Radiochemotherapy versus radiotherapy in locally advanced cervical cancer: a meta-analysis

CRD summary
This review found that the combination of radiotherapy with chemotherapy was associated with significant benefits in response rate and survival in women with locally advanced cervical cancer. The lack of clarity about the treatment regimens and lack of information on follow-up mean that the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the efficacy and side effects of chemotherapy plus radiation treatment (radiochemotherapy) compared with radiation treatment alone in patients with locally advanced cervical cancer.

Searching
The Cochrane Library, MEDLINE, EMBASE, Chinese Biomedical Database, Chinese Scientific Journals Full-text Database and Chinese Journals Full-text Database were searched with no language restrictions. Search terms were reported, but search dates were not. References in appropriate retrieved articles were searched to identify additional articles. Experts in the field were contacted by the reviewers to locate other research including unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared radiochemotherapy with radiotherapy in women with primary, previously untreated, confirmed cervical cancer with no evidence of extrahepatic metastases were eligible for inclusion.

Most of the included trials were conducted in China or the USA; the remaining studies were conducted in England, Romania, Chile or Canada. The mean age of included patients ranged from 39 to 56 years. The stages of cancer of the included patients ranged from I to IV. The chemotherapeutic regimens consisted of treatment with cisplatin in all the trials, but one trial alpha-interferon was used. In a few trials, calcium folinate, bleomycin, etoposide, or ifosfamide were used alongside cisplatin. Outcomes assessed included responses rate and survival at three and five years.

Two reviewers independently performed the study selection; any discrepancies were resolved by discussion with a third reviewer.

Assessment of study quality
Three reviewers independently assessed methodological quality by evaluating the performance of data collection, patient selection,blinding and prevention of verification bias, study design and descriptions of the index tests and reference standards. Any discrepancies were resolved by discussions with the other reviewers.

Data extraction
Data were extracted to calculate risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes; 95% confidence intervals (CIs) were calculated for both.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled risk ratios, weighted mean differences (WMDs) or standardised mean differences (SMDs) and 95% confidence intervals for each summary estimate were calculated using a fixed-effect model. $\chi^2$ and $I^2$ were used to evaluate heterogeneity across the results. If significant heterogeneity was present, the results were summarised using a random-effect model.

Publication bias was evaluated using visual appraisal of the funnel plot.
Results of the review
Eighteen RCTs (n=3,517 patients) were included in the review, with sample sizes in the trials ranging from 55 to 566 patients. Randomisation and the reporting of incomplete data outcomes were judged to be adequate in all the included trials. Eleven studies each adequately reported the concealment of allocation and blinding.

There were significant benefits observed in the radiochemotherapy group in response rate (RR 1.17, 95% CI 1.11 to 1.23; 12 trials; n=1,928 patients), three-year survival (RR 1.13, 95% CI 1.04 to 1.24; three RCTs; n=709 patients), and five-year survival (RR 1.22, 95% CI 1.13 to 1.31; eight RCTs; n=1,562 patients) compared with radiotherapy alone. There was no heterogeneity observed across the trials for these outcomes.

The authors stated that there were no significant differences between the radiochemotherapy group and the radiotherapy group for rectitis, cystitis, nausea and vomiting and myelosuppression, but that there were higher incidence rates for gastrointestinal adverse events and leukopenia (data not reported).

There was no evidence of publication bias from the visual appraisal of the funnel plot.

Authors' conclusions
The combination of radiotherapy with chemotherapy was associated with significant benefits in response rate and survival in women with locally advanced cervical cancer.

CRD commentary
The review addressed a clear question. Inclusion criteria for the interventions, participants and study design were defined, but not for the outcomes. Appropriate databases were searched with no language restrictions. There were some attempts to identify unpublished studies. Although the authors did not report the search dates, the included studies were published between 1999 and 2009. Steps were taken by the reviewers to minimise errors and bias in study selection and the assessment of methodological quality, but were not explicitly reported for data extraction.

There was little information provided on the treatment regimens and schedules used in the included trials. In addition, there was a lack of data on adverse events. The authors acknowledged some of the limitations of the review pertaining to the quality of the trials and the inclusion of patients across a narrow range of prognosis. Additionally, although the authors reported on the handling of incomplete data, there was no information provided on the proportions of patients lost to follow-up.

The lack of clarity about the treatment regimens and lack of information on follow-up mean that the reliability of the authors' conclusions is unclear.

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

Research: The authors stated that further well-designed trials were required with larger sample sizes to fully investigate the effects of radiochemotherapy compared to radiation treatment alone, given the poor conduct of some of the included studies in this review and the heterogeneity of treatment regimens used in the review. The authors listed a range of specific recommendations in the review.

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