Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis


Authors' objectives
To assess the effect on survival of adding concurrent cisplatin to radiotherapy in cervical cancer.

Searching
MEDLINE, Cancerlit, HealthSTAR, and the Cochrane Library were searched to April 2000. The search terms were provided. The authors also searched the reference lists of papers and review articles, and the proceedings of the 2000 meeting of the American Society of Clinical Oncology, for additional studies. Trials reported as either full papers or abstracts, in English, were considered. The authors contacted the writers of one study, which was available only in abstract form, to gain additional data.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion. Eight randomised trials, with a median follow-up ranging from 36 to 104 months, were included.

Specific interventions included in the review
The intervention of interest was external beam radiotherapy plus concurrently administered cisplatin. Studies comparing this with radiotherapy alone or radiotherapy plus non-cisplatin-based chemotherapy were eligible for inclusion. The authors included studies of cisplatin alone or cisplatin combined with other chemotherapeutic agents. Trials of cisplatin-based neoadjuvant chemotherapy were excluded because the mechanism of action may differ from adjuvant therapy (i.e. debulking mechanism of action in neoadjuvant chemotherapy versus possible additive effect in adjuvant cisplatin plus radiotherapy). The interventions included in the review were:

- radiotherapy plus cisplatin versus radiotherapy alone;
- radiotherapy plus cisplatin, bleomycin and vincristine versus radiotherapy alone;
- radiotherapy plus cisplatin plus 5-fluorouracil (5-FU) versus radiotherapy alone;
- radiotherapy plus cisplatin versus radiotherapy plus hydroxyurea;
- radiotherapy plus cisplatin and 5-FU versus radiotherapy plus hydroxyurea;
- radiotherapy, cisplatin plus hysterectomy versus radiotherapy plus hysterectomy; and
- hysterectomy, pelvic lymphadenectomy, radiotherapy, cisplatin and 5FU versus hysterectomy, pelvic lymphadenectomy and radiotherapy.

The dose of cisplatin ranged from 25 mg/m2 weekly to 70 mg/m2 on one day of a 3-week cycle. The doses used were tabulated in full in the article.

Participants included in the review
Studies of women with cervical cancer were eligible for inclusion in the review. A total of 243 participants had high-risk cervical cancer following surgery (1 study), 369 had bulky stage IB cervical cancer prior to surgery (1 study) and 1,529 had locally advanced disease (6 studies). The authors did not provide details about the participants' ages or other demographic characteristics.
Outcomes assessed in the review
The studies had to report survival data to be eligible for inclusion. The survival rate was measured using the number of patients who had died at the end of each study and the number of patients included in survival analyses. The 4-year death rates, abstracted from survival curves, were also assessed. The secondary outcomes included local recurrence, distant metastases, and grade 3 or 4 acute adverse effects.

How were decisions on the relevance of primary studies made?
Two authors reviewed the papers independently to assess whether they met the inclusion criteria. Any disagreements were resolved by consensus.

Assessment of study quality
The authors did not report a formal method for assessing validity. However, they did discuss the quality of randomisation.

Data extraction
Two authors extracted the data independently and resolved any disagreements by consensus. The data extracted were: the number of patients randomised, disease stage, type of systemic therapy, chemotherapy dose, radiation dose and fractionation, control intervention, median follow-up, completeness of follow-up, number of deaths in each group, and the number of patients included in the survival analysis in each trial.

Methods of synthesis
How were the studies combined?
A meta-analysis of survival data was performed using a random-effects model, and assuming a constant hazard ratio of risks for the groups being compared. The results were expressed as relative risks (RRs) with 95% confidence intervals (CIs).

Six sets of studies were identified for subgroup analysis: women with locally advanced disease; women with high-risk early-stage disease (stages IB and IIA); radiotherapy administered alone as control; hydroxyurea added to radiotherapy for controls; cisplatin given as single agent with radiotherapy; and cisplatin plus 5-FU used with radiotherapy.

How were differences between studies investigated?
The authors reported differences between the studies in their narrative synthesis and assessed heterogeneity statistically (Q-test statistic).

Results of the review
Eight randomised trials (n=2,141) were included.

Survival.
The authors found that adding cisplatin to radiotherapy increased survival over radiotherapy alone.

All women with cervical cancer (8 trials): the RR of death by the end of the study was 0.74 (95% CI: 0.64, 0.86, P<0.05) for concurrent cisplatin versus radiotherapy alone. 'End of study' was not clearly defined in terms of time, although the authors did mention 4-year mortality rates in some calculations. There was no statistically-significant heterogeneity among the study findings for death (Q=9.97, P=0.19).

Locally advanced cervical cancer (6 trials): the RR of death for concurrent cisplatin versus radiotherapy alone was 0.78 (95% CI: 0.67, 0.9, P<0.05).

High-risk early-stage disease (2 trials): the RR of death for concurrent cisplatin versus radiotherapy alone was 0.56 (95% CI: 0.41, 0.77, P<0.05).
Recurrence and metastases.

Seven of the 8 studies reported rates of local recurrence. Six trials found improved local control in the cisplatin group. The data were not pooled for this outcome. Six studies reported the distant metastases rates. All found an improvement in the distant metastatic rates when cisplatin was added to radiotherapy. The data were not pooled for this outcome either.

Adverse effects.

Seven studies reported on the acute adverse effects. The data were not pooled for this outcome. The findings were conflicting. Four trials reported on late complications; none detected a significant increase in late toxicity when cisplatin-based chemotherapy was added to radiotherapy. The data were not pooled for this outcome either.

**Authors' conclusions**

The addition of concurrent cisplatin-based chemotherapy to radiotherapy improves survival for women with cervical cancer over a variety of controls and across different stages of the disease (locally advanced, large stage IB tumours prior to surgery and high-risk disease following surgery).

**CRD commentary**

This review addressed an appropriate research question. The general inclusion and exclusion criteria were clearly specified, and the literature search strategy was reasonably comprehensive. Language bias may be evident as non-English language studies were excluded. The reviewers also excluded unpublished studies, apart from papers available in abstract form. They did not approach other experts or industry for additional studies. This means that some relevant studies may have been excluded from the review.

The authors excluded one trial on the basis of small numbers of evaluable patients. This suggests that they used specific criteria to assess the validity of studies and to select them for inclusion, although they did not report these criteria. This makes it difficult to fully assess the quality of the review.

The authors provided a narrative synthesis, describing features of each study. They acknowledged differences in the treatment schedules, doses and study characteristics that may affect their findings. They also conducted a meta-analysis of survival data, after assessing heterogeneity. This strategy appears appropriate. However, the time points for the reported survival rates were vague. The study period was not specified clearly and the 4-year survival models appear to have been based on 3-year survival data in some instances. Some of the data for the meta-analysis were also extracted from survival curves. It may have been difficult to extract these data accurately from graphs if corresponding figures were not provided in the primary studies. There were limited data on the adverse effects and the available information was sometimes contradictory.

The authors' conclusions appear to be supported by the data presented. However, these findings may need further investigation because the largest randomised trial on this topic had different conclusions to the review. The reviewers answered their original research question but many questions remain unanswered, such as the optimal dose and schedule of concurrent cisplatin and the duration of any survival benefit.

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

Practice: The authors concluded that cisplatin can be administered concurrently with radical radiotherapy in cervical cancer.

Research: The authors did not state any implications for further research, but acknowledged that many questions remain unanswered, such as the role of 5-FU combined with concurrent cisplatin and radiotherapy, the optimal dose and schedule of concurrent cisplatin, and the duration of any survival benefit.

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