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Exenterative surgery for recurrent gynaecological malignancies

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ABSTRACT

Background

Cancer is a leading cause of death worldwide. Gynaecological cancers (i.e. cancers affecting the ovaries, uterus, cervix, vulva and vagina) are among the most common cancers in women. Unfortunately, given the nature of the disease, cancer can recur or progress in some patients. Although the management of early-stage cancers is relatively straightforward, with lower associated morbidity and mortality, the surgical management of advanced and recurrent cancers (including persistent or progressive cancers) is significantly more complicated, often requiring very extensive procedures. Pelvic exenterative surgery involves removal of some or all of the pelvic organs. Exenterative surgery for persistent or recurrent cancer after initial treatment is difficult and is usually associated with significant perioperative morbidity and mortality. However, it provides women with a chance of cure that otherwise may not be possible. In carefully selected patients, it may also have a place in palliation of symptoms. The biology of recurrent ovarian cancer differs from that of other gynaecological cancers; it is often responsive to chemotherapy and is not included in this review.

Objectives

To evaluate the effectiveness and safety of exenterative surgery versus other treatment modalities for women with recurrent gynaecological cancer, excluding recurrent ovarian cancer (this is covered in a separate review).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE up to February 2013. We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of clinical guidelines and review articles and contacted experts in the field.

Selection criteria

Randomised controlled trials (RCTs) or non-randomised studies with concurrent comparison groups that included multivariate analyses of exenterative surgery versus medical management in women with recurrent gynaecological malignancies.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. No studies were found; therefore no data were analysed.

Main results

The search strategy identified 1311 unique references, of which seven were retrieved in full, as they appeared to be potentially relevant on the basis of title and abstract. However, all were excluded, as they did not meet the inclusion criteria of the review.

Authors' conclusions

We found no evidence to inform decisions about exenterative surgery for women with recurrent cervical, endometrial, vaginal or vulvar malignancies. Ideally, a large RCT or, at the very least, well-designed non-randomised studies that use multivariate analysis to adjust for baseline imbalances are needed to compare exenterative surgery versus medical management, including palliative care.

PLAIN LANGUAGE SUMMARY

Comparison of exenterative surgery versus medical management for women with recurrent gynaecological malignancies

Background

Cancer is a leading cause of death worldwide. Gynaecological cancers (i.e. cancers affecting the ovaries, uterus, cervix, vulva and vagina) are among the most common cancers in women, with a higher incidence in developing countries. Globally, a woman's risk of developing cancer of the cervix, ovaries or uterus by the age of 65 is 2.2%; cancers of the vulva and vagina are less common. The biology of recurrent ovarian cancer differs from that of other gynaecological cancers; it is often responsive to chemotherapy and is not included in this review.

Review question

Unfortunately, in some women with gynaecological cancer, the disease will return (recur) or progress after initial treatment. Cancer recurrence is defined as the return of cancer after treatment and after a period during which the cancer is undetectable. Although the surgical management of early cancers is relatively straightforward, with lower associated morbidity and mortality, the surgical management of advanced and recurrent cancer is significantly more complicated, often requiring very extensive operations. Pelvic exenterative surgery involves removal of some or all of the pelvic organs, including lower bowel (rectum with or without the sigmoid colon and sometimes the anal canal), bladder, reproductive organs (including womb, fallopian tubes, ovaries, vagina and vulva), pelvic peritoneum (the membrane that lines the pelvis and pelvic organs) and sometimes the perineum (external area around the vagina and anus), with reconstruction. The intent of exenterative surgery should be resection of all tumour with clear histological margins with the aim of cure. It is radical, often mutilating, surgery that is associated with significant postoperative side effects (morbidity) and risk of death (mortality), and it is a major undertaking for both patient and surgeon. However, it may be the only potentially curative treatment option for women with recurrent cancer.

Quality of the evidence

Although two review authors independently checked 1311 articles identified by searching, we found no relevant studies that were suitable for inclusion in the review. Therefore, no evidence is currently available from which to determine whether exenterative surgery is better than, equivalent to or worse than non-surgical treatment in terms of prolonged survival, treatment-related complications and impact on quality of life. This review highlights the need for good-quality studies comparing exenterative surgery versus non-surgical treatment in women with recurrent gynaecological cancer.

BACKGROUND

Description of the condition

Cancer is a leading cause of death worldwide ([WHO 2008](#)). Gynaecological cancers (i.e. cancers affecting the ovaries, uterus, cervix, vulva and vagina) are among the most common cancers in women. Globally, a woman's risk of developing cancer of the

cervix, ovaries and uterus by the age of 65 is 2.2%; cancers of the vulva and vagina are less common. Gynaecological cancers account for 25% of all new cancers diagnosed in women up to 65 years of age in developing countries, compared with 16% in the developed world (GLOBOCAN 2008).

Uterine (womb) cancer is more often a disease of the elderly and obese female population. More than 80% of cases arise from the endometrium (lining of the womb). Endometrial cancer is the most common genital tract cancer among women in developed countries. The worldwide risk that a woman will develop cancer of the uterus by the age of 65 is 0.59%; this rate is twice as high in developed compared with developing countries (GLOBOCAN 2008). The cornerstone of treatment of women with endometrial cancer is surgery, followed, in some patients, by radiotherapy, with or without chemotherapy. The prognosis for women with early-stage disease is good, and many women are cured by surgery alone. Women who present with advanced or recurrent disease have a much poorer prognosis, with a median overall survival of nine to 10 months (Thigpen 2001; Thigpen 2004).

Cervical cancer is the second most common cancer in women up to 65 years of age, and it is the most frequent cause of death from gynaecological cancers worldwide. The incidence of cervical cancer is twice as high in developing countries, where women often present with advanced-stage disease (GLOBOCAN 2008). Over the past three decades, it has become apparent that the main risk factor for the development of cervical cancer is persistent infection by the human papillomavirus (HPV). More than 100 subtypes of HPV are known; the main pathogenic subtypes at greatest risk for forming cancer are 16 and 18, which are responsible for most cases of cervical cancer. Women with cervical cancer are treated primarily by surgery or chemoradiotherapy; a small number require both modalities. For early-stage, small-volume disease, surgery and radiotherapy appear to be equally effective (Eifel 1991), and concurrent chemoradiation is more effective than radiation alone (Green 2005). However, surgery may be more beneficial in younger women, in whom ovaries can be preserved, and vaginal atrophy, stenosis and other long-term sequelae of radiotherapy can be avoided.

Cancer of the vulva is rare; when combined with cancer of the vagina, it accounts for less than 1% of all cancer cases and 8% of gynaecological cancers diagnosed in the UK. In 2008, 1157 new cases of vulvar cancer were diagnosed in the UK, equating to a European age-standardised incidence rate of 2.5 per 100,000 women (Cancer Registration in NI 2011; Cancer Registrations in Wales 2010; ISD Scotland 2011; Office for National Statistics 2011). An estimated 27,000 women worldwide are diagnosed with vulvar cancer each year (Sankaranarayanan 2006), and it has been estimated that the lifetime risk of developing vulvar cancer is around 1 in 293 for women in the UK. Management of women with vulvar cancer usually involves surgery to stage and control the disease and to prevent local recurrence. Chemoradiotherapy may be given as the initial treatment in women with larger, more advanced lesions

involving urethra/bladder or anal canal/rectum, or who are considered unsuitable for surgery. It may also be used as an adjunct to surgery in patients who have inadequate surgical resection margins or lymph nodes involved with cancer.

The biology of recurrent ovarian cancer differs from that of other gynaecological cancers; its management is therefore the subject of several separate reviews, including Al Rawahi 2010.

Description of the intervention

Cancer can recur or progress following primary treatment. Cancer recurrence is defined as the return of cancer after treatment and after a period (minimum of six to 12 months) during which the cancer is undetectable. Progression is defined as metastasis or worsening of cancer during treatment or within six months of treatment. The difference between recurrence and progression is not always clear, and the definition of recurrence includes no standard period of time (American Cancer Society 2013).

Although the surgical management of early-stage cancers is relatively straightforward, with lower associated morbidity and mortality, the surgical management of advanced and recurrent malignancies is significantly more complicated, often requiring very extensive procedures. The main predictor of treatment success in terms of locoregional control and long-term survival is resection of the tumour with histologically clear margins (Höckel 2006).

Pelvic exenterative surgery involves removal of part or all of the pelvic organs, including rectum (with or without the sigmoid colon and sometimes the anal canal), bladder, reproductive organs (including all or part of the vagina and vulva), pelvic peritoneum and sometimes perineum, with reconstruction. Reconstruction can involve repair of the urinary stream, faecal stream, pelvic floor, vagina and vulva/perineum. Since this surgery was first described by Brunschwig in 1948, the development of newer techniques of resection and pelvic reconstruction over the past few decades has led to a considerable reduction in the frequency of complications and in perioperative mortality (Brunschwig 1948; Höckel 2006; Höckel 2008; Lawhead 1989; Shingleton 1989; Stanhope 1990; Symmonds 1975). Reconstruction of pelvic floor defects after extensive surgical resection of genital malignancies presents multiple challenges. The empty pelvis (pelvic 'dead-space') predisposes patients to problems with ileus, haematomas, abscesses and fistulae. Reconstruction of pelvic floor defects with omental flaps, bowel anastomoses and the creation of neo-vaginas has decreased some of these complications (Schmidt 2012; Soper 1989; Buchsbaum 1973). In recent years, surgeons may aim to create neo-vaginas from bowel segments, to achieve primary anastomosis of the rectosigmoid colon and to create a continent bladder when possible, giving patients a much improved quality of life (Schmidt 2012). Of these reconstructions, it is generally accepted that vaginal reconstruction has the lowest "success rate" in terms of function.

The most common indication for exenteration is cervical carcinoma that is persistent or has recurred after chemoradiotherapy

(Höckel 2006), including when this has been used after radical surgery. The intent of exenterative surgery should be resection of all tumour with the aim of cure. Exenterative surgery is a radical, often mutilating procedure associated with significant postoperative morbidity; it is a major undertaking for both patient and surgeon, but it may be the only potentially curative intervention. The reduction in mortality over the past few decades is due to a combination of improvements in case selection, surgical and anaesthetic techniques, use of prophylactic antibiotics, thromboprophylaxis and intensive care monitoring. Despite this, perioperative and postoperative morbidity rates remain significant ($\geq 50\%$). As a result of various improvements in perioperative management, treatment-related mortality has dropped to less than 10%, and five-year survival has increased to 40% to 50% for patients with advanced pelvic malignant disease that was otherwise untreatable (Höckel 2006).

Women with progressive disease are likely to have tumours that differ biologically from tumours in those with recurrent disease; women with progressive disease have a poorer prognosis, so they are unlikely/less likely to be offered exenterative surgery as part of their treatment. We therefore have limited this review to discussion of women with recurrent disease regardless of the type of primary treatment received.

Why it is important to do this review

Limited treatment options are available for women with recurrent cancer; choices depend on extent and site of disease, comorbidities and previous treatment modalities. Exenterative surgery in the management of persistent or recurrent gynaecological cancer after initial treatment is very challenging, requires careful case selection and is associated with significant perioperative morbidity and mortality. However, it provides these women with a chance of cure that otherwise may not be possible. The aim of this review is to examine the available evidence for exenterative surgery compared with other interventions (such as chemotherapy, radiotherapy, chemoradiotherapy or expectant management) in the management of women with recurrent gynaecological cancer. To our knowledge, no previous systematic reviews have addressed this topic.

OBJECTIVES

To evaluate the effectiveness and safety of exenterative surgery versus other treatment modalities for women with recurrent gynaecological cancer, excluding recurrent ovarian cancer (this is covered in a separate review).

METHODS

Criteria for considering studies for this review

Types of studies

For completeness, we searched for relevant RCTs and quasi-randomised trials, but after consulting experts in the field, we did not expect to find such trials. So we also searched for the following types of non-RCTs with concurrent comparison groups.

- Non-randomised trials, prospective and retrospective cohort studies and case series of 30 or more participants were sought for inclusion.
- Case-control studies and case series of fewer than 30 participants were excluded.

To minimise the effects of selection bias (systematic differences between baseline characteristics of the groups compared), we included only studies that provided statistical adjustment for baseline case mix using multivariate analyses (e.g. adjusting for age, stage, performance status, grade) if any constraints were placed on treatment allocation (e.g. women with poor performance status would not be given surgery), or if treatment allocation was based on clinician preference.

Types of participants

Adult women (aged 18 years or older) diagnosed with a recurrent gynaecological cancer. Women with recurrent ovarian cancer were excluded because treatments for these patients have been addressed in a separate Cochrane Review (Al Rawahi 2010).

Types of interventions

Intervention

Exenterative surgery

This may be an anterior (removal of the bladder with or without urethra and formation of urinary diversion; an ileal conduit or a continent urinary diversion with or without hysterectomy, with or without resection of the vagina and perineum), posterior (removal of the rectosigmoid colon and, in some patients, the anal canal with a primary anastomosis or formation of an end colostomy with or without hysterectomy) or total pelvic exenteration. Some more extensive recurrences also require resection of the vulva. We included exenterative procedures for recurrent (or progressive) vulvar cancers as well.

Comparison

Chemotherapy, radiotherapy, chemoradiotherapy or expectant management.

Types of outcome measures

Primary outcomes

- Overall survival: survival until death from all causes.

Secondary outcomes

- Progression-free survival.
- Disease-specific survival.
- Time to relapse/progression.
- Resection margin status.
- Death within 30 days of intervention.
- Adverse events classified according to **CTCAE 2006**.
 - Direct surgical morbidity (e.g. vascular injury; injury to bladder, ureter, small bowel or colon; presence and complications of adhesions; febrile morbidity) intestinal obstruction, anastomotic leak, haematoma, local infection, blood loss.
 - Surgically related systemic morbidity (e.g. chest/wound/urine infection), thromboembolic events (deep vein thrombosis and pulmonary embolism), cardiac events (cardiac ischaemia, myocardial infarction and cardiac failure), lower limb oedema, vulvar oedema, cerebrovascular accident, transfusion reaction, pulmonary oedema.
 - Recovery: delayed discharge, unscheduled re-admission.
 - Abandoned procedure.
- Quality of life (QoL) measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.

Search methods for identification of studies

We intended to include papers in all languages and planned to carry out translations when necessary.

Electronic searches

See [Cochrane Gynaecological Cancer Group](#) methods used in reviews.

We searched the following electronic databases: the Cochrane Gynaecological Cancer Review Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE to February 2013.

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 identified in PubMed all relevant articles found, and by using the 'Related articles' feature, we carried out further searches for newly published articles.

Searching other resources

Unpublished and grey literature

We conducted a Google search for Internet-based resources and open-access publications. We searched Metaregister (<http://www.controlled-trials.com/rct>), Physicians Data Query (<http://www.nci.nih.gov>), <http://www.clinicaltrials.gov> and <http://www.cancer.gov/clinicaltrials> for ongoing trials. If ongoing trials that have not been published had been identified through these searches, we would have asked the principal investigators to supply relevant data.

We searched conference proceedings and abstracts through ZETOC (<http://zetoc.mimas.ac.uk>) and WorldCat Dissertations.

We contacted experts in the field, including Nick Spirtos, Denis Chi, Charlie Chan, Achim Schneider, Christardt Kohler, Michael Hockel, John Shepherd, William Cliby and Neville Hacker.

Handsearching

We handsearched the citation lists of studies that were retrieved in full text, key textbooks and previous systematic reviews.

We handsearched reports of conferences in the following sources.

- *Gynecologic Oncology* (Annual Meeting of American Society of Gynecologic Oncologists).
- *International Journal of Gynecological Cancer* (Annual Meeting of International Gynecological Cancer Society).
- *British Journal of Cancer*.
- British Cancer Research Meeting.
- Annual Meeting of European Society of Medical Oncology (ESMO).
- Annual Meeting of American Society of Clinical Oncology (ASCO).

Data collection and analysis

Selection of studies

We downloaded to the reference management database, EndNote, all titles and abstracts retrieved by electronic searching. We removed all duplicates, and the remaining references were examined independently by two review authors (CA and AB). Studies that clearly do not meet the inclusion criteria were excluded, and copies of the full text of potentially relevant references were obtained. Two review authors (CA and AB) independently assessed the eligibility of retrieved papers. Disagreements were resolved by discussion between the two review authors. We documented reasons for exclusion. All studies were excluded at this stage, as they clearly did not meet the inclusion criteria. From our searches of the grey literature, we did not identify any ongoing randomised controlled trials that met our inclusion criteria. In future updates

of the review, we will employ the methods found in the [Differences between protocol and review](#).

RESULTS

Description of studies

Results of the search

The search strategy identified 567 references in MEDLINE, 737 in EMBASE, 18 in CENTRAL and 10 in the specialised register. When the search results were merged into EndNote and duplicates were removed, 1311 unique references remained. The abstracts of these were read independently by two review authors, and a total of seven full-text copies were retrieved. All seven studies were excluded, as they did not meet the inclusion criteria. We obtained the full text of a potentially relevant systematic review ([Peiretti 2012](#)), but this failed to reveal any studies for inclusion. Two review authors independently searched the grey literature; these searches also yielded no relevant studies (CA and AB).

Included studies

None of the studies that were retrieved in full text met the inclusion criteria.

Excluded studies

Seven references were excluded, after the full text was obtained, for the following reasons.

- One study ([Hathout 2010](#)) was presented as a poster abstract in at the CARO-ACRO 2010 meeting, and although the study authors reported a comparison of pelvic exenteration (n = 15) and salvage radiotherapy (n = 13) for women with locally recurrent cervical cancer, statistical adjustment was not used in any of the analyses.
- One study ([Kasamatsu 2005](#)) reported a comparison of 664 stage IB to IVA participants following surgery or radiotherapy for cervical carcinoma. However, although the study authors presented a breakdown of women with recurrence (n = 193, 67 of which were located in the pelvis alone), they reported outcomes only for those who were given salvage therapy (anterior, posterior or total exenteration (n = 3) vs radiotherapy (n = 5)).
- Three studies ([Robertson 1994](#); [Bramhall 1999](#); [Park 2007](#)) reported on a single cohort of participants, from which all women received total pelvic exenteration for a range of cancer types.
- One reference ([Peiretti 2012](#)) was a systematic review that identified no studies for inclusion in the review.

- One reference ([Monaghan 1985](#)) was a descriptive review that mainly discussed the surgical technique and complications of exenterative surgery.

For further details of all excluded studies, see the table [Characteristics of excluded studies](#).

Risk of bias in included studies

No trials that could be included were found, and therefore the risk of bias tool was not applied.

Effects of interventions

No data were available.

DISCUSSION

Summary of main results

No studies were identified that compared exenterative surgery versus medical management for women with recurrent gynaecological malignancies (other than ovarian cancer, which has been examined in a separate review). Therefore the question of whether exenterative surgery is associated with a survival benefit in terms of overall and recurrence-free survival as well as other important outcomes cannot be answered by this review.

Overall survival and recurrence-free survival were specified as the primary outcomes of interest, as the purpose of exenterative surgery is to cure, but quality of life (before and after exenterative surgery) should be reported if adequate future studies are conducted, as treatment for recurrent gynaecological cancer can have a large impact on a woman's life both psychologically and physically. The prognosis for women with recurrent gynaecological cancer remains poor ([GLOBOCAN 2008](#)).

Quality of the evidence

No studies met the inclusion criteria for this review, resulting in no evidence for assessment.

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature, and all studies were sifted and data extracted independently by two review authors. We were not restrictive in our inclusion criteria with regard to types of studies;

we included non-randomised studies with concurrent comparison groups that used multivariate analyses, as we suspected that we would find no relevant RCTs. Without this constraint, we would have identified some studies for inclusion in the review, but the risk of selection bias coupled with small numbers would have made any sort of conclusion dubious. We attempted to ensure that we did not overlook any relevant evidence and searched a wide range of reasonable-quality non-randomised study designs (case-control studies and case series of few participants were excluded). We had set this figure as 30 *a priori* but were more inclusive than this during the title and abstract sift.

The greatest threat to the validity of the review is likely to be publication bias, that is, studies that did not find the treatment to be effective may not have been published. We were unable to assess this possibility, as we found no studies that met the inclusion criteria.

Agreements and disagreements with other studies or reviews

Few studies in the literature have compared exenterative surgery versus radiotherapy, and we identified no studies comparing exenterative surgery versus chemotherapy or combination therapy. The few that examined the former were excluded (reasons are given above); the main reasons for exclusion were that the numbers were too small or the studies involved a single cohort of participants (which also included non-gynaecological cancers) with no comparison group.

One of the excluded studies published by [Hathout 2010](#) was reported as a conference abstract (no full-text copy was available); investigators examined overall survival (OS) and progression-free survival (PFS) following pelvic exenteration and radiation therapy for locally recurrent cervical cancer, as well as treatment-related toxicities. In this study, 28 women with a central pelvic recurrence were treated with pelvic exenteration or salvage radiotherapy. The initial treatment of these women consisted of radical surgery or radical radiotherapy, with a very small number receiving both treatment modalities. Of the 28 women who experienced recurrence, 13 (46.5%) received salvage radiation with brachytherapy. The remaining 15 women (53.5%) underwent pelvic exenteration. At recurrence, three-year OS was 54% in women salvaged by pelvic exenteration and 44% among those salvaged by radiation therapy. Median survival was similar in both groups at 39 months, and median PFS in women salvaged by exenteration and in those salvaged by radiation therapy was 31 months and 19 months, respectively. This study was excluded from the review because statistical adjustment was not used in any of the analyses. Although neither three-year OS nor median PFS between the groups of women was statistically significant, results demonstrate that exenterative surgery may provide some benefit over salvage radiation therapy; however, the study was at a high risk of bias.

[Robertson et al.](#) examined morbidity and survival among women treated by pelvic exenteration for gynaecological malignancy ([Robertson 1994](#)). They retrospectively reviewed 83 women who underwent exenterative surgery for an advanced gynaecological cancer or for recurrent disease following unsuccessful initial treatment. A total of 54 women underwent anterior exenteration, one woman had a posterior exenteration and the remaining 28 women had total exenterative surgery. This was primary treatment in 31 women, and the remaining 52 women were treated for recurrent disease. Although most women had a gynaecological malignancy, four women in fact had bowel cancer that mimicked a gynaecological cancer. Overall actuarial five- and 10-year survival was 41% and 36%. Both serious morbidity and operative mortality were low, with only three deaths occurring within 30 days of surgery. This study was excluded on the basis that it included only a single cohort of participants with no comparison group, and the women in the study included those with both advanced and recurrent cancer including ovarian and bowel cancer; nonetheless, the study authors demonstrated (1) that survival rates in their study compared favourably with those reported by other institutions, and (2) that for patients with limited options for treatment of advanced primary or recurrent pelvic cancer, exenterative surgery offers a reasonable prospect of survival with good quality of life.

The authors of [Bramhall 1999](#) reported the findings of a phase 2 study of 50 participants with locally advanced pelvic tumours who underwent total pelvic exenteration, with a view to evaluating safety, tolerability and survival. Of the 50 participants, 32 women underwent exenterative surgery for recurrent cervical cancer, seven for rectal cancer, three for vulvar cancer, three for vaginal cancer, two for prostate cancer and three for other tumours. The 30-day mortality and in-hospital mortality rates were 8% and 16%, respectively. The crude morbidity rate was 62%, with 23 participants (46%) having grade III or IV toxicity. Overall median survival was 86 weeks, rising to 111 weeks for participants in whom a complete response was achieved. The study authors concluded that survival and operative mortality rates in patients undergoing exenterative surgery are comparable with those achieved with chemoradiotherapy in advanced pelvic neoplasia. In a prospective study ([Park 2007](#)), 46 women with advanced or recurrent gynaecological cancer were recruited, 44 of whom underwent pelvic exenteration (two women were excluded because of the presence of peritoneal disease). Of the 44 women, 30 underwent total exenteration, 12 had an anterior exenteration and two women had a posterior exenteration. Median disease-free survival was 24 months, and the five-year overall survival rate was 54% (it was not possible to estimate median survival time, as at least half of the women had not died during their time in the study). Twenty-one of the 44 women (48%) had relapse after exenteration, with median time to recurrence of five months. Both of these studies were excluded from the review, as they reported single cohorts of participants with no comparison group, and the latter study included women with both advanced and recurrent cancer, as well as ovarian cancer.

The [Kasamatsu 2005](#) study identified 67 women with recurrent cervical cancer; 24 recurrences occurred centrally and 43 in the pelvic side wall. Of 24 women with a central recurrence, three underwent pelvic exenteration and five received radiotherapy. No details were given about PFS or OS in either group. This study was excluded because the numbers were deemed too small to be interpretable.

The article by [Peiretti 2012](#) was a systematic review that identified no studies for inclusion in the review; it was therefore excluded.

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence on the efficacy and safety of exenterative surgery for women with recurrent gynaecological cancer (other than ovarian cancer, which has been examined in a separate review).

We are, therefore, unable to reach definitive conclusions about the relative benefits and adverse effects of exenterative surgery versus radiotherapy in women with recurrent gynaecological malignancies.

Implications for research

One of the problems with looking at studies comparing surgical and medical management for recurrent gynaecological cancers is that, almost without exception, participants in the medically managed group would have been considered unsuitable for exenteration. Conducting a randomised control trial in this clinically diverse group is unlikely, as multiple factors need to be taken into consideration when management is planned. Most of these factors, such as site of disease, extent of disease and patient comorbidities, will exclude one form of treatment or another. Therefore, the need is great for comparative non-RCTs that include multivariate analysis or statistical adjustment for the comparison of exenterative surgery versus medical management in women with recurrent gynaecological malignancies. These studies should be multicentre and possibly multinational and should attempt to recruit as many women as possible to increase power. Survival should definitely be the primary outcome, as exenterative surgery is performed with curative intent, but other outcomes such as quality of life and severe adverse events should also be reported.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Bramhall 1999	This study reported on a single cohort of participants in which all women received total pelvic exenteration for a range of cancer types
Hathout 2010	This study was presented as a poster abstract at the CARO-ACRO 2010 meeting. Although investigators reported a comparison of pelvic exenteration (n = 15) and salvage radiotherapy (n = 13) for women with locally recurrent cervical cancer, statistical adjustment was not used in any of the analyses
Kasamatsu 2005	This study reported a comparison of 664 stage IB to IVA participants after surgery or radiotherapy for cervical carcinoma. However, although investigators presented a breakdown of women with recurrence (n = 193, 67 of which were located in the pelvis alone), they reported outcomes only for those who were given salvage therapy (anterior, posterior or total exenteration (n = 3) vs radiotherapy (n = 5))
Monaghan 1985	This reference was a review based on a description of the surgical technique and postoperative complications
Monaghan 1997	This reference was a discussion of exenteration and its general benefits and harms in women with gynaecological cancer
Park 2007	This study reported on a single cohort of participants in which all women received total pelvic exenteration for a range of cancer types
Peiretti 2012	This reference was a systematic review that identified no studies for inclusion in the review
Robertson 1994	This study reported on a single cohort of participants in which all women underwent pelvic exenteration for both advanced and recurrent cancer and for a range of cancer types

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy

1. Pelvic Exenteration/
2. Cystectomy/
3. exp Colectomy/
4. (exenterat* or eviscerat* or evidement or cystectomy or colectomy).mp.
5. 1 or 2 or 3 or 4
6. exp Genital Neoplasms, Female/
7. ((gynecolog* or gynaecolog* or uter* or cervi* or endometri* or vulva* or vagina*) adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma* or adenocarcinoma*)).mp.
8. 6 or 7
9. 5 and 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. exp Cohort Studies/
18. (cohort* or prospective* or retrospective*).mp.
19. (case* and series).mp.
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 9 and 20

key:

mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier, pt=publication type, sh=subject heading, ab=abstract, ti=title

Appendix 2. EMBASE search strategy

1. pelvis exenteration/
2. cystectomy/
3. exp colon resection/
4. (exenterat* or eviscerat* or evidement or cystectomy or colectomy).mp.
5. 1 or 2 or 3 or 4
6. exp female genital tract tumor/
7. ((gynecolog* or gynaecolog* or uter* or cervi* or endometri* or vulva* or vagina*) adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma* or adenocarcinoma*)).mp.
8. 6 or 7
9. 5 and 8
10. exp controlled clinical trial/
11. crossover procedure/
12. double-blind procedure/

13. randomized controlled trial/
14. single-blind procedure/
15. random*.mp.
16. factorial*.mp.
17. (crossover* or cross over* or cross-over*).mp.
18. placebo*.mp.
19. (double* adj blind*).mp.
20. (singl* adj blind*).mp.
21. assign*.mp.
22. allocat*.mp.
23. volunteer*.mp.
24. cohort analysis/
25. (cohort* or prospective* or retrospective*).mp.
26. (case* and series).mp.
27. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 9 and 27

key:

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 3. CENTRAL search strategy

1. MeSH descriptor: [Pelvic Exenteration] explode all trees
2. MeSH descriptor: [Cystectomy] this term only
3. MeSH descriptor: [Colectomy] explode all trees
4. (exenterat* or viscerat* or evident or cystectomy or colectomy)
5. #1 or #2 or #3 or #4
6. MeSH descriptor: [Genital Neoplasms, Female] explode all trees
7. ((gynecolog* or gynaecolog* or uter* or cervi* or endometri* or vulva* or vagina*) near/5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma* or adenocarcinoma*))
8. #6 or #7
9. #5 and #8

WHAT'S NEW

Last assessed as up-to-date: 26 February 2013.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2013

Review first published: Issue 2, 2014

Date	Event	Description
11 February 2015	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

CA drafted the clinical sections of the protocol, with input from RN, DPJB and CP; AB drafted the method sections of the protocol. All review authors approved the final version.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.
NHS Cochrane Collaboration Programme Grant Scheme CPG-10/4001/12

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We identified no studies that met the inclusion criteria. In future updates of the review, we will employ the following methods.

Selection of studies

We will obtain copies of the full text of relevant references. Two review authors (CA and AB) will independently assess the eligibility of retrieved papers. We will resolve disagreements by discussion between the two review authors. We will document reasons for exclusion.

Data extraction and management

For included studies, data were abstracted as recommended in Chapter 7 of the [Cochrane Handbook 2008](#). Data on the following were included.

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

- Study design, methodology.
- Study population.
 - Total number enrolled.
 - Participant characteristics.
 - Age.
 - Race.
 - Comorbidities.
 - Previous treatment.
- Gynaecological cancer details at diagnosis.
 - Type of cancer.
 - Stage.
 - Grade.
 - Histology.
 - Original treatment modality.
- Intervention (exenterative surgery) details.
 - Single or multiple centres.
 - Hysterectomy.
 - Cystectomy and formation of urinary diversion.
 - Resection of the vagina +/- perineum.
 - Rectosigmoid colectomy with formation of an end colostomy.
 - Anal resection.
 - Reconstruction undertaken-urinary and faecal stream, pelvic floor, perineum, vulva/vagina.
 - Duration of procedure.
 - Type of surgeon (gynaecological oncologist, urologist, colorectal surgeon, surgeon performing joint procedures).
- Comparison details.
 - Type of treatment or expectant management.
 - Dose (If appropriate).
 - Duration.
 - Combination (If appropriate).
- Risk of bias in study (see below).
- Duration of follow-up.
- Outcomes-overall and progression-free survival, QoL and severe adverse events.
 - For each outcome, outcome definition (with diagnostic criteria if relevant).
 - Unit of measurement (if relevant).
 - For scales, upper and lower limits, and whether high or low score is good.
 - For 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 survival (OS) and progression-free survival (PFS)) data, we will extract the log of the hazard ratio (log(HR)) and its standard error from trial reports; if these are not reported, we will attempt to estimate them from other reported statistics using the methods of [Parmar 1998](#).
- For dichotomous outcomes (e.g. adverse events), we will extract the number of participants in each treatment arm who experience the outcome of interest and the number of participants assessed at endpoint, to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL), we will extract the final value and the standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, to estimate mean differences (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and standard error.

When possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants are analysed in the groups to which they were assigned.

The time points at which outcomes were collected and reported will be noted.

Data will be abstracted independently by two review authors (CA and AB) onto a data abstraction form specially designed for the review. Differences between review authors will be resolved by discussion or by appeal to a third review author (RN).

Assessment of risk of bias in included studies

The risk of bias in included RCTs will be assessed in accordance with guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* using The Cochrane Collaboration tool and the criteria specified in Chapter 8 (Higgins 2011). This will include assessment of the following.

- Sequence generation.
- Allocation concealment.
- Blinding (restricted to blinding of outcome assessors, as not possible to blind participants and healthcare providers to surgical intervention).
- Incomplete outcome data.
 - We will record the proportion of participants whose outcomes are not reported at the end of the study. We will code the satisfactory level of loss to follow-up for each outcome as:
 - ◊ yes, if less than 20% of participants are lost to follow-up and reasons for loss to follow-up are similar in both treatment arms;
 - ◊ no, if more than 20% of participants are lost to follow-up or reasons for loss to follow-up are different between treatment arms; or
 - ◊ unclear, if loss to follow-up is not reported.
- Selective reporting of outcomes.
- Other possible sources of bias.

As we included observational studies, we assessed risk of bias in accordance with the following additional criteria.

Cohort selection

1. Were relevant details provided for criteria used for assignment of participants to treatments?
 - Low risk of bias (e.g. yes).
 - High risk of bias (e.g. no).
 - Unclear risk of bias.
2. Was the group of women who received the experimental intervention (exenterative surgery) representative?
 - Low risk of bias (e.g. yes, as they were representative of women with gynaecological cancer).
 - High risk of bias (e.g. no, as group of participants was selected).
 - Unclear risk of bias (e.g. selection of group was not described).
3. Was the group of women who received the comparison intervention (e.g. chemotherapy) representative?
 - Low risk of bias (e.g. yes, as drawn from the same population as the experimental cohort).
 - High risk of bias (e.g. no, as drawn from a different source).
 - Unclear risk of bias (e.g. selection of group was not described).

We will assess cohort comparability on the basis of study design or analysis of cohort differences.

1. Were there no differences between the two groups or were differences controlled for, in particular with reference to age, FIGO (International Federation of Gynecology and Obstetrics) stage, histological cell type and differentiation?
 - Low risk of bias, if age and at least two other of these characteristics were reported, and any reported differences were controlled for.
 - High risk of bias, if the two groups differed, and differences were not controlled for.
 - Unclear risk of bias, if fewer than three of these characteristics were reported, even if there were no other differences

between the groups, and other characteristics were controlled for.

The risk of bias tool will be applied independently by two review authors (CA and AB), and differences will be resolved by discussion or by appeal to a third review author (RN). Results will be summarised in both a risk of bias graph and a risk of bias summary. Results of meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For time-to-event data, we will use the hazard ratio (HR), if possible.

- For dichotomous outcomes, we will use the risk ratio (RR).
- For continuous outcomes, we will use the mean difference between treatment arms.

Dealing with missing data

We will not impute missing outcome data for the primary outcome. If data are missing, or if only imputed data are reported, we will contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials that cannot be ascribed to sampling variation ([Higgins 2003](#)), by a formal statistical test of the significance of the heterogeneity ([Deeks 2001](#)) and, if possible, by subgroup analyses (Subgroup analysis and investigation of heterogeneity). If evidence of substantial heterogeneity is found, possible reasons for this will be investigated and reported.

Assessment of reporting biases

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.

Data synthesis

If sufficient clinically similar studies are available, their results will be pooled in meta-analyses.

- For time-to-event data, HRs will be pooled using the generic inverse variance facility of RevMan 5.
- For any dichotomous outcomes, the RR will be calculated for each study, and these will then be pooled.
- For continuous outcomes, mean differences between treatment arms at the end of follow-up will be pooled if all studies measured the outcome on the same scale; otherwise standardised mean differences will be pooled.

Random-effects models with inverse variance weighting will be used for all meta-analyses ([DerSimonian 1986](#)).

Subgroup analysis and investigation of heterogeneity

We will subgroup by tumour site and type of primary treatment (chemotherapy, radiotherapy, surgery or any combination).

Sensitivity analysis

Sensitivity analyses will be performed and will exclude studies at high risk of bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Genital Neoplasms, Female [pathology; *surgery]; Neoplasm Recurrence, Local [*surgery]; Pelvic Exenteration

MeSH check words

Adult; Female; Humans