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# Concomitant hydroxyurea plus radiotherapy versus radiotherapy for carcinoma of the uterine cervix (Review)

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[Intervention Review]

# Concomitant hydroxyurea plus radiotherapy versus radiotherapy for carcinoma of the uterine cervix

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# A B S T R A C T

## Background

A number of randomised studies suggest hydroxyurea given alongside radiotherapy improves survival in patients with locally advanced cervix cancer. Following publication of five large randomised trials in 1999 and 2000 concomitant chemoradiotherapy has become standard treatment for these patients. In two of the studies hydroxyurea was given to patients in both control and experimental arms. The precise role of this orally administered cytotoxic drug is not known.

## Objectives

To assess the effectiveness (survival and toxicity) of concomitant radiation and hydroxyurea compared with radiotherapy alone in treating locally advanced cervix cancer.

## Search methods

We searched the following:
Cochrane Gynaecological Cancer Group's Specialised Register
CENTRAL (Cochrane Library on CD ROM, issue 4, 2002)
MEDLINE (Silver Platter, from 1970 to 2001)
EMBASE (from 1980 to 2001)
CANCERLIT (from 1970 to 2001)
PDQ (search for open and closed trials)
LILACS
Meta-register (ongoing trials)

Searches were not language or publication restricted.
Investigators of relevant trials were contacted for further information.

## Selection criteria

Randomized controlled trials comparing concomitant radiotherapy (± surgery) with hydroxyurea versus radiotherapy (± surgery) for locally advanced cervix cancer.

**Data collection and analysis**

Two authors independently reviewed trials for inclusion and extracted data. Discussions on all aspects of data collection and analysis took place among all the authors at regular intervals.

**Main results**

Seven studies were found to be suitable for inclusion from 33 identified as relevant. None of the trials provided adequate evidence to support the use of hydroxyurea owing to small sample size, large numbers of post-randomisation exclusions and questionable rules for censoring, particularly a failure to include treatment-related deaths in the survival analysis. Details of statistical analysis were limited and often confusing, and we felt meta-analysis would lead to unreliable and invalid conclusions. Most studies appeared to be double blind placebo-controlled studies but none give details of power calculations or reasons for stopping recruitment. Only two studies had more than 50 patients. Patients were excluded from analysis in most trials for treatment-related reasons; in one, less than half those recruited were used in the analysis, the remainder having been excluded because of tumour progression or treatment-related conditions e.g. septicaemia, worsening renal/hepatic function. In another trial five out of 20 in the hydroxyurea group died of treatment-related complications but the five-year survival group was presented as 94%.

**Authors' conclusions**

We found no evidence to support the use of hydroxyurea in addition to radiotherapy in the routine treatment of cervix cancer.

# P L A I N   L A N G U A G E   S U M M A R Y

**This review is not appropriate for update since radiotherapy is now routinely combined with cisplatin and there have been no further studies using hydroxyurea.**

No clear evidence to support using hydroxyurea with radiotherapy for locally advanced cervix cancer

The orally-administered cytotoxic, hydroxyurea, may be given alongside radiotherapy for treating cervix cancer. Eight trials comparing concomitant hydroxyurea and radiotherapy with radiotherapy alone were assessed. They were not of sufficient quality to be able to pool the data. Although several trials reported an improvement in survival for patients receiving hydroxyurea, this conclusion was unreliable owing to methodological problems associated with trials including small sample size, a large number of patients excluded from analysis and questionable methods of analysis such as exclusion of treatment related deaths.

# BACKGROUND

Cervical screening in parts of Europe and North America seems to have been effective in reducing the incidence of cervical cancer and associated mortality (Day 1984; Cook 1984; Devesa 1995). However, on a global scale, it is the second commonest cancer in women and is the most prevalent malignancy in some low-income countries (Pisani 2002) where the disease frequently presents as large tumours of advanced stage (Pisani 1999). Over 80% of patients reported to FIGO (International Federation of Gynaecological Oncology) with invasive cancer were treated by radiotherapy (Benedet 1998).

Management of microinvasive disease is very effective, with cone biopsy or simple hysterectomy for FIGO Stage IA disease giving greater than 95% five-year survival (Cannistra 1996). Most patients with early disease, however, present as stage IA or IIA, and are treated by radical radiotherapy or radical surgery. These are thought to be equally effective, but there is only one recently published randomized trial to support this equivalence (Landoni 1997). For such patients, five-year survival is between 80% and 90% (Eifel 1997).

Radical hysterectomy (removal of the uterus with draining lymph nodes) has become standard management for the majority of early cervical cancers, but radiation therapy has been increasingly employed for bulky Stage IB (more than four centimetres) and Stage II tumours, which account for one third of the incidence but half the relapses, as tumour size has been shown to be an important prognostic variable. By targeting the cervix, paracervix and sites of potential regional spread, radiotherapy using external beam irradiation with a vaginal application of a radioactive source to the cervix (brachytherapy) provides a good chance of cure even in advanced disease, with five-year survival rates of 50% to 80% for stage IIB and 25% to 50% for Stage III (Coia L 1990). There are different brachytherapy techniques that apply the radioactive source for short periods of time or for several days.

Cytotoxic chemotherapy, has been shown to give good response rates in patients with good kidney function and no prior radiation therapy. Cisplatin is the most effective single agent (Omura 1996), and has been shown in cell lines to be synergistic with radiotherapy. Mechanisms underlying the interaction between drugs and radiation may include inhibition of potentially lethal or sublethal damage repair, and increasing radiosensitivity of hypoxic cells (Wallner 1987). It has been widely used prior to surgery or radiotherapy with the aim of reducing tumour volume and facilitating local treatment. It may have the additional benefit of controlling micrometastatic disease. A systematic review and meta-analysis of published randomized controlled trials (RCTs) using cytotoxic chemotherapy prior to radiotherapy, however, found insufficient evidence to demonstrate overall survival benefit, despite significant reduction in tumour volume by chemotherapy (Tierney 1999).

The early side effects of radiotherapy and chemotherapy are well known and usually reversible. However, late chronic effects of radiotherapy on the rectum, urinary tract and vagina, whilst uncommon, can be devastating for the women concerned. The addition of chemotherapy to radiotherapy may increase the incidence of such late chronic toxicities.

A systematic review and meta-analysis of RCTs of concomitant chemoradiotherapy has been carried out (Green 2005). This examined the effects of chemoradiotherapy in terms of survival, progression-free survival, local and distant control, and acute and late toxicity. Based on the data analysed, a potential absolute survival benefit of 12% was attributed to the use of chemoradiotherapy, a figure which could not have been appreciated from individual phase 3 trial data. Despite limitations in the RCTs and their analysis, the authors concluded that the weight of evidence favoured the use of chemoradiotherapy. As the results derived from trials of different populations, using different treatment regimens and supportive care facilities were consistent they are potentially generalisable.

Pre-clinical studies in the 1960s showed that hydroxyurea could increase the effectiveness of radiotherapy (Phillips 1966; Sinclair 1968) and in the 1980s workers at Roswell Park and others carried out a number of trials testing the effectiveness of giving hydroxyurea at the same time as radiation for locally advanced cervical cancer. In these trials radiation alone was compared with concomitant radiation and hydroxyurea (Madoc-Jones 1980; Piver 1983; Piver 1987; Piver 1989). Subsequently GOG trials compared concomitant radiation and hydroxyurea with radiation and radiation sensitisers such as misonidazole (Stehman 1993; Stehman 1988). The conclusions of these trials were that hydroxyurea given with radiation improved the survival of patients with locally advanced cervical cancer in comparison with radiation alone or radiation and misonidazole. Thigpen (Thigpen 1995) has stated that concomitant radiation and hydroxyurea was the standard of care current in the mid 1990s, but even in the USA this treatment has not been widely adopted. More recently there have been trials that have compared concomitant radiation and hydroxyurea with concomitant chemoradiotherapy (Whitney 1999). Most trials have used hydroxyurea over a twelve week period.

This review looks at the evidence that concomitant hydroxyurea can improve the effectiveness of radiotherapy. The aim was to examine the data in the light of the hypothesis that hydroxyurea may be an ineffective but toxic agent when combined with chemotherapy in the treatment of carcinoma of the cervix.

# OBJECTIVES

This systematic review aimed to provide a comprehensive and reliable summary of the effects of using concomitant hydroxyurea and radiation therapy.

The specific aim was to review RCTs, comparing the effectiveness (survival and toxicity) of concomitant radiation and hydroxyurea with radiation alone in the treatment of locally advanced carcinoma of the cervix.

# METHODS

## Criteria for considering studies for this review

### Types of studies

The review was restricted to randomized controlled trials comparing concomitant radiotherapy (± surgery) with hydroxyurea versus radiotherapy (± surgery) alone. This comparison allowed us to investigate the effect of adding hydroxyurea to the standard treatment.

Inclusion criteria are:

- Randomized controlled trials in cancer of the uterine cervix
- Trials accruing patients from January 1970
- Trials comparing hydroxyurea plus radiotherapy (with or without surgery) with radiotherapy (with or without surgery) alone
- Where there were trials with multiple arms, two of which made the above comparison, data were extracted for these arms only

Exclusion criteria were:

- Non-randomized trials
- Trials with less than ten patients in total

### Types of participants

Patients with locally advanced cancer of the uterine cervix (FIGO stage IB to IVA) were included.

### Types of interventions

Concomitant hydroxyurea and radiation therapy compared with the same radiotherapy in the treatment of locally advanced carcinoma of the cervix. Where surgery was allowed, conditions for this had to be the same for two arms of the trial.

### Types of outcome measures

Survival and progression-free survival were the primary endpoints, while patterns of local and distant recurrence were analysed as secondary endpoints. We collected and analysed additional data on the type and severity of acute and late toxicity. Where it was available we collected and analysed data on quality of life.

### Search methods for identification of studies

The following electronic databases were searched:

CENTRAL (Cochrane Library on CD ROM, issue 4, 2002)
MEDLINE (Silver Platter, from 1970 to 2001)
EMBASE (from 1980 to 2001)
CANCERLIT (from 1970 to 2001)
PDQ (search for open and closed trials 2003)
LILACS (2003)

For MEDLINE we developed a search strategy consisting of two parts a) and b):

a) the highly sensitive search strategy (HSSS) for RCTs as described in the Cochrane Handbook for Reviewers (Cochrane Handbook), and

b) a search strategy based on terms relating to the review topic:

#1 hydroxyurea
#2 radiotherap*
#3 radiation
#4 therap*
#5 radiation and therap*
#6 #2 or #5 {all radiotherapy, free text}
#7 #1 and #6 {hydroxyurea and radiotherapy, free text}
#8 cancer*
#9 carcinom*
#10 neoplasm*
#11 tumo?r
#12 #8 or #9 or #10 or #11 {all cancer, free text}
#13 #7 and #12 {hydroxyurea and radiotherapy and cancer, free text}
#14 cervix
#15 uteri*
#16 #14 and #15 {all cervix, free text}
#17 #16 and #13 {hydroxyurea and radiotherapy and cancer and cervix, free text}

For databases other than MEDLINE, the search strategy was adapted accordingly.

From the results of the initial searches, 34 relevant articles were identified and scanned.

The reference lists of the relevant papers found were searched for further studies and the authors of all relevant trials were contacted to give information relating to their participation in any hitherto unpublished trials. Papers in all languages were sought, and translations of papers published in languages other than English were carried out.

All relevant articles found were identified on PubMed, and using the 'related articles' feature, a further search was carried out for newly published articles.

SCISEARCH was used to find which articles are cited most often.

Meta-register and links were searched for ongoing trials.

Owing to the fact that some of the studies were published over 25 years ago and the leading investigator has retired, no attempt was made to contact the authors of the studies published in full or in abstract.

### Data collection and analysis

Two authors (PS & JK) independently reviewed potential trials for inclusion and also attempted to extract the following data. For each trial, we sought information on the method of randomization and allocation concealment, the number of patients randomized, analysed and excluded from the investigator's analyses, follow-up and subsequently, details of the design and analysis of the trial. The distribution of patients by age, stage, histology, grade and performance status was extracted, where available. Data on whether surgery was performed and the type of surgery, dose and fractionation of external beam radiotherapy and of the brachytherapy dose, insertions and dose rate were also collected. Also, the proportion of patients in the research treatment and control arms who completed radiotherapy as planned, did not start radiotherapy, and who experienced delay were extracted. The mode, dose and timing of delivery of hydroxyurea obtained, together with the extent to which the drug was delivered as planned.

Survival and progression-free survival were the primary outcomes, while patterns of local and distant recurrence and acute and late toxicity were the secondary outcomes and data on all these outcomes were extracted from the relevant papers. A formal quantitative meta-analysis was planned, but methodological problems encountered in these studies led the authors to decide that this could lead to unreliable and invalid conclusions.

Therefore, this systematic review is confined to a qualitative summary.

# RESULTS

## Description of studies

Thirty-three apparently relevant citations were identified, of which ten were considered potentially eligible trials. However, two of these were excluded (Stehman 1988; Stehman 1993) because they compared the effects of hydroxyurea plus radiotherapy with another radiosensitiser plus radiotherapy (rather than radiotherapy alone) and another was a review of trials (Stehman 1993a). This left seven trials to be included in the systematic review, five published in full and two published as abstracts.

### Piver 1974

The dates when this study was carried out are not listed. Forty-one women were enrolled into the study. Patients received mega voltage radiotherapy to the pelvis to a dose between 40-50 Gy in 2 Gy fractions followed by supplementary intra-cavity and vaginal radium to boost the A point dose to a total of 85 Gy. Patients randomized to hydroxyurea had a dose of 80mg/kg for three days a week and it was planned to give treatment over 12 weeks.

### Piver 1977

The paper does not list when the study began or ended. One hundred and forty-eight women with stage IIB or IIIB carcinoma of the cervix were recruited, but 41 had been reported previously (Piver 1974). Of these 75 women were surgically staged and the remaining 73 were not, and 130 in total were evaluable. The authors reported that in the patients reported previously (Piver 1974), radiation therapy varied in about one third of patients. Since then two standardised regimens were followed. Stage IIB patients received initial therapy of 50Gy in five weeks to the whole pelvis, followed by 30-40Gy to point A. Stage IIIB patients received 60Gy to the whole pelvis and then 25Gy to point A. However a second randomization to split course or continuous radiation meant that the stage IIIB patients either received this pelvic radiation over eight weeks with a two-week gap in the middle weeks or continuously over six weeks. Hydroxyurea was given at a dose of 80mg/kg three days a week for 12 weeks.

### Hreshchyshyn 1979 (GOG4)

One hundred and ninety women with stage IIIB or IVA carcinoma of cervix were recruited into this study between 25th June 1970 and the 4th June 1976. Patients received at least 50 Gy minimum tumour dose to the whole pelvis by external beam radiation given at 2 Gy a day in five to eight weeks. This was followed by a single brachytherapy treatment to give at least a further 20 Gy to point A. The planned drug schedule for patients randomised to hydroxyurea was a dose of 80mg/kg given three days a week for 12 weeks.

### Madoc-Jones 1980

Madoc-Jones in 1980 reported in abstract form a trial carried out at the Washington University School of Medicine. Hydroxyurea was compared with placebo in patients with stage IIB through IVA carcinoma of cervix. It started in 1974 and by 1980, 41 patients had been entered. No details of the radiation schedule were given,

but every third day or twice a week during radiotherapy, patients randomized to hydroxyurea were given a dose of 80mg/kg.

### Piver 1983

This study was initiated in June 1972 and closed for entry to patients in December 1976. The study included 40 patients with FIGO stage IIB carcinoma of cervix who had undergone paraaortic lymphadenectomy and were found to be without histological evidence of metastasis to the paraaortic lymph node. All patients were followed up for between 5.2 and 9.2 years. Radiation treatment was 50 Gy in five weeks to the pelvis followed by intra-cavity radiation to give a further 35-40 Gy to point A. Patients were randomized to receive either a placebo or hydroxyurea at a dose of 80mg/kg by mouth every three days for 12 weeks.

### Piver 1987

The time period in which this study was carried out is not stated. Forty-five patients were entered into the study of which 40 were evaluable for analysis. All patients had stage IIIB disease and were found to have no tumour in paraaortic nodes after a staging lymphadenectomy. The original plan was to give 60 Gy in 6-weeks to the pelvis. However, 16 patients received 60 Gy in eight weeks with a two-week rest after 30 Gy. Twenty-nine patients received continuous therapy. Mega voltage external beam treatment was followed by intracavity radium to give point A a further 25 Gy. Patients received either hydroxyurea 80mg/kg for three days for up to 12 weeks or a placebo.

### Piver 1989

From July 1971 to April 1986, 27 patients with FIGO stage IIIB disease who refused pre-therapy paraaortic lymphadenectomy or medically were not fit for this procedure were randomized to hydroxyurea and pelvic irradiation or placebo plus pelvic irradiation. The radiation and hydroxyurea treatment schedules were the same as described by Piver in 1987. In this case, nine patients received split course radiation, five in the hydroxyurea group and four in the placebo group.

## Risk of bias in included studies

Many methodological problems were encountered with the reports of these trials.

### Design

Three reports (Piver 1977; Hreshchyshyn 1979; Madoc-Jones 1980) gave no details of the method of randomization or allocation concealment, but two (Hreshchyshyn 1979; Piver 1989) did state they were double blind placebo controlled studies and the other (Madoc-Jones 1980) indicated that the randomisation ratio was 2:1 in favour of hydroxyurea. The three remaining study reports (Piver 1974; Piver 1983; Piver 1987) did give sufficient information to indicate properly concealed double-blind placebo controlled trials. None of the reports included details of how sample size was determined and the five trials randomizing fewer than 50 patients would have been seriously underpowered to detect anything, but a large effect of hydroxyurea of the order of 40% (80% power, p=0.05). Only one report (Piver 1974) gave the reason for stopping the trial and it was because it was realised that a high proportion of stage IIIB patients had paraaortic lymph node metastases and may need more optimal treatment. On reading the manuscripts of the studies

of Piver and his colleagues (Piver 1974; Piver 1977; Piver 1983; Piver 1987; Piver 1989) there is some suggestion of duplicate reporting of certain groups of patients and therefore, it is not at all clear to what extent these are actually discrete randomized trials.

**Post-randomization patient exclusion**

In three studies (Madoc-Jones 1980; Piver 1983; Piver 1987), it appears that no patients were excluded after randomization, although this was not stated explicitly and is suspect in at least one case (Piver 1987). In one study (Piver 1974), three women were reported to be excluded, apparently after randomization, because they had recurrent cancer prior to study entry and one other because she had pelvic exenteration during her radiotherapy. All these women were excluded from the hydroxyurea arm. Eighteen women were excluded from the next reported Roswell Park study (Piver 1977) because of refusing treatment, recurrent disease, metastatic disease, drug toxicity, thrombocytopenic purpura, blood urea levels or pelvic exenteration during radiotherapy. However, the distribution of exclusions by treatment is not clear. Two women in another study were excluded from the placebo group, one because she was stage IIB (rather than IIIB) and one because she had undergone pre-therapy surgical staging (Piver 1989).

The greatest attrition of patients post-randomization was in the largest trial (Hreshchyshyn 1979). Of 190 patients entered, 26 (14%) were excluded for reasons of ineligibility (clerical error, wrong stage, wrong cell type, recurrent at entry benign, BUN elevated), 10 from the hydroxyurea and 16 from the control arm. A further 60 patients (32%) were excluded because they were inevaluable (not double blinded, refused treatment, removed by the investigator, chemotherapy violation, periaortic nodes irradiated, improper radiation dose, long duration of radiotherapy, improper radiation field, inadequate data, surgically explored while on protocol, inadequate pathology). Finally, six patients were excluded from the hydroxyurea arm and one from the control arm for the analyses of survival and progression-free survival, because they were unable to tolerate radiotherapy. Together these exclusions represent around half of the randomized patients and there is an imbalance in the level exclusion by treatment arm (43 versus 50).

**Statistical analyses**

The statistical analyses, as well as the assumptions underlying them were variable, but generally poor across the trial reports. No trial mentioned whether the analyses were by intention-to-treat, but given the exclusions described above, this would not have been possible in at least three trials.

The only outcomes reported in the early Roswell Park studies (Piver 1974; Piver 1977) were acute toxicity and the 'no evidence of disease rate' and the minimum follow-up was two years. The 'no evidence of disease rate' was not explicitly defined, but appears to be a crude measure, which seems to ignore the amount of time disease-free and also, deaths do not appear to have been taken into account, at least in Piver 1974. Despite being a difficult outcome to interpret, the effect of hydroxyurea upon it was analysed overall and by stage. However, the statistical test, estimates of effect and their reliability were not provided for one study (Piver 1974); only p-values were given. Acute toxicity on each arm was described, but not quantitatively compared. In Piver 1977 the chi-squared test and Cochrane test (weighted by surgical staging status) were used in the analysis of this outcome.

Hreshchyshyn 1979 reported acute toxicity, response, progression-free interval, survival and acute toxicity results. Formal comparisons between arms were again overall and by stage, but the statistical tests, estimates of effect and their reliability were not provided for any of the outcomes. Also, there was no indication of extent of follow-up.

The only outcome detailed in the trial published as an abstract (Madoc-Jones 1980) was acute chemotherapy toxicity. The level of follow-up was not described, but it was stated that it was too early in follow-up to assess the effect of hydroxyurea on survival.

In two reports (Piver 1983; Piver 1987) the effects of hydroxyurea on acute toxicity and survival were described. One of these (Piver 1987) also examined recurrence rates and progression-free survival. In both cases acute toxicity rates were formally compared using the Fisher Exact or chi-squared test and details of the test statistics are supplied. In one report (Piver 1983) survival curves appeared to be compared using the Lee-Desu test while in the other (Piver 1987) the more usual logrank test was used. Interestingly the rules for censoring deaths differed between these two trials. In one case (Piver 1983), only those women regarded as dying from cervical cancer were treated as failures and those dying from other causes, despite many treatment related deaths, were censored. The other trial treated any death as a failure (Piver 1987), but only used cervical cancer-specific mortality in the analysis of progression-free survival. In the latter study (Piver 1987), progression-free survival and survival were also analysed by the type of radiotherapy given.

The most recent study by Piver (Piver 1989) focussed on acute toxicity, recurrence rates and the disease-free interval. There was no indication as to the statistics used to compare toxicity across arms and only p values were supplied. The recurrence rates were not formally compared. Disease-free interval curves were generated by the Kaplan Meier method, but there was no indication as to what statistics were used to compare them. In this case, patients who died from causes other than cervix cancer were censored, while patients who died from or with any evidence of disease were treated as failures.

**Effects of interventions**

**Piver 1974**

Treatment outcome was given as the no evidence of disease rate at two years. Six out of 13 patients who were stage IIB in the placebo group were disease free (46.1%) compared to seven out of nine (77.7%) in the hydroxyurea group (p = 0.03). In stage IIIB, only one out of nine of the placebo group was tumour free at two years (11.1%) compared to three out of six (50%) of those treated with hydroxyurea.

Marrow depression was greater in patients treated with hydroxyurea. Eleven out of 15 patients had a white count of less that $2.5 \times 10^9$/l. One patient had died of treatment complications. She died of acute enterocolitis and pancytopenia with a white count of 0.1 and a platelet count of $16 \times 10^9$/l. She had received in total 30 Gy pelvic irradiation. She was considered to be a cancer related death as she did not complete her therapy.

**Piver 1977**

Of the stage IIB patients (without proof of paraaortic metastases) 20/27 (74%) receiving hydroxyurea had no evidence of disease

at two years compared to 17/39 (43.5%) of those who received the placebo (P < 0.01). Those who had not been surgically staged included 12/18 (66%) in the hydroxyurea group and 9/24 (37.5%) in the placebo group who were alive without disease at two years (P < 0.05). Eight of the nine patients given hydroxyurea (88%) and having surgical staging with biopsy negative para-aortic nodes were alive without evidence of disease at two years compared to 8/15 (53%) on placebo (p = 0.17).

Of the women with stage IIIB disease (without proof of paraaortic metastases) 12/23 (52.5%) in the hydroxyurea group had no evidence of disease as compared to 9/27 (33%) receiving placebo (p = 0.22). Of these women only 6/23 (26%) who received split course radiotherapy are alive without evidence of disease at two years compared to 15/27 (55.5%) who received continuous radiotherapy irrespective of whether they received hydroxyurea or not (P < 0.07). Of the 14 patients given hydroxyurea and having surgical staging with biopsy negative paraaortic nodes seven (50%) were alive at two years with no evidence of disease compared to 8/14 (57%) who received placebo. Of these 28 women with surgically staged IIIB disease, 11 received continuous therapy and 10 (90%) are alive with no evidence of disease at two years. This compares to 17 women receiving split course therapy of which only five were alive with no evidence of disease at two years (P = 0.005).

Only 2/13 (15%) of patients with metastasis to the paraaortic nodes who received either hydroxyurea or placebo were alive with no evidence of disease at two years.

The incidence of anaemia in the hydroxyurea group (8/60) and placebo group (7/70) appeared similar as did levels of skin and gastrointestinal complications. However, 47/60 (78%) of women in the hydroxyurea group developed leucopenia compared to only 8/70 (11%) in the placebo group.

## Hreshchyshyn 1979

In total, 104 out 190 women were evaluable for toxicity, 97 for progression free survival and survival. Fifty-one of these received hydroxyurea (42 stage IIIB and nine stage IVA) and 46 received placebo (42 stage IIIB and four stage IVA). Response was assessed in 90 patients. Complete clinical response was seen in 68.1% treated with hydroxyurea and in 48.8% of control patients (p =< 0.05). Progression free survival and survival were also better in the hydroxyurea group. Median progression free survival for hydroxyurea treated patients was 13.6 months with a median overall survival of 19.5 months. Median progression free survival of control patients was 7.6 months with a median overall survival of 10.7 months. Myelosuppression was more prevalent among hydroxyurea patients. No patients treated with radiation alone had grade three or four myelotoxicity compared to seven patients treated with hydroxyurea. All patients however, recovered. Other acute toxicities were compatible between the two groups. The incidence of late toxicity was not given.

## Madoc-Jones 1980

No survival advantage had been observed for patients treated with hydroxyurea. However, the hydroxyurea was not well tolerated. There were 28 patients in the hydroxyurea group. Only one patient completed hydroxyurea as per the protocol (80mg/kg every third day for 12-weeks). Twelve patients had the drug discontinued permanently during the course of treatment because

of gastrointestinal or bone marrow toxicity. Fourteen patients had the dose of the drug reduced during or after radiotherapy and three patients discontinued the drug voluntarily because of toxicity.

## Piver 1983

Five-year actual survival was presented for patients without major treatment protocol violations. The five-year survival for all patients analysed by the methodology outlined by the authors was 94% for the hydroxyurea group compared to 53% in the placebo group (p = 0.006). For patients with no major protocol violations, the five-year survival was 93% for the hydroxyurea group and 47% for the placebo group (p = 0.005). However, if one takes into account treatment related deaths, 16 out of 20 patients in the hydroxyurea group were alive at five years compared to nine out of 20 in the placebo group.

The paper states that patients in each group died of postoperative complications after surgical correction of radiation complications. This variable could not be controlled since many of the surgical procedures were not performed at Roswell Park Memorial Institute. Since there were more radiation complications in the placebo than the hydroxyurea group, deaths from postoperative complications in patients were confirmed at autopsy to be without evidence of persisting cervical cancer. These were not considered to be an adverse effect of hydroxyurea relative to placebo.

Table 1 of the paper lists complications to radiation therapy. There were five complications within the radiation group and eight within the placebo arm although it is not stated how many patients exhibited more than one of these complications. Four patients in the hydroxyurea group died of postoperative complications following surgery for treatment induced complications without evidence of persisting cancer. One patient developed leukaemia and died 84 months after treatment. Leukaemia may be a treatment induced complication. By contrast, only two patients in the placebo group died of treatment related complications.

Eighty per cent (18) of the hydroxyurea group developed a white count of less than $2.5 \times 10^9/l$ compared to only 15% (three) of those who were treated with a placebo. Two of the patients in the hydroxyurea group died of acute infection without evidence of disease (meningitis and pneumonia) but as they occurred at seven and eight months respectively after the start of treatment, they may not be treatment related.

## Piver 1987

The estimated five-year progression free survival for all irradiated patients who received hydroxyurea was 60% and 52% for placebo patients. Paradoxically, the estimated five-year survivals were 43% and 50% respectively for the hydroxyurea and placebo patients treated with any form of radiation treatment. An analysis was carried out on patients who received a split course or non-split course of radiotherapy treatment. In those receiving split course radiotherapy, there were six out of eight recurrences in both patients receiving hydroxyurea and placebo. In those who received no split course, there was only one recurrence out of 12 in those receiving hydroxyurea compared to eight out of 17 of those receiving a placebo. An analysis was carried out of those who received continuous radiation treatment and the five-year survival was 91% in the hydroxyurea compared to 60% in the control group (p = 0.06). There were in total six treatment related deaths in this

study although it is not listed whether they were in the placebo or hydroxyurea group.

Piver 1989

Five-year progression free survival was 54% for the hydroxyurea group and 18% for the placebo group. There were six recurrences out of 14 in the hydroxyurea arm and eight out of 11 in the placebo arm. One patient in the hydroxyurea group and two patients in the placebo arm developed radiation induced complications.

The hydroxyurea trials in this review were carried out over the last several decades and they need to be interpreted in the light of trials of concomitant chemotherapy and radiotherapy which have shown a clear improvement in survival over radiotherapy alone (Green 2005) .

## DISCUSSION

On face value, these trials may seem to show an advantage for adding hydroxyurea to radiation to treat advanced cervical cancer. However, there are major methodological flaws and/or limited information with which to assess the methodology in all the published reports. Most appeared to be double-blind placebo controlled trials, but none gave details of power calculations or reasons for stopping recruitment. With the exception of Piver 1977 and Hreshchyshyn 1979, all the trials recruited less than 50 patients, such that they would only be powered to detect extremely large effects. Nevertheless, some trials also reported analyses based on subsets of patients. For example, with only 40 evaluable patients, one study (Piver 1987) reported a subset analysis by radiotherapy type. Apparently there was an advantage if patients received 60 Gy in six weeks along with hydroxyurea rather than a split course treatment. Many would consider a radiation dose of 60 Gy in six weeks along with brachytherapy above tolerance limits.

The use of randomized allocation can only provide an unbiased comparison of the groups being compared if all randomized patients are followed and analysed according to the treatments initially assigned; an intention-to-treat approach (Altman 1991; Lachin 2000; Schulz 2002). If patients are excluded from analyses for reasons that are related to treatment and outcome, this may bias estimates of the effect of treatment. Patients were excluded on an ad hoc basis from most of the trials and in many cases for treatment-related reasons. This particularly affects the GOG 4 (Hreshchyshyn 1979) trial. One hundred and ninety patients were recruited into this study but 93 were ineligible or unevaluable. Many of the ineligibility criteria were secondary to either tumour progression or treatment toxicity. For instance, patients were excluded from the analysis if they developed a septicaemia or severe infection, severe gastrointestinal symptoms or developed impaired hepatic or renal function. Some of these complications were probably treatment related. Also patients who developed progressive disease during treatment were also excluded. Their exclusion from the analysis will almost undoubtedly have altered the conclusions of the study. Similarly, Piver and colleagues excluded from the analysis deaths from treatment related complications. For instance, in the study of stage II patients published in 1983 at least five patients out of 20 in the hydroxyurea group died of treatment related complications. The five year survival of this group is thus presented somewhat misleadingly as 94%.

In the remaining studies conducted by Piver and colleagues, it is uncertain whether some patients are included in all or some of the analyses as in certain cases the recruitment period of the study is not stated. It seems therefore, that intention to treat analyses were not a feature of any of the trials and makes it difficult to establish the degree of overlap in recruitment between these studies. Moreover, there may have been an element of careful selection of patients for these studies. For instance, it took 15 years to recruit 27 patients who refused pre-therapy para aortic lymphadenectomy or were medically unfit for this procedure and were suffering from FIGO stage IIIB disease (Piver 1989).

Outcome definition could also have influenced the results of the analyses. Although the estimated five year survival of patients treated with hydroxyurea and placebo respectively was 43% and 50%, in the randomized study of surgically staged IIIB patients (Piver 1987) five year progression free survival favoured the hydroxyurea patients. Five-year progression free survival in the hydroxyurea group was 60% compared to 52% in the placebo group. This may because in one analysis all deaths were treated as failures and in the other only cervix cancer related deaths were counted. With such small numbers of patients in most of the trials, the censoring rules employed could bias the analyses of the time to event outcomes. Furthermore, even trials by the same institutes and authors report different outcomes, although it is probable that recurrence and survival outcomes were collected in each case. Selective reporting of outcomes on the basis of the results cannot be ruled out and could further present a biased view of the effect of hydroxyurea.

Even if there is a survival advantage attributable to hydroxyurea, overall survival figures are sometimes poor, for example in the GOG 4 study (Hreshchyshyn 1979). The median progression free survival for patients treated with hydroxyurea was only 13.6 months with a median survival of 19.5 months. The estimated four year survival of this group of patients was only 25% compared to 16% in the control group. Moreover all the published studies show an increase in acute toxicity by adding hydroxyurea to radiation. There is some information to indicate that late toxicity is increased by this drug. In the Piver study of patients with stage IIB disease at least five and possibly seven patients out of 20 died of treatment related complications.

This systematic review has found major deficiencies in seven published randomized controlled trials of hydroxyurea plus radiation in the treatment of cervical cancer. None of the trials provided sufficient evidence to support the use of this drug owing to small sample size, a large number of exclusions post-randomization and questionable rules for censoring, particularly a failure to include treatment related deaths in survival analysis. Details on statistical analyses were limited and often confusing. Also, conclusions in some cases were based on subset analysis of just a few patients. Our conclusion is that hydroxyurea clearly adds to acute toxicity and probably increases serious late complications. This was also shown in Stehman 1993 which reports on a Gynecologic Oncology Group trial (protocol 59), All patients received radiotherapy to the pelvis and para aortic nodes to a dose of 45Gy plus hydroxyurea. Extended field radiation and hydroxyurea were not well tolerated. A second randomization to adjuvant cisplatin or observation was planned. Of 55 eligible patients 30 did not proceed to the randomized part of the trial. There is no convincing evidence of the therapeutic effect of this drug. It is

striking that although this drug is given by mouth and is easy to administer, hydroxyurea has never gained widespread acceptance in the oncological community as the standard therapy along with radiation treatment. This conclusion would support the exclusion of this drug from current or future chemoradiotherapy schedules.

# AUTHORS' CONCLUSIONS

## Implications for practice

This review is not appropriate for update since radiotherapy is now routinely combined with cisplatin and there have been no further studies using hydroxyurea.

This review has found no evidence to support the use of hydroxyurea and radiotherapy in the routine practice for cervical cancer. Concomitant radiotherapy and cisplatin-based chemotherapy is the current standard therapy.

## Implications for research

This review found no evidence supporting further research into combining hydroxyurea with radiotherapy, though we note that some groups continue to explore new approaches to using hydroxyurea with other modalities (Beitler 2002)

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# CHARACTERISTICS OF STUDIES

## Characteristics of included studies [ordered by study ID]

### Hreshchyshyn 1979

| | |
|---|---|
| Methods | Randomized, placebo controlled |
| Participants | n=190, FIGO Stage IIIB or IVA ca cx |
| Interventions | RT - Min TD=50Gy by EBRT, 2Gy daily over 5-8 wks, followed by 1 brachytherapy giving further 20Gy to point A.<br>HU - 80mg/kg 3 d a wk for 12 wks. |
| Outcomes | PFI<br>survival<br>Acute chemotherapy toxicity |
| Notes | no details of randomization or allocation concealment |

**Hreshchyshyn 1979**  *(Continued)*

### *Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

### Madoc-Jones 1980

| | |
|---|---|
| Methods | Randomized (2:1 in favour of HU) placebo controlled |
| Participants | n=41, FIGO stages IIB to IVA ca cx |
| Interventions | RT - no details given<br>HU - 80mg/kg every third d/2 x a wk during RT |
| Outcomes | Acute chemotherapy toxicity |
| Notes | no details of randomization or allocation concealment |

### *Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

### Piver 1974

| | |
|---|---|
| Methods | Randomized, double blind, placebo controlled |
| Participants | n=41 FIGO stage IIB or IIIB ca cx |
| Interventions | RT - 40 - 50Gy EBRT in 2Gy fractions followed by ICR & VR. Point A dose = 85Gy.<br>HU - 80mg/kg 3 x wk over 12 wks |
| Outcomes | Acute chemotherapy toxicity<br>NED rate |
| Notes | Trial stopped as high proportion of 3b pts had PA node mets |

### *Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Low risk | A - Adequate |

### Piver 1977

| | |
|---|---|
| Methods | Randomized, double blind, placebo controlled |
| Participants | n=148 FIGO stage IIB or IIIB ca cx (41 previously reported in Piver 1974) |

**Piver 1977**  *(Continued)*

| | |
|---|---|
| Interventions | RT - 50Gy EBRT in 2Gy fractions over 5 wks followed by 23-40Gy brachytherapy to point A for stage 2b<br>60Gy in 2Gy fractions over 6 wks or in 8wks with 2wks rest mid way followed by 25Gy brachytherapy to points A for stage 3b |
| Outcomes | Acute chemotherapy toxicity<br>NED rate |
| Notes | No details of randomization or allocation concealment |

**Risk of bias**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Piver 1983**

| | |
|---|---|
| Methods | Randomized, placebo controlled |
| Participants | n=40, FIGO stage IIB ca cx, post- PAL |
| Interventions | RT - 50Gy EBRT in 5 wks, followed by ICR to give further 35-40Gy to point A.<br>HU - 80mg/kg orally every 3d for 12 wks. |
| Outcomes | Acute chemotherapy toxicity<br>Survival |
| Notes | FU 5.2 y - 9.2y |

**Risk of bias**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Low risk | A - Adequate |

**Piver 1987**

| | |
|---|---|
| Methods | Randomized, placebo controlled |
| Participants | n=45 (40 evaluable), FIGO stage IIIB, tumour-free PA nodes. |
| Interventions | RT - planned - 60Gy EBRT in 6wks, but 16 received 60Gy in 8wks with 2wks rest mid way. EBRT followed by ICR to give point A further 25Gy.<br>HU - 80mg/kg for 3d per wk up to 12wks. |
| Outcomes | Acute chemotherapy toxicity<br>Survival |
| Notes | |

**Risk of bias**

**Piver 1987** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Low risk | A - Adequate |

**Piver 1989**

| | |
|---|---|
| Methods | Randomized, placebo controlled |
| Participants | n=27, FIGO stage IIIB who refused or were not fit for PAL |
| Interventions | RT - planned - 60Gy EBRT in 6wks, but 9 received split course, 5 in HU group and 4 in placebo group. EBRT followed by ICR to give point A further 25Gy. HU - 80mg/kg 3d per wk for 12 wks. |
| Outcomes | Acute chemotherapy toxicity<br>Recurrence rate<br>DFS |
| Notes | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Low risk | A - Adequate |

RT - radiotherapy
ICR - intra-cavitary radium
VR - vaginal radium
HU - hydroxyurea
ca cx - carcinoma cervix
Min TD - minimum tumour dose
EBRT - external beam radiotherapy
PAL - paraaortic lymphadenectomy
FU - follow up
y - year(s)
d - day(s)
wk - week(s)
pts - patients
mets - metastases
NED - no evidence of disease
DFS - disease free survival
PFI - progression-free interval

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Stehman 1988 | compares misonidazole and hydroxyurea |
| Stehman 1993 | compares misonidazole and hydroxyurea |
| Stehman 1993a | review |

## WHAT'S NEW

| Date | Event | Description |
| --- | --- | --- |
| 11 February 2015 | Amended | Contact details updated. |
| 21 August 2007 | Review declared as stable | This review is not appropriate for update since radiotherapy is now routinely combined with cisplatin and there have been no further studies using hydroxyurea. |

## HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 1, 2004

| Date | Event | Description |
| --- | --- | --- |
| 27 March 2014 | Amended | Contact details updated. |
| 13 October 2008 | Amended | Converted to new review format. |
| 1 March 2006 | New search has been performed | New studies sought but none found. |
| 29 November 2002 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

All authors contributed to all aspects of the protocol

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

**Internal sources**

- Medical Research Council, UK.
- NHS R&D, UK.
- MacMillan Cancer Relief, UK.
- University of Liverpool, UK.
- University of Leicester, UK.

**External sources**

- No sources of support supplied

## NOTES

This review is not appropriate for update since radiotherapy is now routinely combined with cisplatin and there have been no further studies using hydroxyurea.

# INDEX TERMS

## Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Combined Modality Therapy; Hydroxyurea [*therapeutic use]; Randomized Controlled Trials as Topic; Uterine Cervical Neoplasms [*drug therapy] [*radiotherapy]

## MeSH check words

Female; Humans