-power field (0.5 mm),³³ 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,³⁴ 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.³³ 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 26 28 32 35} 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%).¹⁹

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%)³⁷; of the ear (96.6%)³⁸; of the face, scalp, and neck (97.8%)³⁷; of the eyelid (98.5%)³⁹; and of the nose (98.8%).³⁷ 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%, $I^2=48\%$).

Ten studies reported local recurrence,^{18 40-48} ranging from 0% (95% confidence interval 0% to 36.9%) in one small study including eight periorbital SCCs⁴⁰ 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%, $I^2=0\%$; 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%, $I^2=0\%$).^{18 41 43-45 48}

In one study with specified mean follow-up of less than two years,⁴⁶ 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%, $I^2=0\%$) in seven studies with mean follow-up of between two and five years,^{18 40-43 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.^{18 40 41 43 45 49} On pooled analysis (comprising 1162 patients), the average regional recurrence was 4.2% (95% confidence interval 2.3% to 6.6%, $I^2=56\%$; fig 12). There was no significant effect on regional recurrence in the sensitivity analysis, which included only the four studies meeting the criteria,^{18 41 43 45} with average recurrence of 3.2% (1.9% to 5.0%, $I^2=29\%$).

Five studies^{18 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%, $I^2=34\%$). 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.⁴⁷ 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.⁴³ Another series including eight patients with periorbital SCC also noted one patient with metastases to the lung,⁴⁰ 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.^{31 50-53} These five studies had a pooled average unspecified recurrence of 4.7% (95% confidence interval 0.7% to 11.7%, $I^2=81\%$; 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.⁵¹⁻⁵³ For these studies, the average unspecified recurrence was 2.2% (95% confidence interval 0.3% to 5.4%, $I^2=61\%$). The remaining studies^{31 50} 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 45 47} with an average of 1.1% (95% confidence interval 0.2% to 2.6%, $I^2=49\%$) 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 periorbital SCCs, one of whom developed regional metastases and lung metastases without evidence of local recurrence, indicating that the tumour had spread subclinically before treatment.⁴⁰

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 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%, $I^2=76\%$; table 4), fig 15).^{15 20 54 55 57 58 64} Three studies

were included in the sensitivity analysis,^{55 58 64} with no significant effect on local recurrence (7.3%, 2.1% to 15.4%, $I^2=87\%$).

The four studies with a mean follow-up period between two and five years^{15 55 58 64} had a pooled average recurrence of 6.1% (95% confidence interval 2.2 to 11.7, $I^2=85\%$). 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.^{20 54 57}

In one study, location in the ear and scalp region was found to be significantly associated with relapse of tumour compared with other sites ($P=0.025$).⁶⁴ 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%).^{54 58} 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%),^{20 57} 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),^{20 58 64} giving an average regional recurrence of 2.6% on pooled analysis (95% confidence interval 0.04% to 8.9%, $I^2=70\%$; fig 16). In both larger studies^{58 64}—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.²⁰ 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.⁵⁹ 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.^{27 56 60-63} Pooled data from 220 treated SCCs from the studies gave an average recurrence of 4.8% (95% confidence interval 0.6% to 12.8%, $I^2=70\%$; fig 17). Two of the studies^{56 63} 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 study⁶³ 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%).^{60 62} 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.^{27 61}

We found five studies including 191 patients that reported deaths as a result of SCC,^{20 58 61-63} with an average of 9.1% of patients dying from their disease on pooled analysis (95% confidence interval 1.4% to 22.8%, $I^2=79\%$; fig 18).^{22 60 63 64 65} 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%),⁶³ 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%).^{58 62} 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),⁶⁵⁻⁷⁰ giving a pooled average local recurrence of 5.2% (95% confidence interval 1.6% to 10.5%, $I^2=0\%$). Of these studies, four were prospective reports (35 SCCs)^{65 67 68 70} and two were retrospective (53 SCCs),^{66 69} with varying follow-up periods from an average of 9.6 months⁶⁸ up to a median of 55 months.⁶⁶ Four studies had no recurrences during follow-up.⁶⁵⁻⁶⁸ 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.⁶⁹ The other reported SCC recurrence occurred 23 months after high dose rate brachytherapy with a ¹⁹²Ir surface mould, and was a 4 cm tumour located on the frontal area.⁷⁰ No patients in this study developed regional or distant metastases after treatment.

One study reported that four (8.3%) of 48 SCCs treated with a radon mould persisted after initial treatment and required treatment by other methods to ablate the lesions.⁶⁹ The study authors attributed their high failure rate to the inclusion of tumours with a high volume, or with a thickness was 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).⁷¹⁻⁷⁵ In one of these studies,⁷³ 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.⁷² In the other three studies, two included patients with asymptomatic perineural invasion in unnamed nerves^{71 74} and one involved named cranial nerves.⁷⁵ 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 those with perineural invasion. These included patients with pinna SCCs,²⁰ trunk and extremity SCCs,^{76 77} and aggressive SCCs after a cardiathoracic transplant.⁷⁸ 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,^{20 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).⁷⁶ Adjuvant radiotherapy was administered to the draining regional lymph nodes in both studies of trunk and extremity SCCs.^{76 77} The irradiation field was not specified in the other studies.^{20 78} 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.⁷⁶ Local recurrence was also reported in two of six patients who developed SCC after cardiothoracic transplantation, one of whom also developed regional recurrence. Another patient in this series also had a systemic relapse, despite local control of their SCC.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.⁷⁵ No deaths attributable to SCC after adjuvant radiotherapy for perineural invasion were reported in any of the remaining three studies (16 patients).^{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 cardiothoracic transplantation between eight months and 54 months after diagnosis.⁷⁸ No deaths were reported in the other studies,^{20 77} 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),⁷⁸ 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.^{71 72 76} Single adverse events recorded were wound infection and serous otitis media,⁷¹ self limiting mucositis, radiation dermatitis and residual mild xerostomia,⁷⁴ and reactive lymphoedema of the leg.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.²⁰ 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.^{27 30 60 79-82} 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^{30 82} 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 study⁸⁰ 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.^{27 60 79 82} 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.⁶⁰ One study separated results according to the number of treatment cycles used with no recurrences after either two or three cycles.⁷⁹ Two studies specified the number of cycles of electrodesiccation as either double⁸⁰ or triple,⁸¹ but this information was not reported for the remaining studies.

Cosmetic outcome was reported in just one of the included studies (41 patients),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.⁸³⁻⁹⁰ Only one study reported recurrence after cryotherapy⁹⁰ 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 contains details of prognostic features of the SCCs included. Sensitivity analysis was not conducted because only one study met our prespecified criteria,⁸⁹ with no reported recurrences (53 patients; 0% to 6.7%).

In five studies,^{83 84 86 88 89} 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%, $I^2=0\%$). None had a mean follow-up of greater than five years, and for three studies,^{85 87 90} 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.⁹¹ 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.⁹⁰ 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).⁹²⁻¹⁰⁵ Three studies separated SCCs according to level or depth of invasion,^{92 95 98} and one was a non-randomised two-arm comparison of topical photodynamic therapy either with or without a 5% glycolic acid penetration enhancer.⁹⁷ 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%, $I^2=71\%$; fig 22). Five studies specified that histological assessment of at least some of the treated areas was done to confirm apparent clinical response.^{93 95 102 104 105}

In eight of the included studies, SCCs that had apparently completely responded to photodynamic therapy initially were observed for recurrence.^{94-96 98 102-105} Pooled recurrence data from these studies (119 SCCs) gave an odds of recurrence of 26.4% (95% confidence interval 12.3% to 43.7%, $I^2=72\%$; 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)¹⁰² 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% 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.¹⁰⁵ None was deemed to have poor appearance in this study. Two further studies described cosmetic results as “very satisfactory”⁹⁷ 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.¹⁰⁶ 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^{58 64}—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 reviews^{108 109} 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.¹¹⁰ 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 Albrecht¹² for improving the quality of case series. Albrecht's suggestions are based on a few published articles¹¹⁵⁻¹¹⁷ and Albrecht'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 17 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 colleagues¹⁷ 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.⁴⁹

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.^{113 121} Although further validation work is required, these systems could be useful tools when designing future clinical trials.

We thank Alemayehu Amberbir (AA) and Joanna Browne (JB) who assisted with data extraction.

Contributors: LL, FB-H, WP, and JL-B contributed to the development of the review questions. WS and LL designed the searches. LL, FB-H, and JL-B assessed the eligibility of studies for inclusion, extracted data, and assessed risk of bias and quality of reporting. JL-B developed the statistical analysis. LL, FB-H, WP, and JL-B contributed to the analysis and interpretation of data. LL drafted the article and all other authors approved the final version, had full access to the data, and take responsibility for the integrity of the data and accuracy of the analysis. LL is the guarantor.

Funding: This systematic review presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (RP-PG-0407-10177).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: LL, FBH, WP, and JLB received support from the NIHR for the submitted

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) v 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=88)

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)

work; all authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: None required.

Data sharing: Statistical code and dataset are available from the corresponding author at Louise.Lansbury@nottingham.ac.uk.

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 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) v 0.4% (0% to 2.1%, 264 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

- 2 Diffey BL, Langtry JAA. Skin cancer incidence and the ageing population. *Br J Dermatol* 2005;153:579-80.
- 3 Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation* 1990;49:506-9.
- 4 Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Derm* 1999;40:177-86.
- 5 Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. *Br J Dermatol* 2006;154:498-504.
- 6 Harwood CA, Mesher D, McGregor JM, Mitchell L, Leedham-Green M, Raftery M, et al. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. *Am J Transplant* 2013;13:119-29.
- 7 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging handbook from the AJCC cancer staging manual. 7th ed. Springer 2010.
- 8 Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol* 2002;146:18-25.
- 9 Lansbury L, Leonardi-Bee J, Perkins W, Goodacre T, Tweed JA, Bath-Hextall FJ. Interventions for non-metastatic squamous cell carcinoma of the skin. *Cochrane Database Syst Rev* 2010;4:CD007869.
- 10 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
- 11 Scottish Intercollegiate Guidelines Network. Observational studies search filter internet. 2013. www.sign.ac.uk/methodology/filters.html#obs.
- 12 Williams H, Bigby M, Diepgen T, Herxheimer A, Naldi L, Rzany B, eds. Evidence-based dermatology. 2nd ed. Blackwell Publishing, 2008.
- 13 Stuart A, Ord JK. Kendall's advanced theory of statistics. 6th ed. Edward Arnold, 1994.
- 14 Baker NJ, Webb AAC, Macpherson D. Surgical management of cutaneous squamous cell carcinoma of the head and neck. *Br J Oral Maxillofac Surg* 2001;39:87-90.
- 15 Rank B. Surgery and skin cancer. *Ann R Coll Surg Engl* 1973;52:148-64.
- 16 Donaldson MJ, Sullivan TJ, Whitehead KJ, Williamson RM. Squamous cell carcinoma of the eyelids. *Br J Ophthalmol* 2002;86:1161-5.
- 17 Griffiths RW, Feeley K, Suvama SK. Audit of clinical and histological prognostic factors in primary invasive squamous cell carcinoma of the skin: assessment in a minimum 5 year follow-up study after conventional excisional surgery. *Br J Plast Surg* 2002;55:287-92.
- 18 van der Eerden PA, Prins EF, Lohuis PJFM, Balm AJ, Vuyk H. Eighteen years of experience in Mohs micrographic surgery and conventional excision for nonmelanoma skin cancer treated by a single facial plastic surgeon and pathologist. *Laryngoscope* 2010;120:2378-84.
- 19 Nemet AY, Deckel Y, Martin PA, Kourt G, Chilov M, Sharma V, et al. Management of periocular basal and squamous cell carcinoma: a series of 485 cases. *Am J Ophthalmol* 2006;142:293-7.
- 20 Shiffman NJ. Squamous cell carcinomas of the skin of the pinna. *Can J Surg* 1975;18:279-83.
- 21 Reifler DM, Hornblase A. Surgical management of squamous cell carcinoma of the lid. *Ophthalm Plast Reconstr Surg* 1986;2:75-82.
- 22 Shiu MH, Chu F, Fortner JG. Treatment of regionally advanced epidermoid carcinoma of the extremity and trunk. *Surg Gynecol Obstet* 1980;150:558-62.
- 23 Thomas SS, Matthews RN. Squamous cell carcinoma of the pinna: a 6-year study. *Br J Plast Surg* 1994;47:81-5.
- 24 Pless J. Carcinoma of the external ear. *Scand J Plast Reconstr Surg* 1976;10:147-51.
- 25 Fitzpatrick P, Harwood AA. Acute epithelioma—an aggressive squamous cell carcinoma of the skin. *Am J Clin Oncol* 1985;8:468-71.
- 26 Mourouzis C, Boynton A, Grant J, Umar T, Wilson A, Macpherson D, et al. Cutaneous head and neck SCCs and risk of nodal metastasis. *J Craniomaxillofac Surg* 2009;37:443-7.
- 27 Knox JM, Freeman RG, Duncan WC, Heaton CL. Treatment of skin cancer. *South Med J* 1967;60:241-6.
- 28 Ang P, Tan AWH, Goh CL. Comparison of completely versus incompletely excised cutaneous squamous cell carcinoma. *Ann Acad Med Singapore* 2004;33:68-70.
- 29 Friedman HI, Cooper PH, Wanebo HJ. Prognostic and therapeutic use of microstaging of cutaneous squamous cell carcinoma of the trunk and extremities. *Cancer* 1984;56:1105-985.
- 30 Werlinger KD, Upton G, Moore AY. Recurrence rates of primary nonmelanoma skin cancers treated by surgical excision compared to electrodesiccation-curettage in a private dermatological practice. *Dermatol Surg* 2002;28:1138-42.
- 31 Yoon M, Chougule P, Dufresne R, Wanebo HJ. Localized carcinoma of the external ear is an unrecognized aggressive disease with a high propensity for local regional recurrence. *Am J Surg* 1992;164:574-7.
- 32 Pua VSC, Huilgol S, Hill D. Evaluation of the treatment of non-melanoma skin cancers by surgical excision. *Australas J Dermatol* 2009;50:171-5.
- 33 Thomas DJ, King AR, Peat BG. Excision margins for nonmelanotic skin cancer. *Plast Reconstr Surg* 2003;112:57-63.

- 34 Tan PY. Incomplete excision of squamous cell carcinoma of the skin: a prospective observational study. *Plast Reconstr Surg* 2007;120:910-6.
- 35 Bogdanov-Berezovsky A, Cohen AD, Glesinger R, Cagnano E, Rosenberg L. Risk factors for incomplete excision of squamous cell carcinomas. *J Dermatolog Treat* 2005;16:341-4.
- 36 Bovill ES, Cullen KW, Barrett W, Banwell PE. Clinical and histological findings in re-excision of incompletely excised cutaneous squamous cell carcinoma. *J Plast Reconstr Aesthet Surg* 2009;62:457-61.
- 37 Mohs FE. Chemosurgery: microscopically controlled surgery for skin cancer. Charles C Thomas, 1978.
- 38 Mohs FE, Larson PO, Irlondo M. Micrographic surgery for the microscopically controlled excision of carcinoma of the external ear. *J Am Acad Dermatol* 1988;19:729-37.
- 39 Mohs FE. Micrographic surgery for the microscopically controlled excision of eyelid cancers. *Arch Ophthalmol* 1986;104:901-9.
- 40 Anderson RL. Results in eyelid malignancies treated with the Mohs fresh tissue technique. *Trans New Orleans Acad Ophthalmol* 1982;30:380-91.
- 41 Pugliano-Mauro M, Goldman G. Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma. *Dermatol Surg* 2010;36:1544-53.
- 42 Vuyk HD, Lohuis PJFM. Mohs micrographic surgery for facial skin cancer. *Clin Otolaryngol* 2001;26:265-73.
- 43 Turner RJ, Leonard N, Malcolm AJ, Lawrence CM, Dahl MG. A retrospective study of outcome of Mohs' micrographic surgery for cutaneous squamous cell carcinoma using formalin fixed sections. *Br J Dermatol* 2000;142:752-7.
- 44 Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. *J Am Acad Dermatol* 2005;53:253-60.
- 45 Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol* 2008;9:713-20.
- 46 Dzubow LM, Rigel DS, Robins P. Risk factors for local recurrence of primary cutaneous squamous cell carcinomas. Treatment by microscopically controlled excision. *Arch Dermatol* 1982;118:900-2.
- 47 Silapunt S, Peterson SR, Goldberg LH. Squamous cell carcinoma of the auricle and Mohs micrographic surgery. *Dermatol Surg* 2005;31:1423-7.
- 48 Malhotra R, Huilgol SC, Huynh NT, Selva D. The Australian Mohs database: periorcular squamous cell carcinoma. *Ophthalmology* 2004;111:617-23.
- 49 Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. *Dermatol Surg* 2002;28:268-73.
- 50 Tomsick RS, Menn H. Squamous cell carcinoma of the fingers treated with chemosurgery. *South Med J* 1984;77:1124-6.
- 51 Mohs FE. Chemosurgery for skin cancer. *Arch Dermatol* 1976;112:211-5.
- 52 Skaria AM. Recurrence of basosquamous carcinoma after Mohs Micrographic Surgery. *Dermatology* 2010;221:352-5.
- 53 Thomas CJ, Wood GC, Marks VJ. Mohs micrographic surgery in the treatment of rare aggressive cutaneous tumors: the Geisinger experience. *Dermatol Surg* 2007;33:333-9.
- 54 Stoll HL Jr, Milgrom H, Traenkle HL. Results of roentgen therapy of carcinoma of the nose. *Arch Dermatol* 1964;90:577-80.
- 55 Abbattucci JS, Boulter N, Laforte T, Lozier JC. Radiation therapy of skin carcinomas: results of a hypofractionated irradiation schedule in 675 cases followed more than 2 years. *Radiother Oncol* 1989;14:113-9.
- 56 Grosch E, Lambert HE. The treatment of difficult cutaneous basal and squamous cell carcinoma with electrons. *Br J Radiol* 1979;52:472-7.
- 57 Podd TJ. Treatment of lower limb basal cell and squamous cell carcinomas with radiotherapy. *Clin Oncol (R Coll Radiol)* 1992;4:44-5.
- 58 Tsao MN, Tsang RW, Liu F-F, Panzarella T, Rotstein L. Radiotherapy management for squamous cell carcinoma of the nasal skin: the Princess Margaret Hospital experience. *Int J Radiat Oncol Biol Phys* 2002;52:973-9.
- 59 Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys* 2004;60:406-11.
- 60 Honeycutt WM, Jansen GT. Treatment of squamous cell carcinoma of the skin. *Arch Dermatol* 1973;108:670-2.
- 61 Holmes ME, Bomford CK, Phil M. The use of a short distance cobalt unit in the treatment of primary skin tumors. *Br J Radiol* 1982;55:225-8.
- 62 Hunter RD, Pereira DT, Pointon RC. Megavoltage electron beam therapy in the treatment of basal and squamous cell carcinomata of the pinna. *Clin Radiol* 1982;33:341-5.
- 63 Matthiesen C, Thompson JS, Forest C, Ahmad S, Herman T, Bogardus C Jr. The role of radiotherapy for T4 non-melanoma skin carcinoma. *J Med Imaging Radiat Oncol* 2011;55:407-16.
- 64 Barysch MJ, Eggman N, Beyeler M, Panizzon RG, Seifert B, Dummer R. Long-term recurrence rate of large and difficult to treat cutaneous squamous cell carcinomas after superficial radiotherapy. *Dermatology* 2012;224:59-65.
- 65 Allan E, Stanton A, Pye D, Collins C, Perry L, Filby M, et al. Fractionated high dose rate brachytherapy moulds—a precise treatment for carcinoma of the pinna. *Radiother Oncol* 1998;48:277-81.
- 66 Rio E, Bardet E, Ferron C, Peuvrel P, Supiot S, Campion L, et al. Interstitial brachytherapy of periorificial skin carcinomas of the face: a retrospective study of 97 cases. *Int J Radiat Oncol Biol Phys* 2005;63:753-7.
- 67 Lee JD, Park KK, Lee M-G, Kim E-H, Rhim KJ, Lee JT, et al. Radionuclide therapy of skin cancers and Bowen's disease using a specially designed skin patch. *J Nucl Med* 1997;38:697-702.
- 68 Svoboda VH, Kovarik J, Morris F. High dose-rate microselectron molds in the treatment of skin tumors. *Int J Radiat Oncol Biol Phys* 1995;31:967-72.
- 69 Ashby MA, Pacella JA, de Groot R, Ainslie J. Use of a radon mould technique for skin cancer: results from the Peter MacCallum Institute (1975-1984). *Br J Radiol* 1989;62:608-12.
- 70 Guix B, Finestres F, Tello J, Palma C, Martinez A, Guix J, et al. Treatment of skin carcinomas of the face by high-dose-rate brachytherapy and custom-made surface molds. *Int J Radiat Oncol Biol Phys* 2000;47:95-102.
- 71 Barrett TL, Greenway HT, Massullo V, Carlson C. Treatment of basal cell carcinoma and squamous cell carcinoma with perineural invasion. *Adv Dermatol* 1993;8:277-305.
- 72 Cotel WL. Perineural invasion by squamous-cell carcinoma. *J Dermatol Surg Oncol* 1982;8:589-600.
- 73 DeAmbrosio K, DeAmbrosio B. Nonmelanoma skin cancer with perineural invasion: report of outcomes of a case series. *Dermatol Surg* 2010;36:133-8.
- 74 Geist DE, Garcia-Moliner M, Fitzek MM, Cho H, Rogers GS. Perineural invasion of cutaneous squamous cell carcinoma and basal cell carcinoma: raising awareness and optimizing management. *Dermatol Surg* 2008;34:1642-51.
- 75 Osguthorpe JD, Abel EA, Lang PG, Hochman M. Neurotropic cutaneous tumors of the head and neck. *Arch Otolaryngol Head Neck Surg* 1997;123:871-6.
- 76 Khan NA, Akhtar S, Kharadi MY, Andrabi WH, Darzi MA. Role of elective irradiation to drainage sites in squamous cell carcinoma of the skin trunk and extremities. *JK Practitioner* 1999;6:35-8.
- 77 Lifeso RM, Rooney RJ, El-Shaker M. Post-traumatic squamous-cell carcinoma. *J Bone Joint Surg Am* 1990;72:12-8.
- 78 Veness MJ, Quinn DI, Ong CS, Keogh AM, Macdonald PS, Cooper SG, et al. Aggressive cutaneous malignancies following cardiothoracic transplantation. The Australian experience. *Cancer* 1999;85:1758-64.
- 79 Reschly MJ, Shenefelt PD. Controversies in skin surgery: electrodesiccation and curettage versus excision for low-risk, small, well-differentiated squamous cell carcinomas. *J Drugs Dermatol* 2010;9:773-6.
- 80 Tromovitch TA. Skin cancer. Treatment by curettage and desiccation. *Calif Med* 1965;103:107-8.
- 81 Whiting DA. Skin tumours in white South Africans. Part V. Treatment of skin tumours. *S Afr Med J* 1978;53:166-70.
- 82 Williamson GS, Jackson R. Treatment of squamous cell carcinoma of the skin by electrodesiccation and curettage. *CMAJ* 1964;90:408-13.
- 83 Kuflik EG. Cryosurgery for skin cancer: 30-year experience and cure rates. *Dermatol Surg* 2004;30:297-300.
- 84 Fraunfelder FT, Zacarian SA, Limmer BL, Wingfield D. Cryosurgery for malignancies of the eyelid. *Ophthalmology* 1980;87:461-5.
- 85 Kuflik EG. Cryosurgical treatment for large malignancies on the upper extremities. *J Dermatol Surg Oncol* 1986;12:575-7.
- 86 Fontana AM, Muti E. Results with cryotherapy in skin tumours. *Panminerva Med* 1975;17:384-9.
- 87 Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. *J Laryngol Otol* 2002;116:893-8.
- 88 Peikert JM. Prospective trial of curettage and cryosurgery in the management of non-facial, superficial, and minimally invasive basal and squamous cell carcinoma. *Int J Dermatol* 2011;50:1135-8.
- 89 Lindemalm-Lundstam B, Dlenback J. Prospective follow-up after curettage-cryosurgery for scalp and face skin cancers. *Br J Dermatol* 2009;161:568-76.
- 90 Holt PJA. Cryotherapy for skin cancer: results over a 5 year period using liquid nitrogen spray therapy. *Br J Dermatol* 1988;119:231-40.
- 91 Graham GF, Clark LC. Statistical analysis in cryosurgery of skin cancer. *Clin Dermatol* 1990;8:101-7.
- 92 Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol B* 1990;6:143-8.
- 93 Lui H, Salasche S, Kollias N, Wimberly J, Flotte T, McLean D, et al. Photodynamic therapy of nonmelanoma skin cancer with topical aminolevulinic acid: a clinical and histologic study. *Arch Dermatol* 1995;131:737-8.
- 94 Baptista J, Martinez C, Leite L, Cochito M. Our PDT experience in the treatment of non-melanoma skin cancer over the last 7 years. *J Eur Acad Dermatol Venereol* 2006;20:693-7.
- 95 Calzavara-Pinton PG. Repetitive photodynamic therapy with topical delta-aminolevulinic acid as an appropriate approach to the routine treatment of superficial non-melanoma skin tumours. *J Photochem Photobiol B* 1995;29:53-7.
- 96 Fink-Puches R, Soyer HP, Hofer A, Kerl H, Wolf P. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. *Arch Dermatol* 1998;134:821-6.
- 97 Ziolkowski P, Osiecka BJ, Oremek G, Siewinski M, Symonowicz K, Saleh Y, et al. Enhancement of photodynamic therapy by use of aminolevulinic acid/glycolic acid drug mixture. *J Exp Ther Oncol* 2004;4:121-9.
- 98 Calzavara-Pinton PG, Venturini M, Sala R, Capezzer A, Parrinello G, Specchia C, et al. Methylaminolevulinic acid-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. *Br J Dermatol* 2008;159:137-44.
- 99 Haddad R, Neshet E, Weiss J, Skornick Y, Kashtan H. Photodynamic therapy for Bowen's disease and squamous cell carcinoma of the skin. *Photodiagnosis Photodyn Ther* 2004;1:225-30.
- 100 Fritsch C, Goerz G, Ruzicka T. Photodynamic therapy in dermatology. *Arch Dermatol* 1998;134:2007-214.
- 101 Harth Y, Hirshowitz B, Kaplan B. Modified topical photodynamic therapy of superficial skin tumors, utilizing aminolevulinic acid, penetration enhancers, red light, and hyperthermia. *Dermatol Surg* 1998;24:723-6.
- 102 Pennington RG, Waner M, Knox A. Photodynamic therapy for multiple skin cancers. *Plast Reconstr Surg* 1988;82:1067-1071.
- 103 Wolf P, Rieger E, Kerl H. Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid. An alternative treatment modality for solar keratoses, superficial squamous cell carcinomas, and basal cell carcinomas? [Published erratum appears in *J Am Acad Dermatol* 1993;29:41.] *J Am Acad Dermatol* 1993;28:17-21.
- 104 Feyh J, Goetz A, Muller W, Konigsberger R, Kastenbauer E. Photodynamic therapy in head and neck surgery. *J Photochem Photobiol B* 1990;7:353-8.
- 105 Kubler AC, Haase T, Staff C, Kahle B, Rheinwald M, Muhling J. Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck. *Lasers Surg Med* 1999;25:60-8.
- 106 Chren MM, Linos E, Torres JS, Stuart SE, Parvataneni R, Boscardin J. Tumor recurrence 5 years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol* 2013;133:1188-96.
- 107 Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD, et al. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. *Dermatol Surg* 2009;35:574-85.
- 108 Gibbons E, Casanas ICC, Fitzpatrick R. A structured review of patient-reported outcome measures for patients with skin cancer. 2013. *Br J Dermatol* 2013;168:1176-86.
- 109 Bates AS, Davis CR, Takwale A, Kneip GJ. Patient-reported outcome measures in nonmelanoma skin cancer of the face: a systematic review. *Br J Dermatol* 2013;168:1187-94.
- 110 Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol* 2011;65:263-79.

- 111 Dinehart SM, Pollack SV. Metastases from squamous cell carcinoma of the skin and lip. An analysis of twenty-seven cases. *J Am Acad Dermatol* 1989;21:241-8.
- 112 Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Derm* 1992;26:976-90.
- 113 Brougham NDLS, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. *J Surg Oncol* 2012;106:811-5.
- 114 Higgins JPT, Green S, eds. Cochrane Handbook of systematic reviews of interventions. Version 5.1.0. 2011. www.cochrane-handbook.org/.
- 115 Moses LE. The series of consecutive cases as a device for assessing outcomes of intervention. *N Engl J Med* 1984;311:705-10.
- 116 Abel U. Erkenntnisgewinn mittels nichtrandomisierter therapiestudien—gaining understanding through nonrandomized therapeutic studies. *Ellipse* 1999;15:48-58.
- 117 Jenicek M, ed. Clinical case reporting in evidence-based medicine. 2nd ed. Arnold, 2001.
- 118 Albrecht J, Meves A, Bigby M. A survey of case reports and case series of therapeutic interventions in the Archives of Dermatology. *Int J Dermatol* 2009;48:592-7.
- 119 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging manual. 7th ed. NYL Springer, 2010.
- 120 Breuninger H, Brantsch K, Eigentler T, Hafner HM. [Comparison and evaluation of the current staging of cutaneous carcinomas] [German]. *J Dtsch Dermatol Ges* 2012;10:579-86.
- 121 Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, Hwang WT, Gelfand JM, Whalen FM, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol* 2013;149:402-10.
- 122 Buethe D, Warner C, Miedler J, Cockerell CJ. Focus issue on squamous cell carcinoma: practical concerns regarding the 7th edition AJCC staging guidelines. *J Skin Cancer* 2011, doi:10.1155/2011/156391.

Accepted: 11 September 2013

Cite this as: *BMJ* 2013;347:f6153

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>.

Tables

Table 1 | Recurrence and death after surgical excision

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	
Ang 2004 (n=50)	Various	Mean 71.1 months (range 28-109)	—	—	—	0.00 (0.00 to 0.07)	—	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
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)	—	0.00 (0.00 to 0.1)	Perineural invasion (8%), orbital invasion (6%)
Fitzpatrick 1985 (n=21)	Eyelids	Not specified	0.05 (0.00 to 0.24)	—	—	—	—	Diameter <2 cm (62%), >2 cm (38%); median duration 52 weeks
Friedman 1984 (n=63)	Trunk and extremities	Non-recurrent group: mean 7.5 years; recurrent group: minimum 5 years	—	—	—	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 I (30%), II (60%), III (10%)
Griffiths 2002 (n=86)	All	Minimum 5 years	0.00 (0.00 to 0.04)	—	—	—	0.08 (0.03 to 0.16)	Median thickness 3.1 mm; mean diameter 13 mm (surviving patients) v 20 mm (patients who died of disease), immunocompromised (3.2%)
Knox 1967 (n=211)	Various	>1 year	—	—	0.00 (0.00 to 0.03)	—	—	Diameter <2 cm (80%), >2 cm (20%)
Mourouzis 2009 (n=194)	Head and neck	30-60 months	—	0.05 (0.02 to 0.09)	—	—	—	Diameter <2 cm (63%), 2-4 cm (33.8%), >4cm (3.2%); histology grade: well/moderately differentiated (78.2%), poorly differentiated (21.8%); perineural invasion (2.3%); perivascular invasion (0.5%)
Nemet 2006 (n=68)	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 <10 mm to >40 mm
Rank 1973 (n=288)	All	2 years	0.01 (0.00 to 0.04)	—	—	—	—	Not specified
Reifler 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 (28.8%), >4 cm (3.8%); invasion of cartilage (21.1%)
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 mean 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	
Yoon 1992 (n=13)	External ear	6 months to 20 years	—	—	—	0.62 (0.32 to 0.86)	—	Stages 0 (5%), I (37.5%), II (32.5%), III (5%), IV (10%); unknown (10%)

SD=standard deviation.

*Percentages indicate proportion of patients in study.

Table 2| Incomplete excision of SCCs after surgical excision

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 6.02mm; 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%), 2-4 cm (33.8%), >4 cm (3.2%); differentiation: well (78.2%), poor (21.8%); perineural invasion (2.3%), 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%), >2 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	Proportion with outcome (95% CI)					Prognostic features*
			Local recurrence	Regional recurrence	Distant metastases	Unspecified recurrence	Patient died of disease	
Anderson 1982 (n=8)	Eyelid	Average 36 months (range 1-57)	0.00 (0.00 to 0.37)	0.12 (0.00 to 0.53)	0.12 (0.00 to 0.53)	—	0.12 (0.00 to 0.53)	No details
Brantsch 2008 (n=615)	All	Mean 43 months (range 1-165)	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%)
Cherpel 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 (range 1-136)	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 <1 cm (25.6%), 1-1.9 cm (46.2%), 2-2.9 cm (15.4%), 3-3.9 cm (6.6%), 4-4.9 cm (2.3%), 5-5.9 cm (1%), 6-7.9 cm (0.5%), 8-10 cm (0.1%); differentiation: well (34.8%), moderate (36.4%), poor (6%); acantholytic (10.4%)
Malhotra 2004 (n=56)	Periocular	Mean 77.3 months	0.04 (0.00 to 0.12)	—	—	—	—	Diameter 0-0.9 cm (57%), 1-1.9 cm (38%), 2-2.9 cm (5%); perineural invasion (4.3%)
Mohs 1976 (n=615)	Various	Up to 5 years	—	—	—	0.01 (0.00 to 0.02)	—	No 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 cm ²
Skaria 2010 (n=54)	Not specified	Mean 59.6 months	—	—	—	0.02 (0.00 to 0.10)	—	No data
Thomas 2007 (n=66)	Various	Mean 45 months	—	—	—	0.04 (0.01 to 0.13)	—	Mean size 3.9 cm ²
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 (37.2%), 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)	—	—	—	No 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	Proportion with outcome (95%CI)				Prognostic features*
				Local recurrence	Regional recurrence	Unspecified recurrence	Patient died of disease	
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	0.03 (0.01 to 0.06)	—	—	—	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 cm ² ; 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, 8-15 daily fractions	Average 44 months (range 12-136)	—	—	0.11 (0.02 to 0.30)	0.08 (0.01 to 0.25)	Mean duration 26 months (range 1-186)
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 7425-7980 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 cm ³ , 175 cm ³ , 341 cm ³ ; 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	2 years	0.03 (0.01 to 0.06)	—	—	—	No data
Shiffman 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)
Stoll 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)	Tumour 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.

Table 5| Local recurrence of SCCs after brachytherapy

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 ¹⁹² Ir 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 mm ³ (16-6300 mm ³); differentiation: well (84%), moderate (16%)	Retrospective
Guix 2000 (n=18)	Facial	High dose rate custom made ¹⁹² Ir 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 (5.8%); lymphatic invasion (14.7%)	Prospective
Lee 1997 (n=3)	Scalp, neck, face	¹⁶⁶ Ho 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 ¹⁹² Ir 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 (n=11)	Any	High dose rate ¹⁹² Ir 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 cm ²	Prospective

*Percentages indicate proportion of SCCs in study.

Table 6 | Studies using adjuvant radiotherapy with surgery to treat previously untreated SCCs that were non-metastatic at presentation

Study and No of SCCs	Reasons for adjuvant radiotherapy	Surgical treatment	Site of adjuvant radiotherapy (local/regional)	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
DeAmbrosio 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
Lifeso 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, I ² , No of patients			
	Local recurrence	Regional recurrence	Distant metastases	Patient died from disease
Adjuvant radiotherapy for perineural invasion ⁷¹⁻⁷⁵	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 ^{20,76-78}	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
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 time	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/cm ² ; total dose 100 J/cm ²	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 100mW/cm ² ; total dose 60-80 J/cm ²	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/cm ² at irradiance of 86 mW/cm ²	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/cm ²	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; 80mW/cm ² for superficial SCCs up to 150 mW/cm ² for nodular and exulcerated SCCs; total dose 96-180 J/cm ²	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/cm ²	1-3 treatments	Mean diameter 1.4±0.8 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/cm ² and near infrared (1.25-1.6 mm) at 50 mW/cm ² 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/cm ² for 3.5-30 min; total dose 15-150 mW/cm ²	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/cm ² ; total dose 100 J/cm ²	1 treatment	Diameter >5 mm
Wolf 1993 (n=6)	Topical 20% ALA oil in water, 4-8 h	Unfiltered light at 100 mW/cm ² for 15 min or red light at 100 mW/cm ² for 30 min; total dose 90 J/cm ²	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/cm ² ; total dose 85-87.6 J/cm ²	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 h before photodynamic therapy; dose not specified	630nm laser light at 100 mw/cm ² ; dose 100 J/cm ²	—	All tumour stage T1
Kubler 1999 (n=9)	mTHPC at 0.15mg/kg, intravenous, 96 h before photodynamic therapy	652 nm red light at 100 mW/cm ² ; total dose 20 J/cm ²	—	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/cm ²	—	Estimated maximal thickness <1 cm

ALA=aminolevulinic acid; MAL=methylaminolevulinic acid; EDTA=ethylenediaminetetraacetic acid; DMSO=dimethyl sulfoxide; mTHPC=meta-tetrahydroxyphenylchlorin.

*Percentages indicate proportion of SCCs in study.

†"Superficial" not defined.

Table 11| Initial response and recurrence of SCCs after photodynamic therapy

Study	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
Topical photosensitiser						
Baptista 2006	4	1 month	0.25 (0.01 to 0.80)	0.00 (0.00 to 0.98), n=1	Median 38 months	—
Calzavara-Pinton 1995	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	40 microinvasive, 31 invasive	3 months	0.8 (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	35	2-4 weeks	0.54 (0.37 to 0.71)	0.69 (0.41 to 0.89), n=16	Median 8 months (range 3-47)	—
Fritsch 1998	36	Not specified	0.75 (0.58 to 0.88)	—	—	—
Haddad 2004	43	21 days	0.74 (0.59 to 0.86)	—	—	—
Harth 1998	5	Not specified	0.8 (0.28 to 0.99)	—	—	—
Kennedy 1990	2 "elevated," 6 "early invasive"	2-3 months	0.00 (0.00 to 0.84), 1.0 (0.54 to 1.0)	—	—	—
Lui 1995	2	3 months	0.00 (0.00 to 0.84)	—	—	—
Wolf 1993	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)	—
Ziolkowski 2004	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
Systemic photosensitiser						
Feyh 1990	5	2 months	1.0 (0.48 to 1.0)	0.00 (0.00 to 0.52), n=5	Maximum 14 months	—
Kubler 1999	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	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

Fig13 Unspecified recurrence of SCCs after Mohs micrographic surgery

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

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 electrodesiccation

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