Effects of different chemotherapy regimens on survival for advanced cervical cancer: systematic review and meta-analysis
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CRD summary
The authors found little evidence for survival benefits of different chemotherapy regimens in women with advanced cervical cancer. However, short-cycle lengths of cisplatin-based regimens, and concurrent chemotherapy and radiotherapy, yielded small benefits. The reliability of these conclusions is unclear, given the uncertain quality and variation within the included trials, and potential methodological flaws in the review process.

Authors' objectives
To assess the effects of different chemotherapy regimens on survival for advanced cervical cancer.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched to 2006. Additional studies were sought through the reference lists of retrieved studies, as well handsearching of journals and cross-referencing authors’ names. Search terms were reported. The search was restricted to journal articles published in English, German, French or Italian.

Study selection
All randomised controlled trials (RCTs) in women comparing advanced cervical cancer chemotherapy plus radiotherapy with radiotherapy alone, or comparing different chemotherapy regimens, were eligible for inclusion in the review. Additionally trials were considered where patients with non-advanced disease were also included, if outcomes could be extracted strictly for those with advanced cervical cancer. RCTs comparing different dosing schemes and schedules of the same agent, or a combination of agents, were acceptable for inclusion, but comparisons were only included if any additional modality of treatment did not systematically differ in the compared arms. RCTs with three or more arms were included if at least two arms addressed an eligible comparison. The primary outcome was median survival.

The included RCTs assessed 52 different chemotherapy regimens; the most frequent regimen was cisplatin monotherapy followed by 5-fluorouracil monotherapy, hydroxyurea monotherapy and adriamycin. Radiation treatment differed between trials; doses ranged from 39 to 65 Gray (Gy).

The authors did not state how the papers were selected for review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Median survival and detailed survival were extracted from the trials. For detailed survival data, the natural logarithm of the relative hazard and its variance were calculated. Estimates from Cox models were used where available, otherwise estimates were imputed from the number of deaths and patients in each arms and the presented log-rank P-value.

Two reviewers independently extracted the data and resolved any disagreements by discussion.

Methods of synthesis
Meta-analyses were performed using a fixed-effect model (when statistical heterogeneity was not significant) or a random-effects model (DerSimonian and Laird when heterogeneity was present). Sensitivity analyses were undertaken on trial dates, regimen type and cycle length and the timing of chemotherapy relative to radiotherapy. Heterogeneity between the trials was investigated using the Q and I² statistics.
Results of the review
A total of 65 trials were included in the review (n=12,233 patients, of which 11,180 patients were considered in survival analyses, sample size range 4 to 926). Fifteen trials used neoadjuvant chemotherapy, 23 trials used concurrent chemotherapy and 27 trials used neither of the two regimens.

Chemotherapy plus radiotherapy versus radiotherapy alone: There were 22 randomised comparisons of chemotherapy plus radiotherapy versus the same radiotherapy alone in advanced cervical cancer where survival date was reported (n=3,837 patients). There was no statistically significant benefit from chemotherapy by either fixed-effect or random-effects models, though there was significant between-study heterogeneity (p=0.04), due mainly to contradictory results in earlier trials. When the analysis was restricted to trials undertaken between 1997 to 2006, the 11 comparisons showed no significant benefit, although there was no evidence of between-study heterogeneity.

Type of regimen: Analysis by regimen showed no survival benefit in trials of platinum monotherapy plus radiotherapy versus radiotherapy alone (three RCTs), nor for combinations of platinum plus non-platinum agents plus radiotherapy versus radiotherapy alone (12 RCTs).

Cycle length: The five trials using cisplatin-based regimens with short length cycles revealed a marginally significant survival benefit (summary relative hazard 0.80, 95% confidence interval (CI): 0.66 to 0.97), although the results were driven by one trial. The 11 trials using platinum-based regimens with longer cycles found a marginally significant deterioration of survival benefit (summary relative hazard 1.18, 95% CI: 1.02 to 1.38). There were low levels of heterogeneity in these analyses.

Timing of chemotherapy in relation to radiotherapy: Twelve trials used neoadjuvant chemotherapy followed by radiotherapy and 10 trials assessed the concurrent administration of chemotherapy with radiotherapy. There was no benefit reported for the neoadjuvant chemotherapy trials and a trend for benefit in the concurrent chemotherapy trials (summary relative hazard 0.85, 95% CI: 0.73 to 1.00) was due to the hydroxyurea trials.

Chemotherapy regimen direct comparison: Three trials (n=743 patients) compared non-platinum-based regimens against a combination of platinum and non-platinum agents (hydroxyurea) yielding superior results for the combination therapy (summary relative hazard 1.57, 95% CI: 1.13 to 2.19), but there was large between-study heterogeneity. Four trials (n=755 patients) compared platinum monotherapy against non-platinum regimens, with nominally better survival noted in the platinum monotherapy patients compared with the non-cisplatin regimens (summary relative hazard 0.74, 95% CI: 0.57 to 0.97), with modest between-study heterogeneity. There was no evidence for any survival differences for comparisons of platinum monotherapy versus platinum combinations with other regimens.

Authors' conclusions
The evidence for survival benefits with chemotherapy in women with advanced cervical cancer was not very encouraging. Small benefits were observed in some trials, especially short-length cycles of cisplatin-based regimens, and concurrent chemoradiotherapy.

CRD commentary
The review addressed a clear question and undertook a comprehensive search for studies. The language restriction suggested that some articles may have been missed and the authors made no apparent attempt to identify unpublished studies. The validity of the included trials was not assessed. Also, there was no assessment of publication bias. The authors made efforts to minimise reviewer bias in some aspects of the review process, but not in all. The absence of reporting on the study selection process and the lack of validity assessment presented a potential threat to the reliability of the findings. The use of meta-analysis was appropriate. Sub-group analyses were undertaken. Heterogeneity between trials was found to be high, but the authors made attempts to minimise its impact. The authors' conclusions reflected the available evidence, but the reliability of these findings is unclear due to uncertain quality and variation within the included trials and potential methodological flaws in the review process.

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