Evidence-based review of the use of cryosurgery in treatment of basal cell carcinoma

Kokoszka A, Scheinfeld N

CRD summary
This review assessed cryosurgery for basal cell carcinoma (BCC). The authors concluded that cryosurgery is an effective treatment for BCC, but there were insufficient data to compare it with other treatments. The evidence was limited by high drop-out rates in the included studies and unexplained variability in the recurrence rates among studies. Hence, the conclusions may not be reliable.

Authors' objectives
To assess the efficacy of cryosurgery in the treatment of basal cell carcinoma (BCC).

Searching
MEDLINE (from 1966), EMBASE (from 1980) and Cancerlit (from 1983) were searched to 2001; the keywords were stated. The Cochrane Database of Systematic Reviews was also searched, and the reference lists in reports, reviews, textbooks and guidelines were checked. Only reports of studies published in the English language were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and non-controlled prospective studies were eligible for inclusion. Retrospective studies and case reports were excluded.

Specific interventions included in the review
Studies of cryosurgery were eligible for inclusion. The included controlled studies compared cryosurgery (two cycles) with aminolevulinic acid photodynamic therapy (ALA-PDT), surgical excision (direct surgery, transposition flaps, or full-thickness graft) or radiation (5 to 10 treatments over 5 to 12 days), or compared one freeze-thaw cycle with two cycles of cryosurgery. Lesions were curetted before cryosurgery in some, but not all of the included studies, while some studies did not provide such details.

Participants included in the review
Studies of patients with BCC were eligible for inclusion. In the included controlled studies, BCC was diagnosed histologically or clinically. Most of the included studies excluded patients with recurrent or morpheaform type BCC, although some studies gave no information on the histological type of BCC. Most of the controlled studies only included lesions of less than 1.5 to less than 2 cm in diameter, and lesions were located in various sites (anywhere, anywhere except the nose or ear, or only on head, neck or face). Lesions in non-controlled studies ranged in size from less than 1 cm to less than 10 cm, and were located in various sites (anywhere, or only on the eyelid, external ear or nose).

Outcomes assessed in the review
Studies that assessed recurrence rate or cosmetic appearance were eligible for inclusion. One of the controlled studies assessed recurrence rates histologically, while the other studies assessed recurrence clinically. In one of the included controlled studies, cosmetic appearance was assessed by the patient and five professionals using Likert Scales. The included studies assessed the outcomes for a minimum of 10 months to a maximum of 13 years.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was not formally assessed, although it was discussed in the text with respect to the appropriateness of data used...
for analysis and the duration of follow-up. The level of evidence provided by each study was scored according to the criteria described by Sackett (Grade A, B or C). The authors did not state who scored the studies.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the recurrence rates were presented for each treatment arm.

**Methods of synthesis**
How were the studies combined?
The studies were grouped according to study design (RCT or prospective non-controlled study). The RCTs were described in the text, while the results from prospective studies were summarised in a table.

How were differences between studies investigated?
Differences between the studies were discussed with respect to type of BCC, sample size, duration of follow-up, cointerventions and year of study.

**Results of the review**
Four RCTs (361 patients) and 13 non-controlled prospective studies (5,846 patients) were included.

All the included controlled studies scored C using Sackett's criteria, owing to the lack of blinding.

**RCTs.**
One RCT (88 patients, 81 patients analysed) found no significant difference between ALA-PDT and cryosurgery in the recurrence of BCC (diagnosed histologically by punch biopsy) after one year (25% versus 15%, P>0.05). It found that ALA-PDT significantly increased the need for re-treatment compared with cryosurgery: 30% (13 out of 44) versus 3% (1 out of 39) (P-value not reported). There were several methodological limitations: the analysis of recurrence did not account for the increased number of repeat treatments required by patients allocated to ALA-PDT, and the short duration of follow-up.

One RCT (96 patients, 48 in each treatment group) found that cryosurgery plus curettage increased recurrence at one year compared with surgical excision (3 out of 48 versus 0 out of 48), but the statistical significance was not reported. The authors found that patients reported better results with excision, but the differences were small: for excision versus cryosurgery, 48 versus 42 patients rated the results as 'good' and 0 versus 6 patients rated the results as 'fair' (P-value not reported). The patients reported no significant difference between treatments on a 10-point visual analogue scale (8.87 versus 7.58). A beautician found no significant difference between treatments in appearance post-treatment, but four clinical professionals rated excision much better than cryosurgery (the data for the beautician and one clinician were reported).

One RCT (84 patients) found that two freeze-thaw cycles reduced recurrence rates in facial BCCs compared with one cycle after follow-up ranging from 10 months to 7 years (4.7% versus 20.6%, P-value not reported on the review).

One RCT (93 patients) found that radiotherapy reduced recurrence at one year compared with cryosurgery: 4% (2 out of 49) versus 39% (17 out of 44) (P-value not reported in the review). Methodological limitations included no details of the type of BCC, and the study was conducted at a time when cryosurgical techniques were evolving.

**Prospective studies.**
The recurrence rates after cryosurgery ranged from 0% (one study with 222 patients followed up for 5 to 10 years; eyelid BCCs, from 0.3 to 3.5 cm in diameter) to 8.2% (one study with 171 patients entered and 84 patients followed up for more than 5 years; BCCs at any site, less than 10 cm in diameter).
Authors' conclusions
Cryosurgery is an effective treatment for BCC. There were insufficient data to compare cryosurgery with other treatments.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and the search terms were stated. Limiting the included studies to those in English might have resulted in the omission of some relevant studies. There was no attempt to locate unpublished studies, thus raising the possibility of publication bias. The methods used to select the studies, assess validity and extract the data were not described; hence, any efforts made to reduce errors and bias cannot be judged. Validity was not formally assessed and only a few aspects of validity were mentioned in the text.

Some information on the RCTs was tabulated, while additional information was presented in the text, but only minimal details of the non-controlled studies were provided. The studies were appropriately grouped by study design and the review correctly focused on the evidence from the RCTs. A narrative synthesis was appropriate given the small number of studies using different comparator interventions.

Some of the recurrence rates obtained from RCTs were reported without P-values or confidence intervals, so the statistical significance of the results was unknown, and it was not always stated whether these statistics were reported in the individual studies. Some of the prospective studies had high drop-out rates (up to 50%), but the influence of this on estimates of recurrence rates following cryosurgery was not mentioned. In addition, some studies only enrolled patients with BCC at specific sites and the results may not generalise to other sites. The recurrence rates in the cryosurgery arm of the RCTs were 6% and 15% after one year, and ranged from 4.2% to 39% after 1 to 7 years. These rates are much higher than those reported for non-controlled trials, but the authors did not discuss this or highlight the variability among controlled studies. In view of this unexplained variability, the evidence on recurrence rates may be limited. Any conclusions about the efficacy of cryosurgery should be treated with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that RCTs are required to compare the efficacy of cryosurgery with other treatments for BCC. They also stated that future studies should assess histological clearance.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.