Published in final edited form as:

Cochrane Database Syst Rev. ; (1): CD006812. doi:10.1002/14651858.CD006812.pub2.

Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

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Abstract

Background—Uterine carcinosarcomas are uncommon with about 35% not confined to the uterus at diagnosis. The survival of patients with advanced uterine carcinosarcoma is poor with pattern of failure indicating greater likelihood of upper abdominal and distant metastatic recurrence.

Objectives—To evaluate the effectiveness and safety of radiotherapy and/or systemic chemotherapy in the management of stage III-IV persistent or recurrent uterine carcinosarcoma.

Search methods—We searched the Cochrane Gynaecological Cancer Group Trials Register, CENTRAL, *The Cochrane Library* 2010, Issue 2, MEDLINE and EMBASE to May 2010. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

Selection criteria—Randomised controlled trials comparing adjuvant radiotherapy and/or chemotherapy in women with uterine carcinosarcoma.

Data collection and analysis—We independently abstracted data and assessed risk of bias. We pooled hazard ratios (HRs) for overall and progression-free survival and risk ratios (RRs) comparing adverse events in women who received radiotherapy and/or chemotherapy in meta-analyses.

Main results—Three trials (579 women, of whom all were assessed at the end of the trials) met the inclusion criteria. Two trials (373 women with stage III-IV persistent or recurrent disease) found that women who received combination therapy had a significantly lower risk of death and

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Editorial group: Cochrane Gynaecological Cancer Group.

Publication status and date: New, published in Issue 1, 2011.

Review content assessed as up-to-date: 7 November 2010.

CONTRIBUTIONS OF AUTHORS

Khadra Galaal is the main author of the review. The protocol was developed by Keith Godfrey. Khadra Galaal and Keith Godfrey sifted references, sought and obtained unpublished data from investigators and prepared the tables. All authors had input in the write up of the review; Khadra Galaal, Raj Naik and Keith Godfrey drafted the clinical sections, Ali Kucukmetin assisted with the clinical sections of the review and Andrew Bryant drafted the methodological and statistical sections.

The authors met regularly to discuss the development of the review.

DECLARATIONS OF INTEREST

None known

disease progression than women who received single agent ifosfamide. There was no statistically significant difference in all reported adverse events, with the exception of nausea and vomiting, which affected significantly more women in the combination therapy group than in the ifosfamide group.

One trial found no statistically significant difference in the risk of death and disease progression in women who received whole abdominal irradiation and chemotherapy, after adjustment for age and FIGO stage (HR = 0.71, 95% CI 0.48 to 1.05 and HR = 0.79, 95% CI 0.53 to 1.18 for overall survival and progression-free survival respectively). There was no statistically significant difference in all reported adverse events, with the exception of haematological and neuropathy morbidities, which affected significantly fewer women in the whole body irradiation group than in the chemotherapy group (RR = 0.02, 95% CI 0.00 to 0.16).

Authors' conclusions—The results of this review are limited to two trials. In the primary treatment/first line therapy of advanced stage metastatic uterine carcinosarcoma, as well as in recurrent disease, adjuvant combination chemotherapy with ifosfamide and paclitaxel should be considered. None of the included studies reported on quality of life.

Medical Subject Headings (MeSH)

Antineoplastic Agents, Alkylating [therapeutic use]; Carcinosarcoma [*drug therapy;*radiotherapy;surgery]; Chemotherapy, Adjuvant [adverse effects; methods]; Ifosfamide [therapeutic use]; Radiotherapy, Adjuvant [adverse effects; methods]; Randomized Controlled Trials as Topic; Uterine Neoplasms [*drug therapy;*radiotherapy;surgery]

MeSH check words

Female; Humans

BACKGROUND

Description of the condition

Uterine carcinosarcomas are uncommon, accounting for 4.3% of all cancers of the uterine corpus in Western Populations (Young 1981). The worldwide annual incidence is between 0.5 and 3.3 cases per 100,000 women (Brooks 2004; Harlow 1986). In the UK the incidence of sarcoma is quoted to be 1 per 100,000 women and of these 87% are carcinosarcomas (Olah 1992). Uterine carcinosarcomas, also called malignant mixed mesodermal tumours (MMT) or malignant mixed mullerian tumours (MMMT) are uncommon tumours with both malignant epithelial and malignant mesenchymal components. Surveillance Epidemiology and End Results (SEER) programme data also demonstrated that carcinosarcoma was the predominant uterine sarcoma (0.82/100,000) followed by leiomyosarcoma (0.64/100,000) and endometrial stromal sarcoma (0.19/100,000) (Harlow 1986).

Uterine carcinosarcomas tend to be aggressive with poor prognosis in comparison to uterine adenocarcinomas (Barwick 1979; Gadducci 2002; Toyoshima 2004). About 35% of carcinosarcomas are not confined to the uterus at diagnosis, and in most reports the median overall survival was about 21 months (Gadducci 2002). The most important prognostic factor is the extent of the tumour at the time of diagnosis, the prognosis being very poor

when the tumour has extended beyond the uterus (Sartori 1997). There has been no significant improvement in survival suggested by some reports (Callister 2004; Chi 1997; Le 2001; Sutton 2000). There is convincing recent evidence that most cases of uterine carcinosarcoma are monoclonal in origin (Szukala 1999; Toyoshima 2004). These data indicate that uterine carcinosarcoma may be metaplastic, with the implication that the sarcomatous components are derived from the carcinomatous elements (McCluggage 2002).

In order to improve survival rates of this aggressive cancer, primary surgical treatment with complete surgical staging and accurate histological diagnosis (pathology) are necessary. In a prospective multi-centre Gynecologic Oncology Group (GOG) study of carcinosarcomas 61 of the 301 patients (20%) with clinical Stage I and II disease were reassigned to pathological Stages III and IV on the basis of lymph node metastases. The study also revealed a recurrence rate of 53% for all carcinosarcomas, with 44% for homologous and 63% for heterologous tumours (Major 1993).

Description of the intervention

As with uterine adenocarcinomas, the mainstay of treatment is surgical removal of the tumour (Menczer 2005), however, the high rates of both local and distant relapse after surgery suggest a need for effective adjuvant therapies (Galaal 2009; Sutton 2000). The survival of patients with advanced uterine carcinosarcoma is poor with a pattern of failure indicating higher likelihood to upper abdominal and distant metastatic recurrence (Spanos 1986). These patients are less likely to benefit from local adjuvant therapy and therefore consideration for systemic adjuvant chemotherapy as well as whole abdominal irradiation has been considered in several studies (Chi 1997; Menczer 2005; Ramondetta 2003; Sutton 1989).

How the intervention might work

Several chemotherapeutic agents have been examined as single agent therapy in uterine carcinosarcoma with response rates as follows: 16% to 19% with adriamycin (Omura 1983), 32% to 36% with ifosfamide (Sutton 1989; Sutton 2000), 19% with cisplatin (Thigpen 2004), and 18% with paclitaxel (Curtin 2001). Doxorubicin, despite being established in the treatment of uterine carcinoma, does not seem to be highly effective in uterine carcinosarcoma (Omura 1983). Combination chemotherapeutic agents have been used in uterine carcinosarcoma with combination therapy appearing to be superior to single-agent treatment in terms of improvement in progression-free and overall survival. However, these combination therapies may be associated with increased toxicity (Homesley 2007; Sutton 2000; Van Rijswijk 1994). Whole abdominal irradiation has been investigated in a retrospective study on early staged uterine carcinosarcoma in the adjuvant setting. This study suggested that the addition of whole abdominal irradiation did not improve survival (Chi 1997).

Why it is important to do this review

Carcinosarcoma is a disease with high recurrence rate (40% to 60%), and tendency to distant metastasis, therefore an effective systemic therapy may improve the outcomes of this disease. Several chemotherapeutic agents have been shown to produce objective response

rates in patients with advanced carcinosarcoma, in addition whole abdominal irradiation has been used in the adjuvant setting (Chi 1997; Ramondetta 2003). These treatment modalities may be associated with some costs in terms of toxicity and quality of life (QoL). Therefore there was a need to assess the effectiveness and safety rigorously.

OBJECTIVES

To evaluate the role of radiotherapy and/or systemic chemotherapy in the management of stage III-IV persistent or recurrent uterine carcinosarcoma.

Specifically we wanted to address the following questions:

- Is adjuvant systemic chemotherapy more effective than adjuvant radiotherapy?
- Is adjuvant systemic combination chemotherapy more effective than single agent chemotherapy?
- Is adjuvant radiotherapy and/or systemic chemotherapy well tolerated?

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

Types of participants—Women of any age with a histological diagnosis of uterine carcinosarcoma of any International Federation of Gynecology and Obstetrics (FIGO) stage (FIGO 2009).

Types of interventions—Surgery followed by radiotherapy and/or systemic chemotherapy. Additionally, we considered any direct comparison between:

- adjuvant radiotherapy or combination chemotherapy
- adjuvant single drug chemotherapy versus combination chemotherapy
- Surgery alone or best supportive care

Types of outcome measures

Primary outcomes: Overall Survival (OS): Survival until death from all causes. Survival was assessed from the time when women were enrolled in the study.

Secondary outcomes

- Progression-free survival (PFS)
- Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
- Grade 3 and 4 chemotherapeutic and radiotherapeutic toxicity, classified according to CTCAE 2006, was extracted and grouped as:

- i. haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
- ii. gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis)
- iii. genitourinary
- iv. skin (stomatitis, mucositis, alopecia, allergy)
- v. neurological (peripheral and central)
- vi. pulmonary

Search methods for identification of studies

Papers in all languages were sought and translations carried out when necessary.

Electronic searches—See: [Cochrane Gynaecological Cancer Group](#) methods used in reviews.

We searched the following electronic databases:

- The Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register
- Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* 2010, Issue 2
- MEDLINE
- EMBASE

The MEDLINE, EMBASE and CENTRAL search strategies based on terms related to the review topic are presented in Appendix 1, Appendix 2 and Appendix 3 respectively.

We searched the databases from January 1966 until May 2010. All relevant articles found were identified on PubMed and using the 'related articles' feature, we conducted a further search for newly published articles.

Searching other resources

Unpublished and Grey literature: We also searched Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials, NHMRC Clinical Trials Register and the UKCCCR Register of Cancer Trials for ongoing trials.

Handsearching: We checked the citation list of relevant publications, abstracts of scientific meetings and list of included studies through hand searching and contacted experts in the field to identify further reports of trials. We hand searched reports of conferences from the following sources:

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologist)

- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society)
- British Journal of Cancer
- British Cancer Research Meeting
- Annual Meeting of the International Gynecologic Cancer Society
- Annual Meeting of the American Society of Gynecologic Oncologist
- British Gynaecological Cancer Society (BGCS)
- Annual Meeting of European Society of Medical Oncology (ESMO)
- Annual Meeting of the American Society of Clinical Oncology (ASCO)
- European Society of Gynecological Cancer (ESGO)
- The [International Society of Gynecological Pathologists](#)

Reference lists: We hand searched the reference lists of all relevant trials obtained by this search for further trials.

Correspondence: We contacted authors of relevant trials to ask if they knew of further data which may or may not have been published.

Data collection and analysis

Selection of studies—All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote, duplicates were removed and the remaining references were examined by two review authors (KG, KG1) independently. These two authors screened titles and abstracts of references identified from the search and eliminated articles that were obviously not relevant to the search question. When both authors determined that the trial was not eligible for inclusion no further action was taken. When one or both of the authors determined that the article may have been eligible for inclusion, we obtained the full text article. Each author then independently determined if these trials were eligible for inclusion. We resolved disagreements about inclusions by discussion. We contacted study authors for further information when papers contained insufficient information to make a decision about eligibility. We were not blinded to article title, authors or journal title.

Data extraction and management—For included trials, we extracted data according to the recommendations in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2008. Two authors extracted data independently and included:

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria

- Study design, methodology
- Study population (participant characteristics, age, stage and postoperative residual disease)
- Number of participants in each arm of the trial
- Total number of intervention groups
- Uterine Carcinosarcoma details (FIGO stage, histology, tumour grade)
- Type of intervention (chemotherapy agents and radiotherapy, dosage and timing of administration relative to surgery)
- Length of follow-up
- Withdrawals from treatment protocol
- Number of participants who experienced delays in treatment or received all, part or none of the proposed treatment
- Risk of bias in study (see below)
- Outcomes: OS, PFS, QoL and adverse events.
 - for each outcome: outcome definition;
 - unit of measurement (if relevant);
 - for scales: upper and lower limits, and whether high or low score is good
 - results: number of participants allocated to each intervention group;
 - for each outcome of interest: sample size; missing participants.

Data on outcomes were extracted as below:

- For time-to-event (overall and progression-free survival) data, we extracted the log of the hazard ratio (log(HR)) and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events), we extracted the number of patients in each group who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).
 - The scales, grades and sites of acute toxicity information were extracted from the trials. The toxicity scales used varied from trial to trial and reporting of toxicity was otherwise inconsistent. Also, the type and severity of side effects will depend on the drugs being used in the individual trials. However, there was some commonality in the types of toxicity documented, namely: nausea and vomiting; diarrhoea/other Gastro Intestinal, leukopenia, thrombocytopenia, anaemia, alopecia, fever/infection, neurological toxicity and renal/GU and in the scales of toxicity used. By analysing the common types, it is possible to get an

indication of the relative levels of serious toxicity associated with chemotherapy regimens and radiation therapy.

We extracted both unadjusted and adjusted statistics, if reported. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in the groups to which they were assigned.

We noted the time points at which outcomes were collected and reported.

Two authors (KG, KG1) abstracted data independently onto a data abstraction form specially designed for the review. Differences between authors were resolved by discussion or by appeal to a third author (AB) when necessary. Where appropriate, we contacted study authors for further information.

Assessment of risk of bias in included studies—The risk of bias in included RCTs was assessed using The Cochrane Collaboration's tool and the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). This included an assessment of:

- sequence generation
- allocation concealment
- blinding (of participants, healthcare providers and outcome assessors)
- incomplete outcome data: We coded a satisfactory level of loss to follow-up for each outcome as:
 - Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
 - No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms
 - Unclear if loss to follow-up was not reported
- selective reporting of outcomes
- other possible sources of bias

The risk of bias tool was applied independently by two authors (KG1, KG) and differences resolved by discussion or by appeal to a third author (AB). Results are presented in the risk of bias table and also in both a risk of bias graph and a risk of bias summary section. Results of meta-analyses were interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect—We used the following measures of the effect of treatment:

- For time-to-event data, we used the hazard ratio (HR), when possible.
- For dichotomous outcomes, we used the risk ratio (RR).

Dealing with missing data—We did not impute missing outcome data; if only imputed data were reported, we contacted study authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity—Heterogeneity between trials was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

Data synthesis—If sufficient, clinically similar studies were available, their results were pooled in meta-analyses. Adjusted summary statistics were used where available; otherwise unadjusted results were used.

- For time-to-event data, we pooled HRs using the generic inverse variance facility of RevMan 5.
- For any dichotomous outcomes, we calculated the RR for each trial and these were then pooled.

We used random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

See Characteristics of included studies; Characteristics of excluded studies

Results of the search

The search strategy identified 445 references in MEDLINE, 745 in EMBASE and 10 in CENTRAL. When the search results were merged into Endnote and duplicates were removed, 895 unique references remained. The title and abstract screening of these references identified 15 trials as potentially eligible for this review. The full text screening of these 15 references excluded 12 for the reasons described in the table Characteristics of excluded studies. The remaining three RCTs (Homesley 2007; Sutton 2000; Wolfson 2007) met our inclusion criteria and are described in the table Characteristics of included studies.

Searches of the grey literature identified one additional relevant ongoing trial (EORTC-55874a).

Included studies

The three included trials (Homesley 2007; Sutton 2000; Wolfson 2007) randomised 579 women, of whom all (100%) were assessed at the end of the trials. Two trials (Homesley 2007; Sutton 2000) reported the comparison of combination chemotherapy versus single agent chemotherapy in the adjuvant setting for advanced or recurrent uterine

carcinosarcoma. Both these trials used ifosfamide as a single agent and in the comparison arm in combination with other chemotherapeutic agents which showed activity in uterine carcinosarcoma, paclitaxel, cisplatin.

The other trial (Wolfson 2007) randomised previously untreated patients with stages I, II, III, and IV primary carcinosarcomas of the uterus or cervix to whole abdominal irradiation (WAI) and combination chemotherapy with Cisplatin and Ifosfamide with Mesna (CIM).

The Homesley 2007 trial

Design: Phase III RCT

Participants: 179 women with histologically confirmed stage III or IV, persistent or recurrent uterine carcinosarcoma not amenable to curative intent by other means. Median age for both arms was 64 years.

Interventions: 91 were randomised to arm 1 (single agent ifosfamide), 18% had stage III, 31% stage IV and 52% had recurrent/persistent disease. 88 were randomised to arm 2 (ifosfamide + paclitaxel), 18% had stage III, 29% had stage IV disease and 52% had recurrent/persistent disease. Because of the reported toxicity when a 5 day schedule of ifosfamide was used (Sutton 2000), a 3 day schedule was used in this trial in both arms.

The trial reported 150 (84%) deaths and 162 (91%) disease recurrences.

The Sutton 2000 trial

Design: Phase III RCT

Participants: This trial looked at 194 women with histologically confirmed advanced or recurrent carcinosarcoma no longer amenable to control by surgery and/or radiotherapy. All patients had to have measurable disease which could be defined in at least two dimensions by palpation or imaging. Median age for arm 1 was 67 years (range 32 to 84), 66 years for arm 2 (range 35 to 83). The two intervention arms were balanced for age, grade, and Gynecologic Oncology Group (GOG) performance status.

Intervention: There were 102 women in arm 1 (ifosfamide) and 92 in arm 2 (ifosfamide + cisplatin). Each patient received 8 cycles of therapy unless there was disease progression or toxicity. The dose of the combination regimen was reduced by 20% early in this trial (1 day) because of toxicity.

Treatment may have contributed to the causes of death in six patients treated with combination chemotherapy, ifosfamide and cisplatin. All six patients received full-dose cisplatin and ifosfamide during the early portion of the study; none had received prior radiotherapy.

The trial reported 175 (90%) deaths and 182 (94%) disease recurrences.

The Wolfson 2007 trial

Design: Phase III RCT

Participants: This trial studied 206 women with previously untreated stages I, II, III, and IV primary carcinosarcomas of the uterus or cervix (without any demonstrable parenchymal hepatic involvement or extra-abdominal distant disease). Of the patients randomised to the WAI arm, 43% had stage III, and in the CIM arm 46% had stage III.

Median age in the WAI arm was 68 years and 65 years in the CIM arm.

Interventions: A total of 105 women were randomised to the WAI arm and 101 to the CIM arm.

The trial reported 122 (59%) deaths and 132 (64%) disease recurrences.

Outcomes reported—All three trials reported overall and recurrence-free survival and used appropriate statistical techniques (HRs to correctly allow for censoring). Prognostic factors were adjusted for in the analysis of survival outcomes in each trial.

The HR in Homesley 2007 was adjusted for performance status. The HR in Sutton 2000 was adjusted for performance status. The HR in Wolfson 2007 was adjusted for age and FIGO stage. For the distribution of these factors at baseline for each trial by treatment arm see the table Characteristics of included studies. Grade 3 and 4 severe adverse events (haematological, gastrointestinal, genitourinary, skin, neurological, pulmonary) were reported in all trials.

Excluded studies

We excluded twelve studies after obtaining the full text (see Characteristics of excluded studies). Nine studies (Asbury 1998; Currie 1996; Curtin 2001; Fowler 2002; Miller 2005; Powell 2010; Ramondetta 2003; Resnik 1995; Sutton 1989) reported the results of non-comparative phase II trials, two (Perez 1979; Toyoshima 2004) were retrospective studies and one (Sutton 2005) had no concurrent control group.

Risk of bias in included studies

Two trials (Homesley 2007; Wolfson 2007) were low risk of bias: they satisfied four of the criteria that we used to assess risk of bias. Sutton 2000 was at high risk of bias as it only satisfied two criteria - see Figure 1, Figure 2.

Two trials (Homesley 2007; Wolfson 2007) reported the method of generation of the sequence of random numbers used to allocate women to treatment arms and concealment of this allocation sequence from patients and healthcare professionals involved in the trial. In Sutton 2000 it was unclear whether the method of assigning women to treatment groups was carried out using an adequate method of sequence generation and there was no attempt to conceal the allocation. None of the trials reported whether the patients, healthcare professionals or outcome assessors were blinded. It was highly likely that all trials reported all the outcomes that they assessed, but it was not clear whether any other bias may have

been present. At least 96% of women who were enrolled were assessed at endpoint in all three trials.

Effects of interventions

All meta-analyses pooled data from two of the included trials (Homesley 2007; Sutton 2000), comparing ifosfamide and combination therapy. Wolfson 2007 compared whole body irradiation and chemotherapy in single trial analyses.

Meta-analyses of survival are based on HRs that were adjusted for important prognostic variables.

For dichotomous outcomes, we were unable to estimate a RR for comparison of whole body irradiation and chemotherapy if one or both treatment groups experienced no events, as in Wolfson 2007 for hepatic and neuropathy adverse event outcomes and in Sutton 2000 for cardiovascular adverse events.

Combination therapy versus ifosfamide

Overall survival: (See Analysis 1.1)

Meta-analysis, assessing 373 participants, found that women who received combination therapy had a significantly lower risk of death than women who received ifosfamide, after adjustment for performance status (HR = 0.75, 95% CI 0.60 to 0.94). The percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) is not important ($I^2 = 0\%$).

Progression-free survival: (See Analysis 1.2)

Meta-analysis, assessing 373 participants, found that women who received combination therapy had a significantly lower risk of disease progression than women who received ifosfamide, after adjustment for performance status (HR = 0.72, 95% CI 0.58 to 0.90). The percentage of the variability in effect estimates that is due to heterogeneity rather than to chance is not important ($I^2 = 0\%$).

Adverse events

Severe nausea/vomiting: (See Analysis 1.3)

Meta-analysis, assessing 365 participants, found that women who received combination therapy had a significantly higher risk of severe nausea or vomiting than women who received ifosfamide (RR = 3.08, 95% CI 1.14 to 8.33). The percentage of the variability in effect estimates that is due to heterogeneity rather than to chance is not important ($I^2 = 0\%$).

Diarrhoea and other gastrointestinal morbidities: (See Analysis 1.4)

Meta-analysis, assessing 365 participants, showed no statistically significant difference in the risk of diarrhoea and other gastrointestinal morbidities in women who received combination therapy and those who received ifosfamide (RR = 1.65, 95% CI 0.45 to 6.06).

The percentage of the variability in effect estimates that is due to heterogeneity rather than to chance may represent moderate heterogeneity ($I^2 = 58\%$).

Haematological morbidities: (See Analysis 1.5)

Meta-analysis, assessing 365 participants, showed no statistically significant difference in the risk of haematological morbidity in women who received combination therapy and those who received ifosfamide (RR = 1.56, 95% CI 0.84 to 2.90). The percentage of the variability in effect estimates that is due to heterogeneity rather than to chance may represent substantial heterogeneity ($I^2 = 78\%$).

Genitourinary morbidities: (See Analysis 1.6)

Meta-analysis, assessing 365 participants, showed no statistically significant difference in the risk of genitourinary morbidity in women who received combination therapy and those who received ifosfamide (RR = 1.68, 95% CI 0.54 to 5.18). The percentage of the variability in effect estimates that is due to heterogeneity rather than to chance is not important ($I^2 = 0\%$).

Cardiovascular morbidities: (See Analysis 1.7)

Two trials (Homesley 2007; Sutton 2000), found no statistically significant difference in the risk of cardiovascular morbidity in women who received combination therapy and those who received ifosfamide (RR = 1.02, 95% CI 0.21 to 4.93 in Homesley 2007 and Sutton 2000 reported only three cases of cardiovascular morbidity, which were of woman in the ifosfamide group).

Hepatic morbidities: (See Analysis 1.8)

One trial reported on hepatic toxicity (Homesley 2007); it reported that single agent ifosfamide was associated with less hepatic toxicity. However, there was no statistically significant difference in the risk of hepatic morbidity in women who received combination therapy and those who received ifosfamide (RR = 2.05, 95% CI 0.73 to 5.74).

Neuropathy: (See Analysis 1.9)

Meta-analysis, assessing 365 participants, found that women who received combination therapy had a significantly higher risk of neuropathy than women who received ifosfamide (RR = 1.64, 95% CI 1.02 to 2.62). The percentage of the variability in effect estimates that is due to heterogeneity rather than to chance is not important ($I^2 = 0\%$).

Whole body irradiation versus combination chemotherapy

Overall survival: (see Analysis 2.1)

There was no statistically significant difference in the risk of death in women who received whole body irradiation and chemotherapy, after adjustment for age and FIGO stage (HR = 0.71, 95% CI 0.48 to 1.05).

Progression-free survival: (see Analysis 2.2)

There was no statistically significant difference in the risk of disease progression in women who received whole body irradiation and chemotherapy, after adjustment for age and FIGO stage (HR = 0.79, 95% CI 0.53 to 1.18).

Adverse events**Gastrointestinal morbidities:** (see Analysis 2.3)

There was no statistically significant difference in the risk of gastrointestinal morbidity in women who received whole body irradiation and chemotherapy (RR = 0.92, 95% CI 0.41 to 2.06).

Haematological morbidities: (see Analysis 2.4)

Women who received whole body irradiation after surgery for treatment of uterine carcinosarcoma were associated with significantly less chance of haematological morbidity compared to those who received chemotherapy (RR = 0.09, 95% CI 0.01 to 0.70).

Genitourinary morbidities: (see Analysis 2.5)

There was no statistically significant difference in the risk of genitourinary morbidity in women who received whole body irradiation and chemotherapy (RR = 0.30, 95% CI 0.09 to 1.07).

Cardiovascular morbidities: (see Analysis 2.6)

There was no statistically significant difference in the risk of cardiovascular morbidity in women who received whole body irradiation and chemotherapy (RR = 0.25, 95% CI 0.03 to 2.22).

Hepatic morbidities: There was no statistically significant difference in the risk of hepatic morbidity in women who received whole body irradiation and chemotherapy. The trial reported only two cases of hepatic morbidity, which were of women in the whole body irradiation group.

Neuropathy: Women who received whole body irradiation after surgery for treatment of uterine carcinosarcoma were associated with significantly less chance of neuropathy compared to those who received chemotherapy. The trial reported nine cases of neuropathy morbidity, which were all of women in the chemotherapy group.

DISCUSSION**Summary of main results**

We found three trials, enrolling 579 women, that met our inclusion criteria. Two of these trials (Homesley 2007; Sutton 2000) compared combination chemotherapy and ifosfamide

alone, whereas the other trial (Wolfson 2007) compared whole body irradiation and combination chemotherapy in women with uterine carcinosarcoma.

When we combined the findings from the two similar trials, adjusting for important prognostic factors, we found that the risk of death and disease progression was lower among women who received combination therapy than among women who received ifosfamide alone (HR = 0.75, 95% CI 0.60 to 0.94 and HR = 0.72, 95% CI 0.58 to 0.90 for overall and progression-free survival respectively). Risk of adverse events was not significantly different for most outcomes but the rate of nausea and vomiting was higher in women who received combination therapy (RR = 3.53, 95% CI 1.33, 9.37). However, it is important to note that treatment may have contributed to the causes of death in six patients treated with combination chemotherapy, ifosfamide and cisplatin (Sutton 2000). Four died of granulocytopenic sepsis, a fifth patient developed severe nausea and vomiting, aspirated and died with adequate granulocytes. The sixth patient suffered a haemorrhagic stroke after chemotherapy with a platelet count of 14,000/mL and granulocyte count of 250/mL. All six patients received full-dose cisplatin and ifosfamide during the early portion of the study; none had received prior radiotherapy.

The other trial (Wolfson 2007) found no significant difference between whole abdominal irradiation and combination chemotherapy in terms of overall and progression-free survival, but did seem to suggest that in general whole body irradiation was associated with less morbidity than combination chemotherapy, where haematological and neuropathic morbidities were significantly lower in women who received whole body irradiation compared to those who received combination chemotherapy (RR = 0.02, 95% CI 0.00 to 0.16) for haematological morbidity and all nine women in the trial experiencing neuropathy morbidity were in the chemotherapy group).

The trials had many strengths. They gave HRs which correctly allowed for censoring and they provided information about adverse events. Both trials recruited a satisfactory number of participants and a reasonably large number of events were observed in the two survival outcomes, but the number of women with adverse events was generally low so lacked statistical power to detect a difference.

Overall completeness and applicability of evidence

To date, two RCTs have compared the effect of ifosfamide with combination of ifosfamide and other chemotherapeutic agents. These trials suggested that combination chemotherapy may be better than single agent therapy in the treatment of advanced staged and recurrent uterine carcinosarcoma. The combination of ifosfamide and paclitaxel was associated with significant improvement in overall and progression-free survival. The evidence from a single RCT suggested no benefit of whole abdominal irradiation over combination chemotherapy.

We were unable to report on quality of life as none of the included trials had QoL assessments. Treatment-related morbidity very often degrades the quality of the time that patients live, which is especially important after the completion of treatment for advanced cancer where patients have poor prognosis and will want to enjoy a comfortable standard of

living during their final months. These issues may be addressed with possible modification of treatment plans or current supportive care.

Quality of the evidence

The amount of available evidence does allow robust conclusions for the comparison of combination therapy and ifosfamide, as there is consistency and commonality in the results, but the comparison of whole body irradiation is restricted to single trial analyses.

The reporting of the methodological quality of the trials showed that two trials (Homesley 2007; Wolfson 2007) were at low risk of bias while Sutton 2000 was at high risk of bias as it only satisfied two of the criteria used to assess risk of bias.

All three trials reported a HR which is the best statistic to summarise the difference in risk in two treatment groups over the duration of a trial, when there is “censoring” i.e. the time to death (or disease progression) is unknown for some women as they were still alive (or disease free) at the end of the trial.

The two similar trials (Homesley 2007; Sutton 2000) gave consistent evidence about all outcomes as individual trials were robust to the findings of the meta-analyses, although in some instances point estimates were not necessarily similar. For survival outcomes there is evidence that combination therapy delays death and disease progression compared to single agent ifosfamide, but we are not sure how safe combination therapy is as there were relatively low numbers of adverse events and it was associated with significantly more grade 3 and 4 nausea and vomiting. A substantial number of women experienced disease progression and death, which helps to ensure high quality evidence.

Potential biases in the review process

We have attempted to reduce bias in the review process by performing a comprehensive search, including a thorough search of the grey literature and ensuring that all studies were sifted and data extracted by three authors independently. We also restricted the included studies to RCTs as they provide the strongest level of evidence available.

Two trials (Homesley 2007; Sutton 2000) included women having primary therapy as well as women with recurrent/persistent disease. This is problematic as survival is often meaningful to patients from the time of diagnosis. However, we could only report time from enrolment in the trial and the time from diagnosis to enrolment was unknown.

The greatest threat to the validity of this review is likely to be the possibility of publication bias i.e. studies that did not find the treatment to have been effective may not have been published. We were unable to investigate this possibility in a funnel plot due to the small number of included trials.

Agreements and disagreements with other studies or reviews

To the best of our knowledge this is the first systematic review on the effects of adjuvant treatments for uterine carcinosarcoma. There are many trials other than RCTs studying adjuvant chemotherapeutic agents at present. These phase II trials, observational studies or

non-controlled trials were limited by small participant numbers and methodological limitations. There are several non systematic reviews on uterine sarcomas and/or uterine carcinosarcoma mainly addressing clinicopathological and prognostic factors (Arrastia 1997).

AUTHORS' CONCLUSIONS

Implications for practice

The optimum chemotherapeutic regimen for advanced uterine carcinosarcoma is still to be defined, although our review has provided evidence that combination chemotherapy improves survival. The combination of ifosfamide and paclitaxel was associated with significant improvement in overall and progression-free survival. While the addition of cisplatin to ifosfamide appears to offer a small improvement in progression-free survival over ifosfamide alone; the added toxicity may not justify the use of this combination.

In advanced stage metastatic uterine carcinosarcoma as well as in recurrent disease, adjuvant combination chemotherapy with ifosfamide and paclitaxel should be considered.

Implications for research

There is a need for a trial that randomly assigns women with advanced uterine carcinosarcoma and no prior treatment to receive either ifosfamide and paclitaxel or platinum and paclitaxel.

In addition we need a randomised trial to determine the effectiveness of adjuvant chemotherapy in early stage uterine carcinosarcoma.

Future trials need to clarify which groups of patients would benefit from which treatment by stratifying patients at trial entry for prior therapies, performance status, site of disease and co-morbidity.

QoL and symptom scores should be assessed as well as primary outcomes such as OS and PFS.

We need to determine the best dose of combination chemotherapy with the least adverse effects in advanced uterine carcinosarcoma.

Further studies (phase II trial) should be set up to investigate the use of newer chemotherapeutic agents in uterine carcinosarcoma.

Acknowledgments

We thank Chris Williams for clinical and editorial advice, Jane Hayes for designing the search strategy and Gail Quinn and Clare Jess for their contribution to the editorial process.

Ram Athavale helped design the protocol.

We also thank Katherine Dean for methodological expertise and advice at the protocol stage.

SOURCES OF SUPPORT

Internal sources

- Northern Gynaecological Oncology Centre, UK.

External sources

- Department of Health, UK.

NHS Cochrane Collaboration programme Grant Scheme CPG-506

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Homesley 2007

Methods	Phase III Randomised Controlled Trial
Participants	<p>179 women with histologically confirmed stage III or IV, persistent or recurrent uterine carcinosarcoma not amenable to treatment with curative intent by other means</p> <p>91 were randomised to arm 1 (ifosfamide alone).</p> <p>88 were randomised to arm 2 (ifosfamide + paclitaxel).</p> <p>Median age for both arms was 64 years.</p> <p>In arm 1 (single agent ifosfamide) 18% had stage III, 31% stage IV and 52% had recurrent/persistent disease</p> <p>In arm 2 (ifosfamide+ paclitaxel) 18% had stage III, 29% had stage IV disease and 52% had recurrent/persistent disease</p> <p>All women had measurable disease by palpation or radiologically (X-ray, MRI, CT or USS) with minimum measurement of 1cm</p> <p>Patients had to have adequate bone marrow function with an absolute neutrophil count > 1,500ml/uL, platelets > 100,000 uL, creatinine clearance of > 50ml/min, bilirubin < 1.5× normal, AST < 3× normal and serum albumin > 3g/dL</p> <p>GOG performance status 0, 1 or 2</p> <p>At least 6 weeks must have passed since RT to the site of current measurable disease</p> <p>Exclusion: patients who received prior chemotherapy for uterine carcinosarcoma. Patients with septicaemia, severe infection, acute hepatitis, GI bleed or performance status 3-4. Patients having other invasive malignancies, prior or current evidence of cancer within the last 5 years, or any cancer therapy determined to be a contraindication for the study protocol. History of congestive cardiac failure unstable angina or myocardial infarction in the last 6 months</p>
Interventions	<p>Arm 1: Ifosfamide 2mg/m² intravenously (IV) daily for three days every 21 days for eight cycles. The starting dose was 1.2mg/m² for patients who had received prior radiotherapy (RT). Mesna was administered either IV or orally, the IV administration consisted of 2g during 12 hours beginning 1 minutes before the ifosfamide infusion; for oral administration, the total dose was 4g in three divided doses of 1.33g administered one hour before and eight hours after the ifosfamide infusion for three days</p> <p>Arm 2: Ifosfamide 1.6mg/m² daily for three days (or was reduced to 1.2mg/m² for patients who had received prior radiotherapy. Paclitaxel 135mg/m² during three hours IV was administered on day 1. Mesna was to be administered as per Arm 1. The premedication for paclitaxel was dexamethasone 20mg orally or IV 12 and 6 hours before paclitaxel, diphenhydramine 50mg IV 30 minutes before paclitaxel. patients in both arms were to receive a maximum of eight cycles of protocol therapy unless disease progression or adverse effects prohibited additional treatment</p>
Outcomes	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> Overall survival (OS) was defined as the observed length of life from study entry to death as a result of any cause or, for the living patients, the date of last contact. Progression -free survival (PFS) was the length of time a patient survived from study entry without tumour progression (defined as reappearance or increasing disease) Response to treatment defined as: <ul style="list-style-type: none"> a. Complete response was the disappearance of all gross evidence of disease lasting for at least 4 weeks

- b. Partial response was a reduction of 50% or greater in the bi-dimensional measurement of each lesion sustained for at least 4 weeks
- c. Increasing disease was a 50% or greater increase in any lesion or the appearance of any new lesion (s) within 8 weeks of entry onto the study
- d. Stable disease was any condition not meeting any of the above criteria

Secondary outcomes: Adverse events believed to be related protocol treatment, assessed according to the GOG Common Toxicity Criteria

Notes	<p>The median duration of follow up was 20 months.</p> <p>Overall the response rate (complete + partial response) was 45% in ifosfamide + paclitaxel arm and 29% in ifosfamide only arm. The odds of response stratified by performance status were 2.21 greater in arm 2 ($P = 0.017$).</p> <p>The median overall survival was 13.5 months in the combination arm and 8.4 months in the ifosfamide only arm</p> <p>Median PFS and OS, respectively, for arm 1 compared with arm 2 were 3.6 versus 5.8 months and 8.4 versus 13.5 months, respectively</p> <p>Intention-to-treat principle was applied to the treatment group comparisons of overall survival, progression-free survival and clinical response. A logrank test stratified by performance status was used to test the independence of treatment with PFS and OS</p>
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Random assignment was carried out with equal probability of assignment to each treatment regimen using a balanced block randomisation to balance assigned treatment regimens within strata defined by institution and performance status (0 to 1 or 2)"
Allocation concealment?	Yes	"The treatment assignment was concealed from institution and the patient until telephone registration with verification of eligibility"
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 179/179 (100%) for time-to-event outcomes and 174/179 (97%) for all adverse events outcomes 214 women were randomised, but 35 were found to be ineligible
Free of selective reporting?	Yes	All important survival and adverse event outcomes have been reported. Survival outcomes have been analysed using appropriate statistical techniques to account for censoring
Free of other bias?	Unclear	Insufficient information to assess whether an additional risk of bias exists

Sutton 2000

Methods	Phase III Randomised Controlled Trial "Treatment was randomly allocated in an unblinded fashion without concealment"
Participants	<p>194 women with histologically confirmed advanced or recurrent carcinosarcoma no longer amenable to control by surgery and/or radiotherapy</p> <p>102 were in arm 1 (ifosfamide) and 92 in arm 2 (ifosfamide + cisplatin)</p> <p>Median age for arm 1 was 67 years (range 32 to 84), 66 years for arm 2 (range 35 to 83)</p> <p>Inclusion criteria: All patients had to have measurable disease which could be defined in at least two dimensions by palpation, X-ray, computed tomography, or</p>

ultrasound. White blood count 3000/mcl, platelet count 100,000/mcl, blood urea nitrogen level 30 mg/dL, creatinine 1.5 mg/dL or creatinine clearance 50 ml/min, serum bilirubin 1.5 times normal, SGOT (ALT) 3 times normal, serum albumin 3 g/dL, and a GOG performance status (PS) of 0 to 2 (Karnofsky score 60%)

Exclusion: Patients must have received no prior chemotherapy. Patients with extensive hepatic metastases, acute hepatitis, septicemia, severe infection, or gastrointestinal bleeding were ineligible. Patients with previous or concomitant malignancy other than non-melanoma skin cancer were ineligible

Written informed consent was obtained from all patients prior to study entry, fulfilling all institutional, state, and federal regulations. Slides documenting the primary cancer were submitted for central pathologic review.

Interventions	<p>Arm 1: ifosfamide alone (1.5 g/m²/day) for 5 days with mesna uroprotection, each course given intravenously every 3 weeks. Ifosfamide doses were reduced by 20% to 1.2 g/m²/day in patients who had previous pelvic radiotherapy. Mesna was administered as a continuous infusion in a dose identical to that of ifosfamide. Each patient received eight cycles of therapy unless there was disease progression or undue toxicity. Ifosfamide doses were reduced 20% for grade 4 white blood count or platelet toxicity, grade 3 or 4 hepatic toxicity, or grade 1 renal or neurologic toxicity.</p> <p>Arm 2: Ifosfamide plus cisplatin (20 mg/m²/day) times 5 days. Because of the unexpected toxicity observed early in the trial in patients receiving combination therapy, doses of both drugs were reduced 20% by giving a 4-day instead of 5-day course of therapy</p>
Outcomes	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> Progression-free survival (PFS) was defined as the period of time from randomisation until progression of disease or death, whichever occurred first, or the date of last contact for patients remaining alive and progression-free Overall survival was measured from the date of study entry to the date of death or date of last contact for patients alive at last contact Response to treatment defined as: <ol style="list-style-type: none"> Complete response Partial response Increasing disease Stable disease <p>Adverse effects were graded using standard GOG criteria. Eligible patients receiving at least one course of treatment were included in the assessment of adverse effects</p>
Notes	<p>All eligible patients were included in the analysis of overall and progression-free survival.</p> <p>All causes of death were considered events in overall and progression-free survival analysis This randomised Phase III study was designed to detect an increase in response from 34% to 54% or a 50% increase of 2.8 months in median progression-free survival with 80% power and type I error set at 0.05 for a one-tailed test. Also, detectable with 76% power and type I error set at 0.05 (one-tailed) a 50% increase of 6.2 months in median survival was planned. Final analysis required the observation of 136 deaths for survival and 150 failures for PFS</p> <p>Site of measurable disease appear to be imbalanced between the two treatment arms. 37% of patients on the ifosfamide arm compared to 59% of patients on the combination arm had measurable disease limited to the pelvis</p> <p>The median number of treatment cycles was 4 with 0 to 8 range</p> <p>Treatment may have contributed to the deaths of 6 patients treated with full doses of ifosfamide and cisplatin for 5 days. The proportion of patients responding to ifosfamide alone versus ifosfamide plus cisplatin therapy was 0.36 versus 0.54 overall, 0.47 versus 0.61 for pelvic, 0.21 versus 0.54 for lung, and 0.33 versus 0.40 for "other" metastatic sites of measurable disease</p> <p>The median progression-free survivals for the ifosfamide was 4 months and for the combination arm it was 6 months (relative risk, 0.73; 95% upper confidence limit, 0.94; P = 0.02). There was no statistically significant difference between the two treatment groups with regard to survival</p> <p>The median duration overall survival for arms was 7.6 and 9.4 months, respectively (relative risk, 0.80, 95% upper confidence limit, 1.03; P = 0.07)</p>
Risk of bias	

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported, "Treatment was randomly allocated".
Allocation concealment?	No	"Treatment was randomly allocated ... without concealment".
Blinding? All outcomes	No	"Treatment was randomly allocated in an unblinded fashion".
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 194/194 (100%) for time-to-event outcomes and 191/194 (98%) for all adverse events outcomes. 224 women were randomised, but 30 were found to be ineligible.
Free of selective reporting?	Yes	All important survival and adverse event outcomes have been reported. Survival outcomes have been analysed using appropriate statistical techniques to account for censoring.
Free of other bias?	Unclear	Insufficient information to assess whether an additional risk of bias exists.

Wolfson 2007

Methods	Phase III Randomised Controlled Trial
Participants	<p>232 enrolled in the study 25 were excluded based on review of histology and one patient was excluded due to inappropriate residual disease as determined by GOG Gynecology/oncology committee review. All were previously untreated patients with stages I, II, III, and IV primary carcinosarcomas of the uterus or cervix (without any demonstrable parenchymal hepatic involvement or extra-abdominal distant disease). 206 patients were in the study, 105 were randomised to whole abdominal irradiation (WAI) arm and 101 to Cisplatin, Ifosfamide with Mesna (CIM) arm. 43% of patients randomised to WAI arm had stage III, and 46% in the CIM arm had stage III. Median age for WAI was 68 years and 65 years for CIM arm.</p> <p>Eligibility required a patient to have a TAH, BSO, and maximal resection of all gross intra-abdominal/pelvic disease, including macroscopically involved pelvic and para-aortic nodes, leaving no residual disease any larger than 1 cm. Peritoneal cytology and RPLND were optional if there were no intraoperative clinical manifestations of residual disease within the abdomen and pelvis. Adequate haematologic (WBC 3000/μL, platelets 100,000/μL, and granulocytes 1500/μL), renal (serum creatinine 1.5 mg% or creatinine clearance 50 mL/min), and hepatic (serum bilirubin 1.5$\times$ the institutional value, serum AST 3$\times$ the institutional value, and serum albumin 3) functions were required. In addition, eligible patients were required to have a GOG Performance Status of 0, 1, or 2 and a normal chest X-ray (no other imaging studies were required). Patients who had received prior hormonal manipulation (not evaluated in this study) were also eligible for entry.</p> <p>Exclusion: patients who had a prior history of receiving radiotherapy and/or chemotherapy or who had a concomitant malignancy (other than non-melanoma skin cancer) within 5 years of being diagnosed with uterine CS were ineligible.</p>
Interventions	<p>Arm 1: Whole Abdominal Irradiation (WAI) was to be delivered by external beam radiation therapy (EBRT) to the abdomen and pelvis that involved a minimum beam energy of 4 MV photons and utilised an anterior/posterior (AP) and posterior/anterior (PA) summated technique. The field borders for WAI involved 1 cm margins on the diaphragm superiorly, the inguinal ligament inferiorly, and the lateral aspect of the peritoneal margin laterally. At the outset of this protocol, the whole abdomen was treated to a total dose of 30 Gy at 1 Gy per fraction, two fractions per day, and 5 days each week with a minimum of 6 h between morning and afternoon fractions (hyperfractionation). Due to slow patient accrual, in August of 1996, the dose fractionation schedule was changed to once-daily fractions of 1.5 Gy for 5 days each week to the same total dose to the whole abdomen of 30 Gy WAI.</p> <p>The true pelvis was treated with a boost requiring a four-field "box" set-up that included not only AP/PA beam portals but also opposed lateral fields. The pelvic field borders included the S1/S2 interspace superiorly, the mid-level portion of the</p>

obturator foramen inferiorly, and 1 cm beyond the widest aspect of the true pelvic laterally. At the initiation of this study, the true pelvis as a boost was treated to a total dose of 20 Gy at 1 Gy per fraction, two fractions per day for 5 days each week with the same 6 h time interval between fractions as was initially done for the WAI (cumulative true pelvic dose of 50 Gy). As stated above, the fractionation schedule was also changed in August of 1996 for this portion of radiotherapy to once-daily fractions of 1.8 Gy for 5 days each week to a total dose of 19.8 Gy (cumulative true pelvic dose of 49.8 Gy)

Arm 2: Cisplatin, Ifosfamide with Mesna (CIM) comprised intravenous (IV) cisplatin (20 mg/m²/day ×4 days) that was to be followed by a 1 h IV administration of ifosfamide (1.5g/m²/day IV×4 days) with mesna (120 mg/m² IV bolus over 15 min on day one, followed by 1.5 g/m²/day IV continuous infusion ×4 days beginning with day one) every 3 weeks for three cycles. It was recommended that hydration be maintained by IV administration of 1 L over several hours preferably with either normal or one-half normal saline prior to initiation of chemotherapy in order to maintain urine output of at least 100 mL/h. IV fluid and electrolyte repletion was permitted as medically indicated during the 4-day course of chemotherapy. Cisplatin administration was required prior to ifosfamide therapy and was to be reconstituted at a concentration of approximately 1 mg/mL and infused at a rate of 1 mg/min.

Dose modifications for toxicities of cisplatin and ifosfamide were permitted but not for mesna administration

Protocol therapy was to be started within 8 weeks following initial surgery

Outcomes	The primary outcome measures for assessing treatment efficacy <ul style="list-style-type: none">Death: An individual's survival is assessed from the date she was registered onto the study to the date of death from any cause or, for living patients, the date of last contact.Recurrence rate: The recurrence-free interval was assessed from the date of entry onto the protocol to date when clinically evident disease was observed. Secondary measures: Adverse events of treatment were classified as being either acute or late toxicities. A toxicity that occurred during study therapy was identified as acute, while those that either persisted or developed after completion of treatment were separately identified as late or chronic toxicities	
Notes	After protocol treatment, patients were evaluated every 3 months for the first 2 years and then every 6 months thereafter by a treating physician with CBC, serum creatinine, serum bilirubin, serum AST, and CA-125 level (required prior to study entry). A chest X-ray was required every 6 months following completion of study treatment for the first 2 years and then yearly thereafter The estimated crude probability of recurring within 5 years was 58% (WAI) and 52% (CIM). The estimated crude probability of surviving at least 5 years following diagnosis was approximately 35% for those randomised to WAI vs. 45% for those randomised to CIM The median duration of follow-up for patients alive at last contact was 5 years and 3 months	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"The list of treatment assignments was created by concatenating randomly selected balanced blocks of permuted treatments"
Allocation concealment?	Yes	"The complete list of treatment assignments remained concealed and only the next unas-signed treatment was revealed after each patient was successfully registered onto the study"
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 206/206 (100%) for time-to-event outcomes and 197/206 (96%) for all adverse events outcomes 232 women were randomised, but 26 were found to be ineligible

Free of selective reporting?	Yes	All important survival and adverse event outcomes have been reported. Survival outcomes have been analysed using appropriate statistical techniques to account for censoring
Free of other bias?	Unclear	Insufficient information to assess whether an additional risk of bias exists

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Asbury 1998	A phase II trial of amonafide in patients with mixed mesodermal tumours of the uterus. Amonafide-a drug that acts through intercalation of tumour DNA-was used to treat 16 patients who had measurable, advanced mixed mesodermal tumours of the uterus. The starting dose was 300 mg/m ² intravenously over 1 hour for 5 consecutive days every 3 weeks Outcome: This dose schedule was associated with poor response rate and substantial toxicity No comparison group
Currie 1996	Phase II trial of hydroxyurea, dacarbazine (DTIC), and etoposide (VP-16) Outcome: Hydroxyurea, dacarbazine (DTIC), and etoposide (VP-16) shows moderate activity in patients with advanced or recurrent carcinosarcoma No comparison group
Curtin 2001	Phase II study of paclitaxel in patients with advanced or recurrent uterine carcinosarcoma who failed to respond to local therapy Outcome: Overall paclitaxel shows 18.2% response rate in patients with uterine carcinosarcoma No comparison group
Fowler 2002	a Phase II group-wide study of the Gynecologic Oncology Group to determine the toxicity and objective response rate of trimetrexate (TMTX) in patients with advanced, persistent, or recurrent mixed mesodermal tumours of the uterus Outcome: Oral TMTX has insignificant activity in uterine carcinosarcoma No comparison group
Miller 2005	Phase II trial of topotecan at a target dose of 1.5 mg/m ² was administered IV daily for 5 days, every 3 weeks, in persistent or recurrent carcinosarcoma of uterus Outcome: Topotecan at this dose and schedule does not appear to have major activity in patients with advanced or recurrent uterinecarcinosarcoma previously treated with chemotherapy No comparison group
Perez 1979	Retrospective study of 54 patients with uterine carcinosarcoma, patients with stage I-II were treated with surgery alone or pre-operative intracavity irradiation, or combination of pre-operative intracavity irradiation and external irradiation. Patients with stage III-IV were treated with surgery alone or combination of surgery and post operative irradiation or irradiation alone Outcome: Patients with stage I-II treated with pre-operative irradiation showed reduced pelvic recurrence rate. None of patients with stage III-IV survived
Powell 2010	Retrospective study of 46 eligible patients with advanced stage (III or IV), persistent or recurrent uterine carcinosarcoma (Malignant mixed Mullerian tumour) and no prior chemotherapy. Patients received paclitaxel at 175 mg/m ² intravenously (IV) over 3 hours plus carboplatin IV over 30 minutes every 3 weeks until disease progression or adverse effects occurred No comparison group
Ramondetta 2003	A phase II trial of cisplatin, ifosfamide, and mesna in patients with advanced or recurrent uterine carcinosarcoma Outcome: None of the patients had complete response, there was partial response in two and stable disease in one patient. Partial response duration was 6 and 9 months No comparison group
Reed 2008	This is a randomised, multicenter study Patients with completely resected, stage I or II, high-grade uterine sarcoma treated with adjuvant pelvic radiotherapy vs observation alone. There were 103 leiomyosarcomas (LMS), 91 carcinosarcomas (CS) and 28 endometrial stromal sarcomas (ESS). Patients were randomised to either observation or pelvic radiation, 51 Gy in 28 fractions over 5 weeks Outcome: median survival of 8.53 years in the radiotherapy arm as opposed to 6.78 years in the observation arm with a hazard ratio of 1.02 (95% CI = 0.68 to 1.53; P = 0.923) Study on early stage uterine sarcoma

Study	Reason for exclusion
Resnik 1995	Phase II study of Etoposide, Cisplatin, and Doxorubicin Chemotherapy in Mixed Mullerian Tumors (MMT) of the uterus, in 54 patients, 23 with early stage I-II, and 19 with stage III-IV Outcome: median survival was 18 months No comparison group
Sutton 1989	Phase II trial of ifosfamide and mesna in mixed mesodermal tumours of the uterus Outcome: Response rate of 32% with 17.9% showing complete response No comparison group
Sutton 2005	Study on adjuvant ifosfamide and cisplatin after primary surgery for stage I or II carcinosarcoma of the uterus. Ifosfamide was given at 1.5g/m ² I.V, 20mg/m ² cisplatin, followed by 120mg/m ² mesna for five days every 21 day for 3 cycles Outcome: Two years progression-free survival was 69% and overall survival was 82%. The five year overall survival was 62% No comparison group
Toyoshima 2004	A retrospective review of six patients with uterine carcinosarcoma treated with paclitaxel and carboplatin Outcome: Four patients had complete response and two had progressive disease. Median progression-free survival was 18 months, median overall survival was 25 months No comparison group

DATA AND ANALYSES

Comparison 1 Combination therapy versus Ifosfamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2	373	Hazard Ratio (Random, 95% CI)	0.75 [0.60, 0.94]
2 Progression-free survival	2	373	Hazard Ratio (Random, 95% CI)	0.72 [0.58, 0.90]
3 G3-4 Nausea/vomiting	2	365	Risk Ratio (IV, Random, 95% CI)	3.53 [1.33, 9.37]
4 Diarrhoea and other GI	2	365	Risk Ratio (IV, Random, 95% CI)	1.51 [0.31, 7.52]
5 Haematological	2	365	Risk Ratio (IV, Random, 95% CI)	1.56 [0.84, 2.90]
6 Genitourinary	2	365	Risk Ratio (IV, Random, 95% CI)	1.68 [0.54, 5.18]
7 Cardiovascular	2	365	Risk Ratio (IV, Random, 95% CI)	0.63 [0.13, 3.11]
8 Hepatic	1	174	Risk Ratio (IV, Random, 95% CI)	2.05 [0.73, 5.74]
9 Neuropathy	2	365	Risk Ratio (IV, Random, 95% CI)	1.59 [0.99, 2.55]

Comparison 2 Whole body irradiation versus chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
2 Progression-free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
3 G3-4 Gastrointestinal	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Haematological	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5 Genitourinary	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6 Cardiovascular	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7 Hepatic	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8 Neuropathy	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1

Comparison 1 Combination therapy versus Ifosfamide, Outcome 1 Overall survival

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 1 Overall survival

Analysis 1.2

Comparison 1 Combination therapy versus Ifosfamide, Outcome 2 Progression-free survival

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 2 Progression-free survival

Analysis 1.3

Comparison 1 Combination therapy versus Ifosfamide,

Outcome 3 G3-4 Nausea/vomiting

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 3 G3-4 Nausea/vomiting

Analysis 1.4

Comparison 1 Combination therapy versus Ifosfamide,

Outcome 4 Diarrhoea and other GI

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 4 Diarrhoea and other GI

Analysis 1.5

Comparison 1 Combination therapy versus Ifosfamide,

Outcome 5 Haematological

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 5 Haematological

Analysis 1.6

Comparison 1 Combination therapy versus Ifosfamide,

Outcome 6 Genitourinary

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 6 Genitourinary

Analysis 1.7

Comparison 1 Combination therapy versus Ifosfamide,

Outcome 7 Cardiovascular

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 7 Cardiovascular

Analysis 1.8

Comparison 1 Combination therapy versus Ifosfamide,

Outcome 8 Hepatic

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 8 Hepatic

Analysis 1.9

Comparison 1 Combination therapy versus Ifosfamide,

Outcome 9 Neuropathy

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 1 Combination therapy versus Ifosfamide

Outcome: 9 Neuropathy

Analysis 2.1

Comparison 2 Whole body irradiation versus

chemotherapy, Outcome 1 Overall survival

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 1 Overall survival

Analysis 2.2

Comparison 2 Whole body irradiation versus chemotherapy, Outcome 2 Progression-free survival

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 2 Progression-free survival

Analysis 2.3

Comparison 2 Whole body irradiation versus chemotherapy, Outcome 3 G3-4 Gastrointestinal

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 3 G3-4 Gastrointestinal

Analysis 2.4

Comparison 2 Whole body irradiation versus chemotherapy, Outcome 4 Haematological

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 4 Haematological

Analysis 2.5

Comparison 2 Whole body irradiation versus chemotherapy, Outcome 5 Genitourinary

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 5 Genitourinary

Analysis 2.6

Comparison 2 Whole body irradiation versus chemotherapy, Outcome 6 Cardiovascular

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 6 Cardiovascular

Analysis 2.7

Comparison 2 Whole body irradiation versus chemotherapy, Outcome 7 Hepatic

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 7 Hepatic

Analysis 2.8

Comparison 2 Whole body irradiation versus chemotherapy, Outcome 8 Neuropathy

Review: Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma

Comparison: 2 Whole body irradiation versus chemotherapy

Outcome: 8 Neuropathy

Appendix 1. Medline search strategy

Medline 1950 to May week 3 2010

1. exp Uterine Neoplasms/
2. (uter* or endometri*).mp.
3. 1 or 2
4. exp Carcinosarcoma/
5. carcinosarcoma*.mp.
6. Mixed Tumor, Mullerian/
7. Mixed Tumor, Mesodermal/
8. (mixed and tumo* and (mullerian or mesodermal)).mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9
11. exp Radiotherapy/
12. radiotherap*.mp.
13. radiation.mp.
14. radiotherapy.fs.
15. 11 or 12 or 13 or 14
16. exp Antineoplastic Agents/
17. Antineoplastic Combined Chemotherapy Protocols/

18. Chemotherapy, Adjuvant/
19. chemotherap*.mp.
20. drug therapy.fs.
21. 16 or 17 or 18 or 19 or 20
22. 15 or 21
23. 10 and 22

key:

mp=title, original title, abstract, name of substance word, subject heading word, unique identifier fs=floating subheading

Appendix 2. Embase search strategy

Embase Ovid 1980 to 2010 wk 20

1. exp uterus cancer/
2. (uter* or endometr*).mp.
3. 1 or 2
4. exp mixed tumor/
5. carcinosarcoma.mp.
6. (mixed and tumo* and (mullerian or mesodermal)).mp.
7. 4 or 5 or 6
8. 3 and 7
9. cancer radiotherapy/
10. exp radiotherapy/
11. radiotherap*.mp.
12. radiation.mp.
13. rt.fs.
14. 9 or 10 or 11 or 12 or 13
15. exp chemotherapy/
16. exp antineoplastic agent/
17. combination chemotherapy/
18. chemotherap*.mp.
19. dt.fs.
20. 15 or 16 or 17 or 18 or 19

21. 14 or 20

22. 8 and 21

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name fs=floating subheading

Appendix 3. Central search strategy

CENTRAL Issue 2 2010

1. MeSH descriptor Uterine Neoplasms explode all trees
2. uter* or endometri*
3. (#1 OR #2)
4. MeSH descriptor Carcinosarcoma explode all trees
5. carcinosarcoma*
6. MeSH descriptor Mixed Tumor, Mullerian explode all trees
7. MeSH descriptor Mixed Tumor, Mesodermal explode all trees
8. mixed and tumo* and (mullerian or mesodermal)
9. (#4 OR #5 OR #6 OR #7 OR #8)
10. (#3 AND #9)
11. MeSH descriptor Radiotherapy explode all trees
12. radiotherap*
13. radiation
14. Any MeSH descriptor with qualifier: RT
15. (#11 OR #12 OR #13 OR #14)
16. MeSH descriptor Antineoplastic Agents explode all trees
17. MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
18. MeSH descriptor Chemotherapy, Adjuvant explode all trees
19. chemotherap*
20. Any MeSH descriptor with qualifier: DT
21. (#16 OR #17 OR #18 OR #19 OR #20)
22. (#15 OR #21)
23. (#10 AND #22)

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 1, 2011

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Searches

In the protocol, we stated:

“The main investigators of any relevant ongoing trials will be contacted for further information, as will any major co-operative trials groups active in this area.”

However, we did not find any relevant ongoing trials or active trials groups, so we did not make these contacts.

Continuous outcome data

Continuous outcome data were not reported in any of the trials so the following sections in the protocol which discussed the handling of data for continuous outcomes were removed as they were unnecessary:

“Data extraction and management

- For continuous outcomes (e.g. quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

Measures of treatment effect

- For continuous outcomes, we will use the mean difference between treatment arms.

Data synthesis

- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled”.

There were also no multiple treatment groups in any of the three included trials and it was not possible to make indirect comparisons so the following methods were removed from the data synthesis section of the review:

“If any trials have multiple treatment groups, the ‘shared’ comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

If possible, indirect comparisons, using the methods of Bucher 1997 will be used to compare competing interventions that have not been compared directly with each other.”

Assessment of reporting biases

Reporting biases were not assessed as there was an insufficient number of included trials in which to compute funnel plots to assess the potential for small study effects such as publication bias so the following was removed from the review:

“Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects such as publication bias. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, further meta-analyses will be performed using fixed effects models.”

Subgroup analysis and investigation of heterogeneity

It was not possible to perform subgroup analysis so the following was removed from the review:

“Sub-group analyses will be performed, grouping the trials by:

- Disease free interval

Factors such as age, stage, length of follow-up, adjusted/unadjusted analysis will be considered in interpretation of any heterogeneity.”

Sensitivity analysis

Sensitivity analyses were not performed as there were an insufficient number of trials in the review. The following was removed from the sensitivity analysis section:

“Sensitivity analyses will be performed excluding trials which did not report (i) concealment of allocation and (ii) blinding of the outcome assessor.”

References to studies included in this review

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- * *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

The addition of chemotherapy and/or radiation treatment after surgery in carcinosarcoma of the womb

Carcinosarcomas of the uterus (womb) are uncommon cancers accounting for 4% of all cancers of the womb. These uncommon cancers have poor prognosis, one of the reasons for the poor survival outcome is the fact that over a third of these cancers (carcinosarcomas) have already spread beyond the womb at the time of diagnosis.

The main treatment is surgery to remove the cancer, however, because of the high rates of both local and distant recurrence after surgery, effective adjuvant therapies are needed. This review has shown that women with high stage disease (stage III-IV persistent or recurrent disease) who received combination chemotherapy with ifosfamide and paclitaxel had lower risk of death and disease progression than women who received ifosfamide alone, after adjustment for performance status.

In addition radiotherapy to the abdomen was not associated with improved survival, as we found in one trial that there was no difference in the risk of death and disease progression in women who received whole abdominal irradiation and chemotherapy, after adjustment for age and stage of disease. Previous studies have shown that doxorubicin despite being established in the treatment of uterine carcinoma, does not seem to be highly effective.

Adverse events were comprehensively reported and showed that more women experienced side effects when they received combination therapy than ifosamide alone and more women experienced side effects when they received chemotherapy than whole body irradiation. The degree to which these treatments affect patients' quality of life remains unknown as quality of life measures were not reported in any of the trials.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Homesley 2007	+	+	?	+	+	?
Sutton 2000	?	-	-	+	+	?
Wolfson 2007	+	+	?	+	+	?

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies