

# Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis (Review)

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC)



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[Intervention Review]

# Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC)<sup>1</sup>

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## ABSTRACT

### Background

After a 1999 National Cancer Institute (NCI) clinical alert was issued, chemoradiotherapy has become widely used in treating women with cervical cancer. Two subsequent systematic reviews found that interpretation of the benefits was complicated and some important clinical questions were unanswered.

### Objectives

We initiated a meta-analysis seeking updated individual patient data (IPD) from all randomised controlled trials (RCTs) to assess the effect of chemoradiotherapy on all outcomes. We pre-specified analyses to investigate whether the effect of chemoradiotherapy differed by trial or patient characteristics.

### Search strategy

We supplemented MEDLINE, LILACS and CANCELIT searches with information from trial registers, by handsearching relevant meeting proceedings and by discussion with relevant trialists and organisations. Searches were updated until October 2009.

### Selection criteria

Both published and unpublished trials were eligible for inclusion provided the patients had been randomised between radiotherapy (with or without surgery) versus concomitant chemoradiotherapy (with or without surgery); that the method of randomisation precluded prior knowledge of the treatment to be assigned; and that the trial had completed patient recruitment before the date of the final analyses.

### Data collection and analysis

We carried out a quantitative meta-analysis using updated information from individual patients from all available RCTs. We sought data from all patients randomised in all eligible trials. We obtained updated information on survival, recurrence and date of last follow up. To avoid potential bias, we requested information for all randomised patients, including those who had been excluded from the investigators' original analyses.

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## Main results

Eighteen trials were identified and 15 of these were eligible for inclusion in the main analysis. On the basis of 13 trials that compared chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio (HR) = 0.81,  $P < 0.001$ ). A larger survival benefit was seen for the two further trials in which chemotherapy was administered after chemoradiotherapy. There was a significant survival benefit for both the group of trials that used platinum-based (HR = 0.83,  $P = 0.017$ ) and non-platinum based (HR = 0.77,  $P = 0.009$ ) chemoradiotherapy, but no evidence of a difference in the size of the benefit by radiotherapy or chemotherapy dose or scheduling was seen. Chemoradiotherapy also reduced local and distant recurrence and progression and improved disease-free survival (DFS). There was a suggestion of a difference in the size of the survival benefit with tumour stage, but not across other patient subgroups. Acute haematological and gastro-intestinal toxicity were increased with chemoradiotherapy, but data were too sparse for an analysis of late toxicity.

## Authors' conclusions

These results endorse the recommendations of the NCI alert, but also demonstrate their applicability to all women and a benefit of non-platinum based chemoradiotherapy. Furthermore, although these results suggest an additional benefit from adjuvant chemotherapy this requires testing in RCTs.

## PLAIN LANGUAGE SUMMARY

### Chemoradiotherapy for cervical cancer: results of a meta-analysis

Women with cervical cancer that is too big to be removed by surgery, or has spread to the tissues around the cervix (often called locally advanced cervical cancer) may be treated with radiotherapy (treatment with x-rays). They might also get chemotherapy (drug treatment) alongside radiotherapy. This is called chemoradiotherapy (or chemoradiation). This review brought together 18 randomised controlled trials (RCTs) that were carried out in many countries. The results of the review showed that women who had chemoradiotherapy for cervical cancer were likely to live for longer than women who had just radiotherapy. Five years after being treated, 66 out of every 100 women who received chemoradiotherapy were still alive compared with 60 out of every 100 who just had radiotherapy. Women who received chemoradiotherapy were also less likely to have the cancer come back or spread to other parts of the body. Chemoradiotherapy helped all women, even those with bigger tumours, or tumours that had spread more. Also, the different drugs that had been used in the trials (cisplatin, 5-fluourouracil or mitomycin-C) all helped women to live longer or stop the cancer from coming back or spreading. Some of the short term side effects were worse for women who received chemoradiotherapy. Doctors can usually help women to cope with the short term side effects of their treatment. Unfortunately, there was not enough information to be certain whether the long-term side effects are worse with chemoradiotherapy or not.

The review also seemed to show that women who have extra chemotherapy (after they have had chemoradiotherapy) live longer than those who just have chemoradiotherapy. However, the researchers are less certain about these results and suggest that new RCTs are needed to find out whether giving extra chemotherapy is better for women with cervical cancer, or not.