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Kokka F, Bryant A, Brockbank E, Jeyarajah A.
Surgical treatment of stage IA2 cervical cancer.
Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD010870.
DOI: [10.1002/14651858.CD010870.pub2](https://doi.org/10.1002/14651858.CD010870.pub2).

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[Intervention Review]

Surgical treatment of stage IA2 cervical cancer

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.

Publication status and date: Edited (no change to conclusions), published in Issue 7, 2018.

Citation: Kokka F, Bryant A, Brockbank E, Jeyarajah A. Surgical treatment of stage IA2 cervical cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD010870. DOI: [10.1002/14651858.CD010870.pub2](https://doi.org/10.1002/14651858.CD010870.pub2).

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ABSTRACT

Background

Cervical cancer is the second most common cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide. Women with International Federation of Gynecology and Obstetrics (FIGO) stage IA2 cervical cancer have measured stromal invasion (when the cancer breaks through the basement membrane of the epithelium) of greater than 3 mm and no greater than 5 mm in depth with a horizontal surface extension of no more than 7 mm. For stage IA2 disease, radical hysterectomy with pelvic lymphadenectomy or radiotherapy is the standard treatment. In order to avoid complications of more radical surgical methods, less invasive options, such as simple hysterectomy, simple trachelectomy or conisation, with or without pelvic lymphadenectomy, may be feasible for stage IA2 disease, considering the relative low risk of local or distant metastatic disease. The evidence for less radical tumour excision and for the role of systematic lymphadenectomy in stage IA2 cervical cancer is not clear.

Objectives

To evaluate the effectiveness and safety of less radical surgery in stage IA2 cervical cancer.

Search methods

We searched the Cochrane Gynaecological Cancer Group trials register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE up to September 2013. We also searched registers of clinical trials and abstracts of scientific meetings.

Selection criteria

We searched for randomised controlled trials (RCTs) that compared surgical techniques in women with stage IA2 cervical cancer.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. We found no trials and, therefore, no data were analysed.

Main results

The search strategy identified 982 unique references, which were all excluded on the basis of title and abstract because it was clear that they did not meet the inclusion criteria. We identified one relevant large ongoing trial, so it is anticipated that we will be able to add this evidence to this review in the future.

Authors' conclusions

We found no evidence to inform decisions about different surgical techniques in women with stage IA2 cervical cancer. In the future, the results of one large ongoing RCT should allow comparison of different types of surgery.

PLAIN LANGUAGE SUMMARY

Surgical treatment of stage IA2 cervical cancer

Background

Cervical cancer is the second most common cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide. Cervical cancer is staged (classified using a universally adopted system called International Federation of Gynecology and Obstetrics (FIGO) staging) according to how advanced the disease is and whether the cancer has spread beyond the cervix. Stage I cervical cancer is confined to the cervix. Stage I is divided into stage IA and IB. Stage IA is the earliest stage of cervical cancer where the cancer is so small it cannot be seen with the naked eye. Stage IA is subdivided further to stages IA1 and IA2. Stage IA2 means the cancer has grown between 3 and 5 mm into the cervical tissues, but it is still less than 7 mm wide.

It is well recognised that survival rates from the disease decrease as the stage at which the diagnosis is made increases. In women with stage IA2 cervical cancer it has been reported that between 95% and 98% survived five years after diagnosis with standard surgery.

For stage IA2 disease, surgery or radiotherapy have been the treatment of choice. Standard surgery is a radical hysterectomy and bilateral pelvic lymphadenectomy. It involves the removal of the womb, the cervix, the upper part of the vagina and the tissues around the cervix (parametrial tissue), as well as the lymph nodes (glands) in the pelvis (pelvic lymphadenectomy). Although this type of surgery has excellent results, it can result in side effects, such as organ injury (bladder, bowel, blood vessel, nerve) and long-term side effects, such as sexual or bladder dysfunction, pelvic cyst formation and lymphoedema (swelling) of the legs. One main disadvantage of radical hysterectomy is that it leaves the woman incapable of bearing children. As cervical cancer is common in women aged 25 to 35 years, this is an important consideration for many women.

The alternative surgical treatment is a radical trachelectomy and bilateral pelvic lymphadenectomy. Radical trachelectomy involves removing the cervix, the upper part of the vagina and the parametrial tissue and the pelvic lymph glands, but retaining the body of the womb. This treatment is well established and appears to be safe and effective in preserving fertility and has a high chance of conception. Late miscarriage and premature labour are the most serious side effects in pregnancies where the woman has had a trachelectomy.

Methods

This review aimed to assess less invasive types of surgery such as simple hysterectomy, conisation (removal of the central cervical tissue) with or without pelvic lymphadenectomy for women with stage IA2 disease. We searched the literature from 1966 to September 2013. We then checked 982 titles and abstracts, but found no relevant completed clinical trials that met the inclusion criteria only one on-going trial.

Findings

We identified one large ongoing, multicentre randomised controlled trial (RCT, a study in which women are allocated at random (by chance alone) to receive one of two treatments: standard versus less radical treatment) that looked at this subject. The results of this trial will be published in the future.

Currently there is absence of evidence that any form of surgical technique is better, equal or worse in prolonging survival, improving quality of life or are associated with fewer side effects. The review highlights the need to assess, once completed, the results of the ongoing RCT in order to compare different types of surgery.

BACKGROUND

Description of the condition

Cervical cancer is the second most common cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide (GLOBOCAN 2008). A woman's risk of developing cervical cancer by age 65 years ranges from 0.69% in developed countries to 1.38% in developing countries (GLOBOCAN 2008). The age-standardised rate of cervical cancer varies between countries from 4 to 30 cases per year in 100,000 women under 75 years of age. In Europe, about 60% of women with cervical cancer are alive 5 years after diagnosis (EUROCare 2003).

Cervical cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO) system (Benedet 2003), which is based on findings from clinical examination (Appendix 1). Stage I cervical cancer is confined to the cervix. Stage I is divided into stage IA and IB. Stage IA is the earliest stage of cervical cancer where the cancer is so small it cannot be seen with the naked eye; however, visual inspection with a colposcope after application of acetic acid (vinegar) may demonstrate features suggestive of invasion (Shastri 2013). Stage IA is subdivided further to stages IA1 and IA2. Women with FIGO stage IA2 cervical cancer have measured stromal invasion (when the cancer breaks through the basement membrane of the epithelium) of greater than 3 mm and no greater than 5 mm in depth with a horizontal surface extension of no more than 7 mm.

It is well recognised that survival rates decrease with increasing stage at presentation. Women with lesions less than 4 cm in diameter and confined to the cervix (FIGO stage IB1) at presentation have a five-year survival rate of 92%, while women with cancer spread beyond the true pelvis to adjacent organs (FIGO stage IVA) have a five-year survival rate of only 17% (Jemal 2008).

Survival in cervical cancer is negatively associated with the incidence of pelvic and para-aortic lymph node metastasis. The incidence of pelvic and para-aortic lymph node metastasis in cervical cancer increases with stage (Eifel 1997), and this increase becomes more significant for stage IB2 and above (21% pelvic lymph node metastasis in tumours less than 3 cm versus 35% pelvic lymph node metastasis in tumours greater than 3 cm) (Piver 1975). In women with FIGO stage IA2 cervical cancer, the mean incidence of pelvic lymph node metastasis is 10% (Magrina 2001). However, evidence suggests that correctly staged IA2 cases have much lower incidence of lymph node metastases (Creasman 1998; Rogers 2009).

Description of the intervention

For stage IA2, radical hysterectomy with pelvic lymphadenectomy or radiotherapy have been the standard treatments depending on age, medical co-morbidities and other clinicopathological features (ESGO 2010; Hoskins 1976; Morley 1976; NCI 2014; Newton 1975; NICE 2010). Both treatments (surgical and radiotherapy) have similar efficacy (Eifel 1993). This review will focus on the surgical management of stage IA2 cervical cancer.

In the surgical treatment of stage IA2 cervical cancer, pelvic lymph nodes are removed by open or laparoscopic procedure because the cancer can spread to these lymph nodes first. Obturator nerve injury, lymphocyst formation and lymphoedema are side effects specifically associated with the removal of the lymph nodes. In order to avoid the morbidity of complete lymphadenectomy, sentinel lymph node (SLN) biopsy may be used to target lymph

node metastases (Lecuru 2011). The SLN is the first node to receive lymphatic drainage from the primary tumour, so when nodal metastases occur, the SLN will theoretically be the first node involved. If the SLN does not contain metastatic malignant cells, then the remainder of the lymph nodes are presumed to be negative for metastatic disease. The SLN approach for cervical cancer is not routinely practised as yet and is largely limited to clinical studies/trials.

The primary site of the cervical cancer is removed with radical hysterectomy or radical trachelectomy, depending on whether the woman wants to preserve fertility.

Radical hysterectomy involves the removal of the cervix, uterus, the upper part of the vagina (removal of a vaginal cuff with the aim of a tumour-free margin of 2 cm) and the tissues around the cervix (parametrial tissue). Although this type of surgery has excellent treatment outcomes, it does carry potentially significant side effects including: vascular (blood vessel), ureteric, bladder injury, deep venous thrombosis, pulmonary embolism, fistula formation and urinary/bowel/sexual dysfunction (Achouri 2013; Bergmark 1999; Frumovitz 2005; Kadar 1983; Low 1981; Sood 2002).

An alternative surgical option for women with stage IA2 cervical cancer, who are interested in future fertility, is radical trachelectomy. Radical trachelectomy involves removing the cervix, upper part of the vagina (removal of a vaginal cuff with the aim of a tumour-free margin of 2 cm) and the parametrial tissue (Shepherd 1998). Radical trachelectomy is a well-established conservative approach and appears to be safe and effective in when performed by an experienced surgeon in allowing a high chance of future conception. Late miscarriage and prematurity are the most serious issues in pregnancies following trachelectomy. In addition, women who become pregnant after radical trachelectomy need to deliver by elective caesarean section, since a permanent suture is placed around the upper cervix to prevent the cervix opening prematurely in pregnancy. Although caesarean section is generally considered a safe operation, it is still a major abdominal surgery with all its associated risks. Other side effects of radical trachelectomy include ureteric and bladder injury, and fistula formation. These risks are higher when extensive cervical and parametrial tissue is removed (Burnett 2003; Dargent 2000; Nishio 2009; Plante 2004; Shepherd 2006; Ungár 2005). Of note, parametrial involvement with cancerous cells in clinical stage IA2 disease is uncommon (Schmeler 2011). In women who underwent radical surgery for clinical stage IA1 or IA2 and IB1 cervical cancer, the incidence of parametrial involvement in women with tumour size 2 cm or less, negative pelvic lymph nodes and depth of invasion 10 mm or less was 0.6% (Covens 2002). Other studies showed similar results and women at low risk for parametrial spread are considered those with negative pelvic lymph nodes, no lymphovascular space invasion (LVSI) and tumours less than 2 cm (Frumovitz 2009; Kinney 1995; Steed 2006; Stegeman 2007; Strnad 2008; Wright 2007).

The clearance of the central cervical cancer and the removal of the pelvic lymph glands can be performed by a combination of approaches (abdominal or vaginal, laparoscopic or robotic) (Persson 2012; Wright 2012).

Surgical treatment of stage IA2 cervical cancer (Review)

Why it is important to do this review

In order to avoid complications of more radical surgical methods, while not negatively impacting on cancer recurrence or survival rates, less invasive options, such as simple hysterectomy, simple trachelectomy or conisation, with or without pelvic lymphadenectomy, may be feasible for stage IA2 disease, considering the relative low risk of local or distant metastatic disease. The evidence for less radical tumour excision and the therapeutic role of systematic lymphadenectomy in stage IA2 cervical cancer is not clear.

OBJECTIVES

To evaluate the effectiveness and safety of less radical surgery in stage IA2 cervical cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Types of studies

- Randomised controlled trials (RCTs).

Types of participants

Adult women (aged 18 years or older) with a confirmed histological diagnosis of stage IA2 cervical cancer.

Types of interventions

Intervention for central tumour clearance

Simple hysterectomy

- abdominal: open or laparoscopic
- vaginal: local excision of the cervix (knife cone biopsy, large loop excision of the transformation zone (LLETZ), needle excision of the transformation zone (NETZ), trachelectomy

versus

Radical hysterectomy

- abdominal: open or laparoscopic
- vaginal

or

Radical trachelectomy

- abdominal (open or laparoscopic)
- vaginal

Intervention for systematic pelvic lymph node dissection

- systematic pelvic lymph node dissection (open or laparoscopic procedure)

versus

- no systematic pelvic lymph node dissection

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) (or disease progression or recurrence).
- Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
- Adverse events, classified according to [CTCAE 2006](#), for example: direct surgical morbidity (e.g. injury to bladder, ureter, vascular, nerve, small bowel or colon, presence and complications of adhesions, febrile morbidity, intestinal obstruction, haematoma, local infection); surgically related systemic morbidity (chest infection, thrombo-embolic events, cardiac events, cerebrovascular accident, length of stay, delayed discharge, unscheduled re-admission); radiotherapy toxicity; long-term surgical complications (bladder/bowel dysfunction, fistula/lymphocyst formation, lymphoedema, psychosexual complications); other side effects not categorised above.
- Grades of toxicity extracted and grouped as: haematological (leukopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage); gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis) and genitourinary.

Search methods for identification of studies

We searched for papers in all languages and carried out translations, if 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; Cochrane Register of Controlled Trials (CENTRAL); MEDLINE and EMBASE from 1966 to September 2013.

The CENTRAL, MEDLINE AND EMBASE search strategies are presented in [Appendix 2](#); [Appendix 3](#); and [Appendix 4](#), respectively.

All relevant articles found were identified on PubMed and, 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 (www.controlled-trials.com/rct), Physicians Data Query (www.nci.nih.gov), www.clinicaltrials.gov and www.cancer.gov/clinicaltrials for ongoing trials. Two ongoing trials were identified through these searches; however, these studies are still actively recruiting and only one was a definitive Phase 3 comparative trial (NCT01658930).

We searched conference proceedings and abstracts through ZETOC (zetoc.mimas.ac.uk) and WorldCat Dissertations.

We also contacted an expert in the field: Mr David Oram.

Handsearching

We handsearched the citation lists of included studies, key textbooks and previous systematic reviews.

We handsearched reports of conferences in the following sources:

- Society of Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncology);
- *International Journal of Gynecological Cancer* (Biannual Meeting of the International Gynaecological Cancer Society);
- *British Journal of Cancer* (BJC);
- British Society of Gynaecological Cancer (BGCS);
- British Cancer Research Meeting;
- Annual Meeting of European Society of Medical Oncology (ESMO);
- Annual Meeting of the American Society of Clinical Oncology (ASCO).

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database Endnote and removed duplicates. Two review authors (FK, AB) independently examined the remaining references. There were several case reports and retrospective studies in this area; however, none were of sufficient quality or met the inclusion criteria, so we did not alter our inclusion criteria to accommodate non-randomised studies (see [Agreements and disagreements with other studies or reviews](#) for details of these studies). We excluded all studies at this stage, as they clearly did not meet the inclusion criteria. We identified one ongoing RCT that met our inclusion criteria. In future updates of the review, we will include the results of this trial and 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 367 references in MEDLINE, 762 in EMBASE and 236 in CENTRAL. When the search results were merged into Endnote and duplicates were removed, there were 982 unique references. Two review authors (FK, AB) independently read the abstracts and excluded all studies because they did not meet the inclusion criteria.

Two review authors (FK, EB) independently searched the grey literature; these searches also did not identify any relevant studies.

We identified two relevant ongoing trials ([NCT01048853](#); [NCT01658930](#)), but one trial is an early Phase trial examining conservative surgery and does not have a comparison group ([NCT01048853](#)). The [NCT01658930](#) trial is a definitive Phase 3 trial comparing simple hysterectomy versus radical hysterectomy in women with low-risk early-stage cervical cancer (see [Characteristics of ongoing studies](#)).

Risk of bias in included studies

We found no completed trials and, therefore, the 'Risk of bias' tool was not applied.

Effects of interventions

No data were available for analysis.

DISCUSSION

Summary of main results

We identified no relevant and eligible completed RCTs examining different surgical techniques in women with stage IA2 cervical cancer, therefore the question of whether different types of surgery are associated with a survival benefit, in terms of OS and PFS, cannot be answered by this review.

The prognosis for women with stage IA2 cervical cancer treated with standard surgery is excellent with a five-year survival of 95% to 98% ([Cancer Research UK](#)). In order to change our practice to less radical or non-radical surgery, we must ensure that the oncological outcomes remain excellent. QoL may be of less importance in women with stage IA2 disease than in women with more advanced disease, where prognosis is not as good. However, its relevance as a secondary outcome remains high, especially as many women will be younger at the time of diagnosis and, therefore, potentially have years where adverse effects may have an impact. In current and future trials, primary survival outcomes, as well as a thorough examination of QoL and severe short- and long-term adverse events and toxicity of adjuvant treatment as secondary outcomes, should be reported. This would allow a full examination of the benefits and harms of different surgical techniques and aftercare to aid decision making for women and their clinicians.

Quality of the evidence

No completed studies met the inclusion criteria for this review, resulting in no evidence to assess.

Potential biases in the review process

We performed a comprehensive search, including a thorough search of the grey literature, and two review authors independently sifted all references. We were restrictive in our inclusion criteria with regards to types of studies, as we planned to include only RCTs due to high risk of selection bias in non-randomised studies. Our search strategies were designed with an RCT filter so it was not possible to ascertain whether relaxing our inclusion criteria would have identified relevant non-randomised studies that used appropriate statistical adjustment or were of adequate quality. We attempted to re-run the searches without the RCT filter, but there were a substantial number of references identified and we decided that highlighting a lack of evidence from RCTs was a significant finding in itself and thought it was better to highlight the need for RCTs rather than report the results of low-quality studies that may be misleading.

The greatest threat to the validity of the review is likely to be publication bias, that is, studies that found insignificant or unfavourable results may not have been published. We were unable to assess this possibility, as we did not find any studies that met the inclusion criteria, despite searching the grey literature.

Agreements and disagreements with other studies or reviews

Less radical or non-radical surgery in carefully selected women with stage IA2 cervical cancer may reduce the morbidity of radical surgical treatments, especially the long-term side effects of autonomic dysfunction. Based on previous reviews ([Reade 2013](#); [Schmeler 2011](#)), and retrospective studies ([Covens 2002](#); [Frumovitz 2009](#); [Kinney 1995](#); [Steed 2006](#); [Stegeman 2007](#); [Strnad 2008](#); [Wright 2007](#)), which suggest there is a very small risk of parametria and pelvic lymph node metastasis in low-risk stage IA2 cervical cancer, less radical or non-radical surgery may be an option in these cases. However, this systematic review of the current literature found no RCTs and there is a lack of evidence that this is a safe and effective alternative treatment.

However, we identified two ongoing trials examining different surgical techniques in women with stage IA2 cervical cancer, although only one meets our inclusion criteria (see [Characteristics of ongoing studies](#))

1. NCT01048853: conservative surgery for women with cervical cancer

- US multicentre trial comparing standard surgery (radical hysterectomy or radical trachelectomy and pelvic lymph node with or without para-aortic lymph node dissection) in low-risk, early-stage cervical cancer versus conservative surgery (simple hysterectomy and pelvic lymph node dissection).
- Women desiring future fertility undergo cervical conisation and pelvic lymph node dissection only.

The estimated primary completion date is August 2015.

2. NCT01658930: radical versus simple hysterectomy and pelvic node dissection in patients with early-stage cervical cancer

- International, multicentre trial comparing standard surgery (radical hysterectomy and pelvic lymph node dissection) in low-risk, early-stage cervical cancer versus conservative surgery (simple hysterectomy and pelvic lymph node dissection).

The estimated primary completion date is September 2019.

However, these are ongoing trials (and only the [NCT01658930](#) is a comparative Phase 3 trial), therefore the question of whether

different types of surgery are associated with a survival benefit in terms of OS and PFS cannot be answered by this review.

AUTHORS' CONCLUSIONS

Implications for practice

We are unable to reach any conclusions as to the effectiveness and safety of different surgical techniques in the treatment of stage IA2 cervical cancer. Consequently, clinical practice is likely to remain unchanged and unchallenged. It is very unlikely that any clear recommendation about the type of surgery that should be offered can be made from non-randomised studies alone. Surgical trials often present a greater challenge than trials examining other treatment modalities, but this should not be cited as a reason for not conducting one. Trialists need to be pro-active in this area as there is currently a substantial gap in the evidence.

Implications for research

We found no evidence to inform decisions about different surgical techniques in women with stage IA2 cervical cancer. Hopefully, the one large current ongoing RCT identified ([NCT01658930](#)) and the possibility that the other ongoing trial ([NCT01048853](#)) will progress to a definitive Phase 3 trial, will allow an assessment of the role of less conservative surgery in stage IA2, low-risk cervical cancer in the future. These multicentre trials aim to recruit large numbers of participants and this will help to increase the power of the trials and the nature of the [NCT01658930](#) trial should at the very least offer internal validity as it is multicentre in Canada. A sufficiently large trial could also consider factors such as histological type of tumour, presence or absence of lymphovascular space invasion, depth of stromal invasion, tumour size, age, adjuvant treatment in an attempt to assist in individualising treatment in clinical practice.

ACKNOWLEDGEMENTS

We thank Jo Morrison 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. We also thank Mr David Oram for his expert opinion and the referees for many helpful suggestions and comments.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.

REFERENCES

References to ongoing studies

NCT01048853 {published data only}

NCT01048853. Conservative surgery for women with cervical cancer. clinicaltrials.gov/show/NCT01048853 (accessed 9 May 2014).

NCT01658930 {published data only}

NCT01658930. Radical versus simple hysterectomy and pelvic node dissection in patients with early stage cervical cancer. clinicaltrials.gov/show/NCT01658930 (accessed 9 May 2014).

Additional references

Achouri 2013

Achouri A, Huchon C, Bats AS, Bensaid C, Nos C, Lecuru F. Complications of lymphadenectomy for gynecologic cancer. *European Journal of Surgical Oncology* 2013;**39**(1):81-6.

Benedet 2003

Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz AP, et al. Carcinoma of the cervix uteri. *International Journal of Gynaecology and Obstetrics* 2003;**83** Suppl 1:41-78.

Bergmark 1999

Bergmark K, Avall-Lundqvist E, Dickman PW, Henningssohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. *New England Journal of Medicine* 1999;**340**:1383-9.

Burnett 2003

Burnett AF, Roman LD, O'Meara AT, Morrow CP. Radical vaginal trachelectomy and pelvic lymphadenectomy for preservation of fertility in early cervical carcinoma. *Gynecologic Oncology* 2003;**88**(3):419-23.

Cancer Research UK

Cancer Research UK. Cervical cancer statistics and outlook: outcome overall and by stage. www.cancerresearchuk.org/cancer-help/type/cervical-cancer/treatment/cervical-cancer-statistics-and-outlook#stage (accessed 9 May 2014).

Covens 2002

Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, et al. How important is removal of the parametrium at surgery for carcinoma of the cervix?. *Gynecologic Oncology* 2002;**84**(1):145-9.

Creasman 1998

Creasman WT, Zaino RJ, Major FJ, DiSaia PJ, Hatch KD, Homesley HD. Early invasive carcinoma of the cervix (3 to 5 mm invasion): risk factors and prognosis. A Gynecologic Oncology Group study. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 1):62-5.

CTCAE 2006

CTCAE. Common terminology criteria for adverse events. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf (accessed 9 May 2014).

Dargent 2000

Dargent D, Martin X, Sacchetoni A, Mathevet P. Laparoscopic vaginal radical trachelectomy: a treatment to preserve the fertility of cervical carcinoma patients. *Cancer* 2000;**88**(8):1877-82.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. Egger M, Davey Smith G, Altman DG (eds). *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd Edition. London: BMJ Publication Group, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Eifel 1993

Eifel PJ. Radiotherapy versus radical surgery for gynecologic neoplasms: carcinomas of the cervix and vulva. *Frontiers Radiation Therapy Oncology* 1993;**27**:130-42.

Eifel 1997

Eifel PJ, Berek J, Thigpen JT. Cancer of the cervix, vagina and vulva. In: deVita VTJ, Hellman S, Rosenberg SA editor(s). *Cancer: Principles and Practice of Oncology*. 5th Edition. Philadelphia, PA: J.B. Lippincott Co, 1997:1433-77.

ESGO 2010

European Society of Gynaecological Oncology. Algorithms for management of cervical cancer. www.esgo.org/Education/Documents/Algorithms%20english%20version.pdf (accessed 9 May 2014).

EUROCORE 2003

Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, et al: EUROCORE Working Group. EUROCORE-3: survival of cancer patients diagnosed 1990-94 - results and commentary. *Annals of Oncology* 2003;**14**(Suppl 5):v61-118.

Frumovitz 2005

Frumovitz M, Sun CC, Schover LR, Munsell MF, Jhingran A, Wharton JT, et al. Quality of life and sexual functioning in cervical cancer survivors. *Journal of Clinical Oncology* 2005;**23**:7428-36.

Frumovitz 2009

Frumovitz M, Sun CC, Schmeler KM, Deavers MT, Dos Reis R, Levenback CF, et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. *Obstetrics and Gynecology* 2009;**114**(1):93-9.

GLOBOCAN 2008

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Cancer incidence and mortality worldwide: IARC cancer. globocan.iarc.fr (accessed 9 May 2014).

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoskins 1976

Hoskins WJ, Ford JH, Jr Lutz MH, Averette HE. Radical hysterectomy and pelvic lymphadenectomy for the management of early invasive cancer of the cervix. *Gynecologic Oncology* 1976;**4**(3):278-90.

Jemal 2008

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics. *CA: A Cancer Journal for Clinicians* 2008;**58**:71-96.

Kadar 1983

Kadar N, Saliba N, Nelson JH. The frequency, causes and prevention of severe urinary dysfunction after radical hysterectomy. *British Journal of Obstetrics and Gynaecology* 1983;**90**:858-63.

Kinney 1995

Kinney WK, Hodge DO, Egorshin EV, Ballard DJ, Podratz KC. Identification of a low-risk subset of patients with stage IB invasive squamous cancer of the cervix possibly suited to less radical surgical treatment. *Gynecologic Oncology* 1995;**57**(1):3-6.

Lecuru 2011

Lecuru F, Mathevet P, Querleu D, Leblanc E, Morice P, Daraï E, et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *Journal of Clinical Oncology* 2011;**29**(13):1686-91.

Low 1981

Low JA, Mauger GM, Carmichael JA. The effect of Wertheim hysterectomy upon bladder and urethral function. *American Journal of Obstetrics and Gynecology* 1981;**139**:826-34.

Magrina 2001

Magrina JF. The prognostic significance of pelvic and aortic lymph node metastases. *CME Journal of Gynecologic Oncology* 2001;**6**:302-6.

Morley 1976

Morley GW, Seski JC. Radical pelvic surgery versus radiation therapy for stage I carcinoma of the cervix (exclusive of microinvasion). *American Journal of Obstetrics and Gynecology* 1976;**126**(7):785-98.

NCI 2014

National Cancer Institute (NCI). Cervical cancer treatment (PDQ®): stage IA cervical cancer. www.cancer.gov/cancertopics/pdq/treatment/cervical/HealthProfessional/page6 (accessed 9 May 2014).

Newton 1975

Newton M. Radical hysterectomy or radiotherapy for stage I cervical cancer. A prospective comparison with 5 and 10 years follow-up. *American Journal of Obstetrics and Gynecology* 1975;**123**(5):535-42.

NICE 2010

National Institute for Health and Care Excellence. Laparoscopic radical hysterectomy for early stage cervical cancer: guidance. www.nice.org.uk/guidance/IPG338/Guidance/pdf (accessed 9 May 2014).

Nishio 2009

Nishio H, Fujii T, Kameyama K, Susumu N, Nakamura M, Iwata T, et al. Abdominal radical trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer in a series of 61 women. *Gynecologic Oncology* 2009;**115**(1):51-5.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Persson 2012

Persson J, Imboden S, Reynisson P, Andersson B, Borgfeldt C, Bossmar T. Reproducibility and accuracy of robot-assisted laparoscopic fertility sparing radical trachelectomy. *Gynecologic Oncology* 2012;**127**(3):484-8.

Piver 1975

Piver MS, Chung WS. Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. *Obstetrics and Gynecology* 1975;**46**(5):507-10.

Plante 2004

Plante M, Renaud MC, François H, Roy M. Vaginal radical trachelectomy: an oncologically safe fertility-preserving surgery. An updated series of 72 cases and review of the literature. *Gynecologic Oncology* 2004;**94**(3):614-23.

Reade 2013

Reade CJ, Eiriksson LR, Covens A. Surgery for early stage cervical cancer: how radical should it be?. *Gynecologic Oncology* 2013;**131**(1):222-30.

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Rogers 2009

Rogers LJ, Luesley DM. Stage 1A2 cervical carcinoma: how much treatment is enough?. *International Journal of Gynecologic Cancer* 2009;**19**(9):1620-4.

Schmeler 2011

Schmeler KM, Frumovitz M, Ramirez PT. Conservative management of early stage cervical cancer: is there a role for less radical surgery?. *Gynecologic Oncology* 2011;**120**(3):321-5.

Shastri 2013

Shastri SS, Mittra I, Mishra G, Gupta S, Dikshit R, Badwe R. Vinegar screening could slash cervical cancer mortality by one-third in low-resource countries. <http://am.asco.org/vinegar-screening-could-slash-cervical-cancer-mortality-one-third-low-resource-countries> 2013.

Shepherd 1998

Shepherd JH, Crawford RA, Oram DH. Radical trachelectomy: a way to preserve fertility in the treatment of early cervical cancer. *British Journal of Obstetrics and Gynaecology* 1998;**105**(8):912-6.

Shepherd 2006

Shepherd JH, Spencer C, Herod J, Ind TE. Radical vaginal trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer-cumulative pregnancy rate in a series of 123 women. *British Journal of Obstetrics and Gynaecology* 2006;**113**(6):719-24.

Sood 2002

Sood AK, Nygaard I, Shahin MS, Sorosky JI, Lutgendorf SK, Rao SS. Anorectal dysfunction after surgical treatment for cervical cancer. *Journal of the American College of Surgeons* 2002;**195**:513-9.

Steed 2006

Steed H, Capstick V, Schepansky A, Honore L, Hiltz M, Faught W. Early cervical cancer and parametrial involvement: is it significant?. *Gynecologic Oncology* 2006;**103**(1):53-7.

Stegeman 2007

Stegeman M, Louwen M, van der Velden J, ten Kate FJ, den Bakker MA, Burger CW, et al. The incidence of parametrial tumor involvement in select patients with early cervix cancer is too low to justify parametrectomy. *Gynecologic Oncology* 2007;**105**(2):475-80.

Strnad 2008

Strnad P, Robova H, Skapa P, Pluta M, Hrehorcak M, Halaska M, et al. A prospective study of sentinel lymph node status and parametrial involvement in patients with small tumour volume cervical cancer. *Gynecologic Oncology* 2008;**109**(2):280-4.

Ungár 2005

Ungár L, Pálfalvi L, Hogg R, Siklós P, Boyle DC, Del Priore G, Smith JR. Abdominal radical trachelectomy: a fertility-preserving option for women with early cervical cancer. *BJOG* 2005;**112**(3):366-9.

Wright 2007

Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F, et al. Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. *Cancer* 2007;**110**(6):1281-6.

Wright 2012

Wright JD, Herzog TJ, Neugut AI, Burke WM, Lu YS, Lewin SN, et al. Comparative effectiveness of minimally invasive and abdominal radical hysterectomy for cervical cancer. *Gynecologic Oncology* 2012;**127**(1):11-7.

CHARACTERISTICS OF STUDIES

Characteristics of ongoing studies [ordered by study ID]

NCT01048853

Trial name or title	NCT01048853: Conservative Surgery for Women With Low-risk, Early Stage Cervical Cancer Objectives: to learn if "conservative surgery" is a safe and feasible option for women with low-risk cervical cancer (stage IA2 or IB1, Grade 1 or 2)
Methods	Single arm multicentre and multi-national trial Study type: interventional Study design: Endpoint classification: safety/efficacy study Intervention model: single group assignment Masking: open label Primary purpose: treatment
Participants	Women with stage IA2 or IB1 cervical cancer
Interventions	Conservative surgery: Pelvic Lymphadenectomy with or without simple hysterectomy (or cone biopsy in women who want to preserve their fertility)
Outcomes	Primary outcome measures: Immediate failure rate (time frame: 5 years)

NCT01048853 (Continued)

The immediate failure rate is defined as residual disease in the simple hysterectomy specimen
Secondary outcome measures: cervix cancer recurrence rate (time frame: at 2 years)

Starting date	August 2009 until an estimated primary completion date of August 2015 (final data collection date for primary outcome measure)
Contact information	Kathleen Schmeler: Tel: 713-745-3518 Jacalyn B Gano: Tel: 713-794-1422
Notes	<p>clinicaltrials.gov/show/NCT01048853</p> <p>Estimated enrolment = 100</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Squamous cell carcinoma of the cervix (any grade) or histologically confirmed grade 1 or 2 adenocarcinoma of cervix 2. FIGO stage IA2 or IB1 disease 3. Tumour diameter $\leq$ 2 cm on physical examination and imaging studies (if performed) 4. No LVSI present on biopsy or previous cone 5. Cone margins and ECC specimen negative for invasive cancer, CIN 2, CIN 3 or adenocarcinoma-in-situ (1 repeat cone and ECC permitted) 6. Women eligible for the study if the cone and ECC were performed prior to pre-enrolment in the study, provided the above pathological eligibility criteria are met and the cone and ECC were performed within 12 weeks prior to pre-enrolment in the study 7. Women must sign approved ICD 8. If woman is of childbearing potential, must have a negative blood or urine pregnancy test prior to surgery 9. Women who have had a simple hysterectomy (cut-through hysterectomy) prior to enrolment are eligible, provided the above pathology criteria are met. If lymphadenectomy was performed, the lymph nodes must be negative. If lymphadenectomy was not performed, women will undergo this procedure as part of the study 10. $<$ 10 mm of cervical stromal invasion <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Clear cell, neuroendocrine, adenosquamous, serous carcinoma or other high-risk histologies 2. Grade 3 adenocarcinoma 3. FIGO stage IA1, IB2, II, III or IV disease 4. Tumours $>$ 2 cm in diameter on physical examination or imaging studies (if performed) 5. Presence of LVSI 6. Cone margins or ECC specimen positive for invasive cancer, CIN2, CIN3 or adenocarcinoma-in-situ (1 repeat cone permitted) 7. Neoadjuvant radiotherapy or chemotherapy for cervical cancer 8. Women unwilling or unable to provide informed consent for the study 9. $\geq$ 10 mm of cervical stromal invasion

NCT01658930

Trial name or title	NCT01658930: A Randomised Phase III Trial Comparing Radical Hysterectomy and Pelvic Node Dissection vs Simple Hysterectomy and Pelvic Node Dissection in Patients With Low-Risk Early Stage Cervical Cancer
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NCT01658930 (Continued)

Objectives: to determine if a simple hysterectomy is as good as a radical hysterectomy in preventing cancer of the cervix from returning, and whether, because less tissue surrounding the uterus is removed during surgery, there are fewer side effects after the surgery and in the long-term

Methods	<p>Phase 3 multicentre RCT in the Canada</p> <p>Study type: interventional</p> <p>Study design:</p> <p>Allocation: randomised</p> <p>Endpoint classification: safety/efficacy study</p> <p>Intervention model: parallel assignment</p> <p>Masking: open label</p> <p>Primary purpose: treatment</p>
Participants	<p>Women with low-risk early stage cervical cancer; women desiring future fertility undergo cervical conisation and pelvic lymph node dissection only</p>
Interventions	<p>Active comparator: radical hysterectomy: this procedure may be performed abdominally, laparoscopically, robotically or vaginally. The uterus, cervix, medial one-third of parametria, 2 cm of the uterosacral ligaments and upper 1-2 cm of the vagina are to be removed en bloc. The uterine artery is ligated laterally to the ureters and the ureters are unroofed to the ureterovesical junction</p> <p>Experimental: simple hysterectomy: this procedure may be performed abdominally, laparoscopically, robotically or vaginally. Extrafascial hysterectomy involves removal of the uterus with cervix without adjacent parametria. The uterine arteries are transected medial to the ureters at the level of the isthmus and the uterosacral ligaments are transected at the level of the cervix. Surgeons should pay special attention to make sure that the whole cervix is removed. As such, a maximum of 0.5 cm of vaginal cuff can be removed to ensure the complete removal of the cervix</p>
Outcomes	<p>Primary outcome measures</p> <ul style="list-style-type: none"> • PRFS (time frame: 7 years) • PRFS, the primary endpoint of this study, is defined as the time from randomisation to the time of documented evidence of recurrence within the pelvic field <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Efficacy comparison between treatment arms (time frame: 7 years) • Compare the 2 treatment arms with respect to: <ul style="list-style-type: none"> ◦ extrapelvic relapse-free survival ◦ relapse-free survival (any site) ◦ overall survival ◦ treatment-related toxicity ◦ patient reported outcomes including global quality of life and measures of sexual health ◦ cost-effectiveness and cost-utility ◦ sentinel node detection ◦ parametrial involvement ◦ involvement of surgical margins ◦ pelvic node involvement
Starting date	<p>September 2012 until an estimated primary completion date of September 2019 (final data collection date for primary outcome measure) and estimated study completion date of September 2020</p>
Contact information	<p>marie.plante@crhdq.ulaval.ca (Clinical Investigator)</p> <p>ahiltz@ctg.queensu.ca (Study Coordinator)</p>

NCT01658930 (Continued)

lshepherd@ctg.queensu.ca (Senior NCIC Investigator)

Notes

Estimated enrolment = 700

Inclusion criteria

- Histologically confirmed adenocarcinoma, squamous or adenosquamous cancer of the cervix diagnosed within 12 weeks prior to randomisation. Diagnosis has been made by LEEP, cone or cervical biopsy and has been reviewed and confirmed by the local reference gynaecological pathologist
- Classified as low-risk early-stage cervical cancer. These patients include: FIGO stage IA2 (FIGO Annual Report 2009), defined as: evidence of disease by microscopy; for women who underwent a LEEP or cone. Histological evidence of depth of stromal invasion of 3.0-5.0 mm based on the local reference pathologist's measurement of the LEEP or cone specimen. Histological evidence of lateral extension that is not greater than 7.0 mm based on the local reference pathologist's measurement of the LEEP or cone specimen. Negative margins for women who underwent a cervical biopsy only; radiological evidence of < 50% stromal invasion based on pelvic MRI. FIGO stage IB1 (FIGO Annual Report 2009) with favourable (low risk) features, defined as: a clinically visible lesion or a microscopically diagnosed lesion measuring > 5 mm depth of invasion or > 7 mm in lateral extension; histological evidence of < 10 mm stromal invasion based on the local reference pathologist's measurement of the LEEP or cone specimen. Note: this criterion will not apply to women who underwent a cervical biopsy only; radiological evidence of maximum dimension of ≤ 20 mm as seen by pelvic MRI; and radiological evidence of < 50% stromal invasion based on pelvic MRI. Note: women are eligible irrespective of the presence or absence of LVSI
- The histological grade of cervical cancer must be 1, 2, 3 or not assessable (FIGO Annual Report 2009)
- Physical examination, recto-vaginal examination and visualisation of the cervix by speculum or colposcopic examination have been done after the initial diagnostic procedure (LEEP, cone or biopsy) and prior to randomisation. Staging criteria described in 5.1.2 of the trial protocol must be satisfied based on these examinations.
- Chest x-ray or CT scan of chest AND pelvic MRI* done after initial diagnostic procedure (LEEP, cone or biopsy) and prior to randomisation

The CT should be a 16-slice (or higher) helical scanner. Oral and intravenous contrasts are required (unless there is a contraindication to the use of contrast) with scan obtained in the portal phase at a slice thickness of ≤ 5 mm. Pelvic MRI should be performed on a 1.5- or 3-Tesla magnet with pelvic phased-array coils. The MR pulse sequences will consist of T1 gradient echo in the axial plane at 5-mm slice thickness and fast spin echo in the axial, sagittal and coronal planes at 4-mm slice thickness. The short axis (perpendicular to the tumour's long axis) with a 3-mm slice thickness is required in the best plane to show the maximum thickness of stromal invasion. Use of an anti-peristaltic drug is mandatory while intravenous use of gadolinium or diffusion-weighted imaging is optional.

* Note: pelvic MRI is not required if the woman has stage IA2 disease and underwent a LEEP or cone.

- After consideration of a woman's medical history, physical examination and laboratory testing, women must be suitable candidates for surgery as defined by the attending physician/investigator.
- Women must have no desire to preserve fertility.
- Women fluent in English, French or Spanish must be willing to complete the Quality of Life Questionnaire and the Sexual Health Questionnaire. The baseline assessments must be completed within 6 weeks prior to randomisation. Inability (illiteracy in English, French or Spanish, loss of sight, or other equivalent reason) to complete the questionnaires will not make the woman ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the woman ineligible. As additional Gynecologic Cancer Intergroups join the study, more translations of some of the questionnaires may be added.

Women fluent in English or French who reside in Canada and the UK must agree to participate in the economic evaluation component of this trial and complete the Health Economics Questionnaire. Similarly, women fluent in English or French accrued from other Gynecologic Cancer Inter-

NCT01658930 (Continued)

groups who are participating in the economic evaluation must be willing to complete the Health Economics Questionnaire.

- Women's consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each woman must sign a consent form prior to enrolment in the trial to document their willingness to participate.
- Women must be accessible for treatment and follow-up. Investigators must assure themselves the women randomised on this trial will be available for complete documentation of the treatment, adverse events and follow-up.
- Surgery is to be done within 8 weeks of randomisation.
- Women must be ≥ 18 years old.

Exclusion criteria

- Women with FIGO IA1 disease [FIGO Annual Report, 2009].
- History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours, Hodgkin's lymphoma or non-Hodgkin's lymphoma curatively treated with no evidence of disease for > 5 years.
- Women with evidence of lymph node metastasis on preoperative imaging or histology.
- Women who have had or will receive neoadjuvant chemotherapy.
- Women who are pregnant.

CT: computed tomography; ECC: endocervical curettage; FIGO: International Federation of Gynecology and Obstetrics; LEEP: loop electrosurgical excision procedure; LVSI: lymphovascular space invasion; MRI: magnetic resonance imaging; PRFS: pelvic relapse-free survival; RCT: randomised controlled trial.

APPENDICES

Appendix 1. Cervical cancer staging

<i>International Federation of Gynecology and Obstetrics (FIGO) classification for cervical cancer</i>	
STAGE	CHARACTERISTICS
I	Carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to a measured stromal invasion with a maximal depth of 5 mm and a horizontal extension of not > 7 mm. Depth of invasion should not be > 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.
IA ₁	Measured stromal invasion of not > 3 mm in depth and extension of not > 7 mm.
IA ₂	Measured stromal invasion of > 3 mm and not > 5 mm in depth with an extension of not > 7 mm.
IB	Clinical lesions confined to the cervix or preclinical lesions $> IA$. All gross lesions even with superficial invasion are stage IB cancers.
IB ₁	Clinical lesions not > 4 cm in size.
IB ₂	Clinical lesions > 4 cm in size.

(Continued)

II	The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall; the carcinoma involves the vagina, but not as far as the lower third.
IIA	No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina.
IIB	Obvious parametrial involvement, but not into the pelvic sidewall.
III	The carcinoma has extended onto the pelvic wall; on rectal examination there is no cancer-free space between the tumour and the pelvic wall; the tumour involves the lower third of the vagina; all cases with a hydronephrosis or non-functioning kidney should be included, unless they are known to be due to other causes.
IIIA	No extension onto the pelvic wall, but involvement of the lower third of the vagina.
IIIB	Extension onto the pelvic wall or hydronephrosis or non-functioning kidney.
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.

Appendix 2. CENTRAL search strategy

1. MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees
2. (cervi* near/5 (cancer* or neoplas* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*))
3. #1 or #2
4. MeSH descriptor: [Hysterectomy] explode all trees
5. MeSH descriptor: [Conization] this term only
6. MeSH descriptor: [Lymph Node Excision] explode all trees
7. (hysterectom* or trachelectom* or cone biopsy or conization or conisation or lymphadenectom* or (lymph* near/5 (dissect* or excis* or surg*)))
8. #4 or #5 or #6 or #7
9. #3 and #8

Appendix 3. MEDLINE search strategy

MEDLINE Ovid

1. Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or neoplas* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)).mp.
3. 1 or 2
4. exp Hysterectomy/
5. Conization/
6. exp Lymph Node Excision/
7. (hysterectom* or trachelectom* or cone biopsy or conization or conisation or lymphadenectom* or (lymph* adj5 (dissect* or excis* or surg*))).mp.
8. 4 or 5 or 6 or 7
9. 3 and 8
- 10.randomized controlled trial.pt.
- 11.controlled clinical trial.pt.
- 12.randomized.ab.
- 13.placebo.ab.
- 14.clinical trials as topic.sh.

Surgical treatment of stage IA2 cervical cancer (Review)

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15.randomly.ab.
16.trial.ti.
17.10 or 11 or 12 or 13 or 14 or 15 or 16
18.9 and 17

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
ab=abstract
ti=title
sh=subject heading

Appendix 4. EMBASE search strategy

EMBASE Ovid

1. exp uterine cervix tumor/
2. (cervi* adj5 (cancer* or neoplas* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)).mp.
3. 1 or 2
4. exp hysterectomy/
5. uterine cervix conization/
6. uterine cervix biopsy/
7. exp lymph node dissection/
8. (hysterectom* or trachelectom* or cone biopsy or conization or conisation or lymphadenectom* or (lymph* adj5 (dissect* or excis* or surg*))).mp.
9. 4 or 5 or 6 or 7 or 8
- 10.3 and 9
- 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. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
- 18.placebo*.mp.
- 19.(double* adj blind*).mp.
- 20.(singl* adj blind*).mp.
- 21.assign*.mp.
- 22.allocat*.mp.
- 23.volunteer*.mp.
- 24.11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
- 25.10 and 24

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

WHAT'S NEW

Date	Event	Description
25 July 2018	Amended	Not for update until SHAPE trial (NCT01658930) published.

HISTORY

Protocol first published: Issue 12, 2013

Review first published: Issue 5, 2014

Date	Event	Description
23 October 2014	Amended	On-going trial (NCT01658930) added. Contact information updated.

CONTRIBUTIONS OF AUTHORS

Andrew Bryant and Fani Kokka prepared the final version of the review.

Eleanor Brockbank and Arjun Jeyarajah gave final approval of the version to be published.

The team of authors have reviewed this version and comments have been incorporated.

DECLARATIONS OF INTEREST

There are no conflicts of interest.

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 did not identify any trials 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. We will assess the eligibility of retrieved papers independently by two review authors (FK, AB). 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 will be abstracted as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* 2012. This will include data on the following:

- 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
 - co-morbidities
 - previous treatment

- cervical cancer details at diagnosis
 - stage
 - grade
 - histology
- intervention details
 - simple hysterectomy
 - abdominal (open or laparoscopic)
 - vaginal
 - local excision (knife cone biopsy, LLETZ, NETZ, trachelectomy)
 - extent of tumour excision (cervical, parametrial, vaginal tissue removed)
 - no systematic pelvic lymph node dissection
- comparison details
 - radical hysterectomy
 - abdominal (open or laparoscopic)
 - vaginal
 - radical trachelectomy
 - abdominal (open or laparoscopic)
 - vaginal
 - systematic pelvic lymph node dissection
 - (open or laparoscopic procedure)
 - extent of lymphadenectomy (pelvic with or without para-aortic, number of lymph nodes removed)
- risk of bias in study (see below)
- duration of follow-up
- outcomes - OS and PFS, 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
 - results: number of participants allocated to each intervention group
 - for each outcome of interest: sample size; missing participants

We will extract data on outcomes as below.

- For time-to-event (OS and 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 women in each treatment arm who experience the outcome of interest and the number of women assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL), we will extract the final value and standard deviation of the outcome of interest and the number of women assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) (if trials measured outcomes on the same scale) or standardised mean differences (SMD) (if trials measured outcomes on different scales) between treatment arms and the standard error.

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

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

Two review authors (FK, EB) will independently abstract the data onto a form specially designed for the review. We will resolve differences by discussion or by appeal to a third review author (AB).

Assessment of risk of bias in included studies

We will assess the risk of bias in included RCTs in accordance with guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) using The Cochrane Collaboration's 'Risk of bias' tool and the criteria specified in Chapter 8. This will include assessment of:

- sequence generation;
- allocation concealment;
- blinding (restricted to blinding of outcome assessors as not possible to blind participants and healthcare providers);

- 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:
 - low risk, if less than 20% of participants are lost to follow-up and reasons for loss to follow-up are similar in both treatment arms,
 - high risk, no, if more than 20% of participants are lost to follow-up or reasons for loss to follow-up are different between treatment arms,
 - unclear risk if loss to follow-up is not reported or reported in insufficient detail to make a judgement;
- selective reporting of outcomes;
- other possible sources of bias.

We will apply the 'Risk of bias' tool and resolve differences by discussion or by appeal to a third review author (AB). We will summarise results will be summarised in both a risk of bias graph and a risk of bias summary figure. We will interpret results of meta-analyses in light of the findings with respect to risks 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 RR.
- For continuous outcomes, we will use the MD between treatment arms.

Dealing with missing data

We will not impute missing outcome data for the primary outcome. If data are missing or 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

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity (I^2 statistic) 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 there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this.

Assessment of reporting biases

We will generate and examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias.

Data synthesis

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

- For time-to-event data, we will pool HRs using the generic inverse variance facility of Review Manager 5 ([RevMan 2012](#)).
- For any dichotomous outcomes, we will calculate the RR for each study and will then pool these.
- For continuous outcomes, we will pool the MDs between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale; otherwise, we will pool the SMD.

If any trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups and comparisons between each treatment group and will treat the split comparison group as independent comparisons.

We will use random-effects models with inverse variance weighting for all meta-analyses ([DerSimonian 1986](#)).

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses, grouping the trials by:

- histological type of tumour;
- presence or absence of LVSI;
- depth of stromal invasion;
- tumour size;
- age of the participants;
- type or procedure (open or laparoscopic, abdominal or vaginal);
- adjuvant treatment.

Sensitivity analysis

We will perform sensitivity analyses excluding studies at high risk of bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Neoplasm Staging; Uterine Cervical Neoplasms [pathology] [*surgery]

MeSH check words

Female; Humans