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

CRD summary
The authors concluded that evidence on squamous cell carcinoma of the skin was extremely limited. Accurate comparisons of treatment effects was not possible, and the significance of apparent differences between treatments should be interpreted cautiously. The authors acknowledged the poor quality of the evidence and their recommendation for cautious interpretation of the treatment comparisons seems appropriate.

Authors' objectives
To assess the effectiveness of treatments for non-metastatic squamous cell carcinoma of the skin.

Searching
MEDLINE and EMBASE were searched up to December 2012 for publications in English. The search strategy was available as a separate online appendix. Reference lists of included studies and relevant reviews were manually searched.

Study selection
Eligible for inclusion were observational studies that assessed the effectiveness of interventions for primary, previously untreated, non-metastatic, invasive, squamous cell carcinoma of the skin in adults (18 years or older). Studies that used a surgical intervention were required to include more than 20 participants. Studies of complementary therapies were excluded. Primary outcomes were recurrence (local, regional, distant) of squamous cell carcinoma during follow-up, and quality of life. Secondary outcomes were initial response to treatment, adverse events, cosmetic appearance, or death due to disease.

The included studies were published from 1964 to 2012. Some studies included all disease sites while others were in specific areas of the body (such as head and neck). Interventions included: various types/regimens of surgical excision; external radiotherapy; brachytherapy; radiotherapy plus surgery; curettage and electrodesiccation; cryotherapy; and photodynamic therapy. Other interventions with less robust evidence (such as laser therapy, topical imiquimod, 5-fluorouracil, interferon, retinoids, cetuximab, and combination systemic treatments) were also reported in the review, but will not be discussed here further. Participants differed in prognostic factors and overall disease severity; definitions for some outcomes may have differed between studies.

Three reviewers independently screened studies for inclusion; discrepancies were resolved through consensus.

Assessment of study quality
Two reviewers independently assessed study quality based on bias associated with completeness of outcome data, selection of participants, and study design. Studies were considered poor quality (with a score of 0 to 3), intermediate (4 to 7), or good quality (8 to 10). Discrepancies between reviewers were resolved through consensus or referral to a third reviewer.

Data extraction
The number of outcome events were extracted to calculate proportions of events (%) and their variances.

Two reviewers independently extracted data; discrepancies were resolved through referral to a third reviewer.

Methods of synthesis
A meta-analysis using a random-effects model was used to pool proportions of outcome events and their 95% confidence intervals by type of intervention and type of outcome. Statistical heterogeneity was assessed using I².

Subgroup analysis was performed based on mean follow-up (under two years; two to five years; over five years).
Sensitivity analysis was conducted based on studies meeting three specified criteria (as reported in the review).

Adverse events were described narratively, where reported.

Results of the review

One hundred and eighteen studies were included in the review; 106 were non-comparative studies and 12 were single case reports. Just over half the studies (56%) were considered intermediate quality, 13% were poor quality, and 30% high quality. Follow-up duration ranged from four weeks up to 20 years (where reported).

**Surgical excision:** The pooled local recurrence rate after surgical excision was 5.4% (95% CI 2.5 to 9.1; 12 studies), but there was evidence of significant heterogeneity ($I^2=81\%$). Local recurrence rates were highest in the ear region after surgical excision (14.1%, 95% CI 10.2 to 18.5; three studies; $I^2=0\%$). The pooled average number of deaths attributable to disease after surgical excision was 4.1% (95% CI 1.7 to 7.6; eight studies; $I^2=58\%$).

**Mohs micrographic surgery:** The pooled cure rate at five years was 97.4% (95% CI 96.2 to 98.3; 16 studies; $I^2=48\%$). The pooled average local recurrence rate after Mohs micrographic surgery was 3.0% (95% CI 2.2 to 3.9; 10 studies; $I^2=0\%$), and recurrence in regional lymph nodes was 4.2% (95% CI 2.3 to 6.6; six studies; $I^2=56\%$). The pooled average number of deaths attributable to disease was 1.1% (95% CI 0.2 to 2.6; four studies; $I^2=49\%$).

**External radiotherapy:** The pooled local recurrence rate after external radiotherapy was 6.4% (95% CI 3.0 to 11.0; seven studies; $I^2=76\%$). Regional lymph node failure was 2.6% (95% CI 0.04 to 8.9; three studies; $I^2=70\%$). The pooled average number of deaths attributable to disease was 9.1% (95% CI 1.4 to 22.8; five studies; $I^2=79\%$).

**Brachytherapy:** The average local recurrence rate after brachytherapy was 5.2% (95% CI 1.6 to 10.5; six studies; $I^2=0\%$). None of the studies reported on deaths attributable to disease.

**Radiotherapy plus surgery:** The average local recurrence rate after treatment for perineural invasion was 18.2% (95% CI 3.8 to 39.8; five studies; $I^2=37\%$) and for other types of carcinoma was 11.1% (95% CI 2.4 to 25.0; four studies; $I^2=35\%$). The average number of deaths due to disease was 11.1% (95% CI 0.4 to 33.1; $I^2=45\%$) for perineural invasion, and 13.9% (95% CI 0.05 to 50.2; $I^2=74\%$) for other types of carcinoma.

**Curettage and electrodesiccation:** Recurrence (not specified) after curettage and electrodesiccation was 1.7% (95% CI 0.6 to 3.4; eight studies; $I^2=59\%$).

**Cryotherapy:** The average recurrence of disease after cryotherapy was 0.8% (95% CI 0.1 to 2.2; eight studies; $I^2=0\%$).

**Photodynamic therapy:** The average proportion of participants having complete response to treatment was 72.0% (95% CI 66.9 to 76.8% - figures taken from forest plot; 18 study arms; $I^2=71\%$) using a fixed-effect model. The pooled recurrence rate in participants who had completely responded initially to photodynamic therapy was 26.0% (95% CI 12.0 to 44.0 - figures taken from forest plot; 10 study arms; $I^2=72\%$).

Other findings (including distant and unspecified recurrence rates) and findings from subgroup and sensitivity analyses were reported in the review.

Authors’ conclusions

The evidence base for squamous cell carcinoma of the skin was extremely limited. Accurate comparisons of treatment effects was not possible, and the significance of apparent differences between treatments should be interpreted cautiously.

**CRD commentary**

The review question and supporting inclusion criteria were broadly defined. The literature search was limited by language and attempts did not appear to have been made to locate unpublished data, which meant that potentially relevant data may have been missed. Each stage of the review was conducted independently by several reviewers, which minimised the potential for reviewer error and bias.

Study quality was assessed, but ultimately most studies were non-comparative retrospective observational studies which
would have inherent limitations. There were considerable differences between studies in participant and study characteristics, and this was reflected in the high levels of heterogeneity for some outcomes. A fixed-effect model appears to have been used to combine studies for photodynamic therapy, which did not seem appropriate given the high heterogeneity reported. Otherwise, use of a random-effects model seemed appropriate. The authors acknowledged the small sample sizes for some outcomes, and stated that caution was needed when comparing outcomes after different treatments. Confidence intervals were wide for some findings, which reduced the robustness of the results. In addition, the included studies were published over a wide time span, during which treatment methods would have changed.

The authors' acknowledged the limitations of the evidence and their recommendation for cautious interpretation of treatment comparisons seems appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that photodynamic therapy could not be recommended for the treatment of squamous cell carcinoma of the skin.

**Research:** The authors stated that there was a need for well-designed comparative studies to help stratify patients by risk factors, and optimise their clinical management.

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