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[Intervention Review]

Type II or type III radical hysterectomy compared to chemoradiotherapy as a primary intervention for stage IB2 cervical cancer

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ABSTRACT

Background

Cervical cancer is the fourth most common cancer in women, with 528,000 estimated new cases globally in 2012. A large majority (around 85%) of the disease burden occurs in low- and middle-income countries (LMICs), where it accounts for almost 12% of all female cancers. Treatment of stage IB2 cervical cancers, which sit between early and advanced disease, is controversial. Some centres prefer to treat these cancers by radical hysterectomy, with chemoradiotherapy reserved for those at high risk of recurrence. In the UK, we treat stage IB2 cervical cancers mainly with chemoradiotherapy, based on the rationale that a high percentage will have risk factors necessitating chemoradiotherapy postsurgery. There has been no systematic review to determine the best possible evidence in managing these cancers.

Objectives

To determine if primary surgery for stage IB2 cervical cancer (type II or type III radical hysterectomy with lymphadenectomy) improves survival compared to primary chemoradiotherapy.

To determine if primary surgery combined with postoperative adjuvant chemoradiotherapy, for stage IB2 cervical cancer increases patient morbidity in the management of stage IB2 cervical cancer compared to primary chemoradiotherapy.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 3), MEDLINE via Ovid (1946 to April week 2, 2018) and Embase via Ovid (1980 to 2018 week 16). We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of included studies up to April 2018.

Selection criteria

We searched for randomised controlled trials (RCTs), quasi-RCTs or non-randomised studies (NRSs) comparing surgery to chemoradiotherapy in stage IB2 cervical cancers.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria, abstracted data, assessed risk of bias and analysed data using standard methodological procedures expected by Cochrane.

Main results

We identified 4968 records from the literature searches, but we did not identify any RCTs that compared primary surgery with chemoradiotherapy in stage IB2 cervical cancer.

We found one NRS comparing surgery to chemoradiotherapy in IB2 and IIA2 cervical cancers which met the inclusion criteria. However, we were unable to obtain data for stage IB2 cancers only and considered the findings very uncertain due to a high risk of selection bias.

Authors' conclusions

There is an absence of high-certainty evidence on the relative benefits and harms of primary radical hysterectomy versus primary chemoradiotherapy for stage IB2 cervical cancer. More research is needed on the different treatment options in stage IB2 cervical cancer, particularly with respect to survival, adverse effects, and quality of life to facilitate informed decision-making and individualised care.

PLAIN LANGUAGE SUMMARY

Surgery or chemoradiotherapy for stage IB2 cervical cancer

The issue

Treatment of cervical cancers that are larger than 4 cm still thought to be confined to the cervix (classified as stage IB2 cervical cancer) is controversial. Some clinicians believe that a combination of radiotherapy (high-energy rays) and chemotherapy (anti-cancer drugs), together known as chemoradiotherapy or chemoradiation, is better when the tumours are larger than 4 cm. This is based on the argument that the chance of the cancer returning after surgery is high, therefore most women will need chemoradiotherapy, even if they have surgery initially. The other school of thought is that these tumours are so large that they do not respond well to chemoradiotherapy and women with this stage of cervical cancer would benefit from surgery despite being at high risk of needing chemoradiotherapy after surgery. However, there are concerns about toxicity and complications related to the use of both surgery and chemoradiotherapy in women with cervical cancer, as receiving both treatments can increase morbidity. Therefore, many centres have moved towards providing only chemoradiotherapy. As there remains uncertainty about which treatment (surgery or chemoradiotherapy) is better for women with stage IB2 cervical cancer, we conducted this systematic review to try and answer this question.

How we conducted the review

We searched for evidence that compared chemoradiotherapy to surgery (type II or type III radical hysterectomy with bilateral pelvic lymphadenectomy) from 1946 to April 2018. We searched for both randomised controlled trials (where people taking part are put into groups at random) and non-randomised studies (in which a defined group of people (the cohort) are followed over time).

What we found

We only found one non-randomised study that compared surgery with chemoradiotherapy, but this study combined data on stages IB2 to IIA. Although it met the inclusion criteria, we could not analyse the data as we could not extract data specific to stage IB2 cervical cancers, therefore we considered the findings of this study to be uncertain with respect to our review question.

Conclusions

At present, there is no high-certainty evidence to inform us of which of the current treatment options (chemoradiotherapy or radical surgery) is better for stage IB2 cervical cancer. Women with stage IB2 cervical cancer should be counselled regarding this uncertainty and potential side effects, and the choice of treatment should take into account the availability of the treatments in a particular health resource and patient preference.

Ideally, a large multicentred trial is needed to determine which of the two treatments are better for treating women with stage IB2 cervical cancer. However, because of the relative rarity of stage IB2 cancer, and the potential complications resulting from combining surgery and chemoradiotherapy, clinicians might continue to treat most women with chemoradiotherapy, and trials in this field might not be feasible.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Chemoradiotherapy versus radical surgery for stage IB2 cervical cancers

Patient or population: women (18 years and older) diagnosed with stage IB2 cervical cancer

Setting: hospital

Intervention: chemoradiotherapy

Comparison: radical hysterectomy

Outcomes	Relative effect* (95 % CI) CRT vs RH	Nº of participants (studies)	Certainty of the evidence (GRADE)
Overall survival (5-year)	—	—	The only included study reported death rates as overall survival (instead of hazard ratios). The risk of death with CRT was greater than that with primary RH (OR 3.02, 95% CI 1.53 to 5.98)*; however this evidence is of very low certainty due to a high risk of selection bias.
Progression-free survival (5-year)	—	—	The only included study reported progression rates as progression-free survival (instead of hazard ratios), which are the same data as shown below for recurrence.
Recurrence	OR 2.26 (1.24 to 4.14)	215 (1)	⊕⊕⊕⊕ Very low^a
Adverse events: lymphoedema	Not estimable	—	The only included study reported that lymphoedema occurred less frequently with CRT than with primary RH.

* As reported by study authors.

CI: confidence interval; **CRT:** chemoradiotherapy; **OR:** odds ratio; **RH:** radical hysterectomy

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

^aDowngraded due to high risk of selection bias in this retrospective study.

BACKGROUND

Description of the condition

Cancer is a leading cause of death worldwide. Cervical cancer is the fourth most common cancer in women, with a global estimate of 528,000 new cases in 2012 ([GLOBOCAN 2013](#)). The vast majority (around 85%) of the global burden occurs in low- and middle-income countries (LMICs), where it accounts for almost 12% of all female cancers. Cervical cancer remains the most common cancer in women in Eastern and Middle Africa. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of 10 (87%) cervical cancer deaths occur in less resourced or low-income countries. Mortality varies 18-fold between the various parts of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe, and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Middle Africa (22.2) and Eastern Africa (27.6) ([GLOBOCAN 2013](#)). Staging of cancer of the cervix is shown in [Table 1](#). Stage IB2 cancers are those confined to the cervix that are larger than 4 cm in diameter.

Description of the intervention

Radical hysterectomy, with bilateral pelvic lymphadenectomy (removal of the uterus with its surrounding tissues and lymph

nodes in the pelvis), is currently the gold standard surgical treatment for early stage cervical cancer if fertility preservation is not required. Pelvic lymphadenectomy is combined with radical hysterectomy to identify involvement of the pelvic lymph nodes and to remove microscopically involved nodes ([Panici 2006](#)). The Gynaecological Cancer Group of the European Organization for Research and Trials in Cancer (EORTC) has adopted an international classification of different types of radical hysterectomy to standardise variations in technique and extent of surgery ([Mota 2007](#)). Modified radical hysterectomy (type II) comprises of removal of the uterus, the cervix and upper 1 cm to 2 cm of the vagina ([Figure 1](#)). The arteries supplying the uterus are ligated (tied off) at the point of intersection with the ureter, rather than closer to the uterus as in non-radical hysterectomy. The resection (cutting out of tissues) should include the medial half of the parametria (tissues surrounding the cervix) and proximal uterosacral ligaments (ligaments attaching the cervix to the bones in the pelvis). Radical hysterectomy (type III; [Figure 1](#)), consists of removal of the uterus with the upper third of the vagina and parametrial tissues. The uterine vessels are ligated at their origin, and the whole width of the parametrium removed on both sides, along with the removal of as much of the uterosacral ligaments as possible. Extended radical hysterectomy (type IV), is similar to type III, but three-quarters of the vagina and paravaginal tissues are excised ([Mota 2007](#)).

Figure 1. Figure 1 shows the difference between type II and type III radical hysterectomy (Frederick 2011).

Concurrent chemotherapy and radiotherapy (chemoradiotherapy) has been widely used for first-line treatment of cervical cancer. A systematic review, based on 13 trials, showed a 6% absolute improvement in five-year overall survival with chemoradiotherapy over the same dose of radiotherapy (Meta-Analysis Group MRC-CTU 2008). The absolute overall survival benefit varied according to stage of disease in the Medical Research Council (MRC) meta-analysis and was 10% for stages I to IIA, 7% for stage IIB, and 3% for stage III to IVA (Meta-Analysis Group MRC-CTU 2008).

Traditionally, early cervical cancers have been treated with surgery and advanced cancers with chemoradiotherapy. However, there is no consensus regarding the ideal treatment for stage IB2 cervical cancers, which sit between early and advanced disease. Some gynaecological oncologists prefer to treat these cancers by radical hysterectomy, with chemoradiotherapy reserved for those demonstrated on subsequent histology to be at high risk of recurrence (Sedlis 1999). In the UK, stage IB2 is treated mainly by chemoradiotherapy, based on the rationale that a high proportion of cases will have risk factors necessitating adjuvant (additional) chemoradiotherapy. Both surgery and chemoradiotherapy can be associated with morbidity, therefore the combination of surgery and chemoradiotherapy increases the risk of morbidity from treatment. In view of the morbidity from combined treatment, it is generally accepted that either concurrent chemotherapy with radiotherapy, or surgery alone, should be used in the treatment of cervical cancer and a combination of surgery and chemoradiotherapy should be avoided, if possible, to reduce morbidity (Landoni 1997a).

Since stage IB2 cancers are bulky, some centres perform a type III radical hysterectomy to excise a wide margin of normal tissue around the cancer. Others advise primary chemoradiotherapy, based on the fact that stage IB2 cancers are often poorly differentiated and commonly associated with lymphovascular space invasion, so are at a greater risk of lymph node involvement, which would then indicate the need for adjuvant chemoradiotherapy (Alleyn-Mike K 2013; Havrilesky 2004; Zivanovic 2008a). A Gynecologic Oncology Group (GOG) study of clinical and pathologic predictors of surgically treated cervical carcinoma confirmed that risk factors for recurrence include large tumour diameter, depth of stromal invasion, and lymphovascular space invasion (Sedlis 1999).

Even when there is no lymph node involvement, these risk factors increase the probability of cancer recurrence at three years from 2% to 31% (Landoni 1997b). Eighty-eight per cent (88%) of stage IB2 cervical cancers are associated with these risk factors for recurrence and will need postoperative radiotherapy (Yessaian 2004). Both these studies support the argument of primary treatment of stage IB2 cervical cancers with chemoradiotherapy to avoid morbidity from multimodal treatment. Those favouring radical surgery as the first therapeutic approach cite the possibility of identifying the extent of disease, including occult (hidden) intraperitoneal spread and undetected para-aortic metastasis, with adequate staging and arrangement of subsequent treatment. However, most studies concentrate on survival outcomes and not on quality of life (Yessaian 2004).

How the intervention might work

Radical hysterectomy (removal of uterus, cervix and tissues surround the cervix) is performed to remove 2 cm of normal tissue surrounding the cancer and any involved lymph nodes.

Radiation therapy works by selectively damaging the DNA of the dividing tumour cells. This damage to the DNA is achieved either through direct or indirect ionisation of the atoms that make up the DNA chain. Radiotherapy is aimed at a defined area, or field, killing or halting any cancer cells sensitive to radiotherapy in the field. Concurrent weekly chemotherapy with cisplatin improves the response to radiotherapy by sensitising the cancer cells to the ionising radiation within the radiotherapy field.

Why it is important to do this review

The treatment of stage IB2 cervical cancer remains controversial. Many gynaecological oncologists treat women with this stage of cancer with concurrent chemoradiotherapy rather than surgery, because of the increased risk of lymph node involvement and other associated high-risk factors for cancer recurrence that often warrant chemoradiotherapy postoperatively (Sedlis 1999). Others, argue that bulky tumours respond less well to concurrent chemoradiotherapy and hence advocate primary surgery, accepting the need for chemoradiotherapy after surgery and the associated increase in morbidity (Landoni 1997b). Gynaecological cancer treatment can have a major impact on quality of life. Beyond primary treatment and disease management, managing long-term consequences of a cancer diagnosis and the effects of treatments are important aspects of cancer care. Therefore, it is important to establish if surgery (type II radical hysterectomy or type III radical hysterectomy) should be offered for women with stage IB2 cervical cancers as the primary (first-line) treatment, given that the need for postoperative chemoradiotherapy in these women is very high (Yessaian 2004). Currently, there are no systematic reviews to determine the most appropriate treatment for stage IB2 cervical cancers.

OBJECTIVES

To determine if primary surgery for stage IB2 cervical cancer (type II or type III radical hysterectomy with lymphadenectomy) improves survival compared to primary chemoradiotherapy.

To determine if primary surgery combined with postoperative adjuvant chemoradiotherapy, for stage IB2 cervical cancer increases patient morbidity in the management of stage IB2 cervical cancer compared to primary chemoradiotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials (RCTs) and if we did not identify any RCTs, we would consider the inclusion of non-randomised studies (NRSs) with concurrent comparison groups, specifically: quasi-randomised trials, prospective and retrospective before-after studies, and case series of 30 or more women. We excluded case-control studies.

In order to minimise selection bias for NRSs, we planned to include only studies that used statistical adjustment for baseline factors

using multivariate analyses (e.g. age, race, comorbidity, grade of cancer, presence of lymphovascular space invasion, size of the primary tumour).

Types of participants

We included women (18 years and older) diagnosed with a stage IB2 cervical cancer (squamous cell cancers and adenocarcinomas).

Types of interventions

- Intervention: radical surgery for stage IB2 cervical cancers with or without postoperative adjuvant chemoradiotherapy.
- Control: chemoradiotherapy for stage IB2 cervical cancers.

Types of outcome measures

Primary outcomes

- Overall survival: survival until death from all causes
- Progression-free survival (or 'disease progression')

Secondary outcomes

- Percentage of women who have chemoradiotherapy after surgery for stage IB2 cervical cancer
- Percentage of women who did not have radical hysterectomy due to intraoperative diagnosis of involved nodes
- Quality of life, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication
- Effect of different histological types and lymph node status based on survival
- Adverse events, classified according to Common Terminology Criteria for Adverse Events (CTCAE V.4.03, 2010), for example: direct surgical morbidity (e.g. injury to bladder, ureter, vascular, small bowel or colon):
 - presence and complications of adhesions
 - febrile morbidity
 - intestinal obstruction
 - haematoma, local infection
 - surgically-related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism))
 - cardiac events (cardiac ischaemia and cardiac failure)
 - cerebrovascular accident recovery: delayed discharge, unscheduled readmission
 - chemotherapy toxicity
 - radiotherapy toxicity
- Treatment toxicity, grouped as:
 - haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
 - gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis)
 - genitourinary skin (stomatitis, mucositis, alopecia, allergy)
 - neurological (peripheral and central)
 - pulmonary

Search methods for identification of studies

Electronic searches

We searched for papers in all languages and did not identify any papers in any languages other than English.

We searched the following electronic databases.

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 3), in the Cochrane Library ([Appendix 1](#)).
- MEDLINE via Ovid (1946 to April 2018, week 2) ([Appendix 2](#)).
- Embase via Ovid (1980 to 2018, week 16) ([Appendix 3](#)).

We used the 'related articles' feature of PubMed to perform a further search for newly published articles.

Searching other resources

Unpublished and grey literature

For ongoing trials we searched the following.

- ISRCTN (metaRegister of Controlled Trials) (www.isrctn.com/page/mrct).
- Physicians Data Query (www.cancer.gov/publications/pdq).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictpr/en).
- NIH NCI trials database (www.cancer.gov/clinicaltrials).

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

Handsearching

We handsearched the following publications to identify reports of conferences.

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncology).
- American Society of Gynaecologic Oncology.
- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society).
- British Journal of Cancer.
- British Cancer Research Meeting.
- Annual Meeting of the 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 a reference management database ([Endnote](#)), and removed duplicates. Two review authors (VN, GA) independently examined the remaining references. We excluded those studies that clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors (VN, JT) independently assessed the eligibility of the retrieved papers. Reasons for exclusion are documented in the table [Characteristics of excluded studies](#).

Data extraction and management

For included studies, where possible we extracted the following data as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Trial information

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
- Total number enrolled

Patient characteristics

- Age
- Comorbidities
- Primary treatment
- Grade and type of cervical cancer
- Adjuvant treatment received
- Intervention details: type II radical hysterectomy/type III radical hysterectomy versus radiotherapy or chemoradiotherapy. Women who had positive lymph nodes (i.e. lymph nodes to which the cancer has spread) identified during radical hysterectomy and did not have completion of the procedure were excluded from the analysis
- Type of assessment measures used (generic or disease-specific or combination)
- Reporting of complications
- Interview or self-assessment
- Risk of bias in study (see below)
- Duration of follow-up
- Outcomes – symptom assessment, response to treatment, identification of disease recurrence, number and sites of recurrences, quality of life, sexual function, lymph node status, open surgery versus minimally invasive surgery
- For each outcome: outcome definition (with diagnostic criteria if relevant)
- Results: number of participants allocated to each intervention group
- For each outcome of interest: sample size; missing participants

Where possible, we extracted results as follows.

- For time-to-event data (survival and disease progression) - log of the hazard ratio [log(HR)] and its standard error from trial reports. If these were not reported, we attempted to estimate the log(HR) and its standard error using the methods of Parmar 1998. For dichotomous outcomes (e.g. adverse events or deaths) - the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint.
- Quality of life data (as reported by study authors).
- Both unadjusted and adjusted statistics.

- All data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in groups to which they were assigned.
- We noted the time points at which outcomes were collected and reported.
- Three review authors (VN, GA, JT) independently abstracted data onto a data abstraction form specially designed for the review. We resolved differences between review authors by appeal to a fourth review author (TL).

For studies that included women with various stages of cervical cancer, we planned to extract data for women with stage IB2 disease only.

Assessment of risk of bias in included studies

We assessed the risk of bias using the Cochrane tool for assessment of risk of bias and the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of:

- selection bias;
- performance bias;
- detection bias;
- attrition bias;
- reporting bias; and
- other bias.

Three review authors (VN, GA, JT) applied the 'Risk of bias' tool independently and there were no differences in opinion. We judged each item as being at high, low or unclear risk of bias, as set out in the criteria provided by Higgins 2011. In the 'Risk of bias' table, we provided a quotation from the study report or a statement, or both, as justification for the judgement made for each item.

Measures of treatment effect

We used the following measures of treatment effects where possible.

- For dichotomous data: risk ratio (RR) with 95% confidence intervals (CIs).
- For continuous data: mean difference (MD) or standardised mean difference (SMD) between treatment arms with 95% CIs.
- For time-to-event data: hazard ratios (HRs) with 95% CIs.

Dealing with missing data

We did not impute missing data.

Assessment of heterogeneity

We did not assess heterogeneity as we did not perform any analyses. In future versions of this review, we plan to assess heterogeneity meta-analyses by visual inspection of forest plots: by estimation of the percentage 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, where possible, by subgroup analyses.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis we had planned to investigate reporting biases (such as publication bias) using funnel plots.

Data synthesis

We did not synthesise any data. In future versions of this review, we plan to use random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986), using Review Manager 2014 software.

Subgroup analysis and investigation of heterogeneity

We had planned to perform a subgroup analysis according to histological type (squamous cell versus adenocarcinoma) but there were insufficient data.

Summary of findings for assessing the certainty of the evidence

We created a 'Summary of findings' table in Review Manager 5 using the GRADE approach and GRADEPro GDT (Guyatt 2008; Review Manager 2014). For assessments of the overall certainty of evidence from RCTs, we would have downgraded the evidence from 'high certainty' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence,

serious inconsistency, imprecision of effect estimates or potential publication bias. We graded evidence from sound NRSs as 'low certainty', and downgraded this to 'very low certainty' for serious limitations. We included the following outcomes in [Summary of findings for the main comparison](#).

- Overall survival.
- Progression-free survival.
- Recurrence.
- Adverse events.

RESULTS

Description of studies

Results of the search

We identified 4968 records from our searches. After screening these references on titles and abstracts, we retrieved 30 full-text articles. We excluded 29 of these 30 articles with full-text screening (Figure 2), for the reasons described in the table of [Characteristics of excluded studies](#). Searches of the *Cochrane Database of Systematic Reviews* and the System for Information on Grey Literature in Europe (SIGLE) using the keyword 'radiotherapy or chemoradiotherapy, compared to surgery in stage IB2 cervical cancers' yielded no relevant references.

Figure 2. Flow of citations in the systematic review.

We searched ISRCTN (metaRegister of Controlled Trials) (www.isrctn.com/page/mrct), Physicians Data Query (www.cancer.gov/publications/pdq), ClinicalTrials.gov (www.clinicaltrials.gov), International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/en/) and NIH NCI trials database (www.cancer.gov/clinicaltrials), and found no studies.

We also searched conference proceedings and abstracts through ZETOC (zetoc.mimas.ac.uk), and WorldCat Dissertations (www.worldcat.org).

Included studies

We identified no randomised controlled trials (RCTs) or good quality non-randomised studies (NRSs) that compared primary surgery with chemoradiotherapy in stage IB2 cervical cancer. However, we identified one retrospective study that compared primary surgery with chemoradiotherapy in 215 women with stages IB2 to IIA cervical cancer, and which performed multivariate analysis to account for variation in baseline factors ([Park 2012](#)). The primary surgery and chemoradiotherapy groups comprised 147 and 68 women, respectively, with 110 (74.8%) and 53 (77.9%) women with stage IB2 in each group. The group that underwent primary surgery was significantly younger than the chemoradiotherapy group (mean age of 47 versus 54 years, $P < 0.001$). We wrote to the study authors to request data for the participants with stage IB2 cancers, but unfortunately have been unable to obtain these to date.

Excluded studies

We excluded 29 studies, including three NRSs of radical hysterectomy versus chemoradiation in women with stage IB2 cervical cancer ([Bradbury 2015](#); [Ryu 2007](#); [Zivanovic 2008a](#)). We excluded these three studies because they did not perform multivariate analysis to control for baseline variation between the groups. We excluded the Landoni trial as it compared primary surgery to radiotherapy in stage IB and IIA cancers ([Landoni 1997a](#)). These studies are discussed further in the [Discussion](#) section of the review.

Risk of bias in included studies

We judged the only included study to be at a high risk of bias overall ([Park 2012](#)). Whilst this study attempted to control for baseline risk factors, selection bias could have had an important impact on the findings, as women who were at low risk of needing postoperative chemoradiotherapy may have been selected for primary surgery, therefore the primary surgery group may have comprised of women with a better prognosis than the primary chemoradiotherapy group.

Effects of interventions

See: [Summary of findings for the main comparison Chemoradiotherapy versus radical surgery for stage IB2 cervical cancers](#)

No RCTs contributed data for the effects of radical hysterectomy compared with chemoradiotherapy for stage IB2 cervical cancer.

[Park 2012](#) was a retrospective study that included women with stage IB2 and IIA cervical cancers, and we could not distinguish data (or obtain it separately from the authors) for women with stage IB2 cancers. At a median follow-up of 40 months, this study found chemoradiotherapy to be associated with a higher risk of progression (reported as odds ratio (OR) 2.26, 95% confidence interval (CI) 1.24 to 4.14; 20/68 versus 27/147) and death (OR 3.02, 95% CI 1.53 to 5.98; 17/68 versus 23/147) compared with primary surgery. Grade 3 to 4 treatment-related early complications were more frequent with adjuvant therapy and chemoradiotherapy alone, occurring in one (2.1%), 24 (24.2%), and 21 (30.9%) participant(s) in the radical hysterectomy alone group, radical hysterectomy plus chemoradiotherapy group, and chemoradiotherapy group,

respectively. Grade 3 to 4 late complications were observed in one (2.1%), one (1%), and six (8.8%) participant(s) of these groups, respectively. Lymphoedema of the lower extremities was more frequent among women undergoing surgery, reported as occurring in six (12.5%), nine (9.1%), and one (1.5%) participant(s) in these groups, respectively ($P = 0.058$). Overall, the women who had surgery and chemoradiotherapy had more side effects compared to those in the surgery or chemoradiotherapy only groups. The surgery only group had higher lymphoedema rates compared to the chemoradiotherapy group, after excluding the women who needed chemoradiotherapy after surgery. In this study, 53.1% (69 of 147) of women needed chemoradiotherapy after surgery.

DISCUSSION

Summary of main results

We did not find any high-certainty evidence on the relative benefits and risks of primary surgery compared with chemoradiotherapy for stage IB2 cervical cancer.

Overall completeness and applicability of evidence

Evidence on primary surgery compared with chemoradiotherapy for stage IB2 cervical cancer is incomplete and more research is needed.

Certainty of the evidence

We graded the limited evidence available from [Park 2012](#) as very low certainty.

Potential biases in the review process

To our knowledge there were no biases in the review process.

Agreements and disagreements with other studies or reviews

Surgery is the standard treatment for early cervical cancer, and chemoradiotherapy is the standard treatment for advanced cervical cancer, as it has been established that the addition of chemotherapy to radiotherapy reduces the incidence of distant metastases ([Meta-Analysis Group MRC-CTU 2008](#)). To our knowledge, no reviews and few studies have compared the effects of chemoradiotherapy and primary surgery for stage IB2, which falls between the definitions of early and advanced cervical cancers.

The [Landoni 1997a](#) trial compared primary surgery to radiotherapy in stage IB and IIA cancers. After a median follow-up of 87 months, the overall survival in both groups was similar. Forty-seven cases of stage IB2 were treated with surgery and 45 cases were treated with radiotherapy. Five-year survival in patients with stage IB2 cancer was 70% for the surgery group and 72% for the radiotherapy group. Though this is the only randomised trial available to date that compared surgery to radiotherapy, radiotherapy on its own is not a standard treatment, and hence this trial is not relevant to current clinical practice.

We excluded four potentially eligible non-randomised studies (NRSs) from this review ([Bradbury 2015](#); [Rungruang 2012](#); [Ryu 2007](#); [Zivanovic 2008a](#)). Findings of all of these studies favoured primary surgery over primary chemoradiotherapy in terms of overall survival. However, their findings were not adjusted for

differences between groups at baseline and therefore would be at critical risk of selection bias, since women thought to have lower risk stage IB2 disease would be more likely to have had surgery rather than chemoradiotherapy.

[Rungruang 2012](#) looked at the outcomes in women with stage IB2 cervical cancer from the Surveillance, Epidemiology and End Results (SEER) public database from 2000 to 2006. The study authors reviewed 369 participants who received chemoradiotherapy and 401 who received surgery as a primary treatment. Participants undergoing primary surgery had longer overall survival compared to participants who received primary chemoradiotherapy. However, participants who received primary chemoradiotherapy had larger tumour mean diameters and were likely to be of the Afro-Caribbean race.

[Zivanovic 2008a](#) conducted a retrospective review of 82 participants and also reported higher three-year overall survival with primary surgery compared with chemoradiotherapy, although the difference was not statistically significant. More than half of the patients (52%) in the primary surgery group also received postoperative radiotherapy, therefore, the treatment groups in this study were too confounded to be meaningful for the purposes of our review. [Ryu 2007](#) compared several different modalities of treatment (radical hysterectomy, radical hysterectomy with adjuvant radiotherapy or chemoradiotherapy, neoadjuvant chemotherapy and chemoradiation treatment only) in stage IB2 cervical cancers. They found that participants with primary surgery had the best survival, but findings were at a high risk of selection bias and statistical adjustments were not performed to control for baseline differences.

[Bradbury 2015](#) evaluated the outcomes in women with stage IB2 cervical cancer; 67 (72.8%) who underwent primary surgery and 25 (27.2%) who underwent primary radiotherapy/chemoradiotherapy. Thirty-nine of 67 women (46.3%) in the surgery group required adjuvant treatment after surgery because of positive lymph nodes in 77.4% of cases. The median follow-up was 57.5 months (range: 3 to 137 months). Thirty-two women (34.8%) had disease recurrence: six women (16.7%) in the group undergoing surgery alone, 15 women (48.4%) in the group requiring adjuvant treatment after surgery, and 11 women (44%) in the group having primary radiotherapy/chemoradiotherapy. Overall survival and progression-free survival were higher for women undergoing surgery alone (91.7% and 83.3%) compared with women requiring adjuvant treatment after surgery (54.8% and 51.4%) and those having primary radiotherapy or chemoradiotherapy (60% and 56%) ($P = 0.0004$ and $P = 0.005$, respectively).

These non-randomised studies confirm that a high proportion of women undergoing primary surgery end up needing adjuvant treatment anyway. In addition, preliminary research suggests that a simple hysterectomy after primary chemoradiotherapy, in the presence of confirmed residual disease, might improve survival ([Castelnau-Marchand 2015](#)). Therefore, more research on the best treatment options for stage IB2 is required before we can be certain about the most effective approach to treating stage IB2.

AUTHORS' CONCLUSIONS

Implications for practice

Chemoradiotherapy is more effective than radiotherapy for the primary treatment of advanced cervical cancer ([Meta-Analysis Group MRC-CTU 2008](#)), yet it remains unknown whether chemoradiotherapy or primary surgery is the best approach for stage IB2 cervical cancer. Women with stage IB2 cervical cancer have a high chance of cancer recurrence after surgery, which is usually treated with chemoradiotherapy. The morbidity risk of combined surgery and chemoradiotherapy cancer treatment is higher than either treatment on its own, therefore, in the absence of good evidence to guide clinical management, centres will need to individualise care based on multidisciplinary team discussion and the woman's preferences.

Implications for research

Given the lack of high-certainty evidence on the best primary treatment for stage IB2 cervical cancer, high-quality randomised controlled trials (RCTs) are needed. Studies should measure health-related quality of life measures, using an appropriately validated scale, as well as the more traditional morbidity markers, to determine the balance between achieving improved survival with a detriment to quality of life. This should be considered against a background of technological advances in surgery and in radiotherapy. Currently, sentinel lymph node sampling is reducing the morbidity of lymphoedema and advanced methods of delivering radiotherapy is reducing toxicity.

Because of the high risk of lymph node metastasis, some centres perform a two-stage procedure, including a systematic lymphadenectomy followed by radical hysterectomy if the lymph nodes are negative. Sentinel lymph node assessment might change this approach and provide a useful tool to guide treatment in stage IB2 cancers.

There are currently two registered ongoing trials recruiting women with stage IB2 cervical cancers comparing neoadjuvant chemotherapy and radical surgery with chemoradiotherapy ([NCT00039338](#); [NCT01566240](#)).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Park 2012

Methods	Retrospective case-cohort study
Participants	215 patients with stage IB2 and IIA2 cervical cancer (tumour diameter > 4 cm on magnetic resonance imaging) who underwent radical hysterectomy followed by tailored adjuvant therapy (n = 147) or primary chemoradiotherapy (n = 68) at two tertiary referral centres between 2001 and 2010
Interventions	Radical hysterectomy with tailored adjuvant therapy and primary chemoradiotherapy

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Park 2012 (Continued)

Outcomes	The outcome measures were 5-year survival, recurrence rates and the rates of complications
Notes	We did not include this study in the analysis as we could not extract data for stage IB2 cancers separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Retrospective study
Allocation concealment (selection bias)	High risk	Through control of multivariate factors, there could have been bias, as patients who were treated with primary chemoradiotherapy were significantly older than the primary surgery group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Retrospective study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	There was no blinding and the outcome of recurrence or survival could not have been changed
Incomplete outcome data (attrition bias) All outcomes	High risk	Could have missed many cases that were not documented or not followed up
Selective reporting (reporting bias)	High risk	No mention of lost to follow-up. Only analysis of complete data is provided

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alleyne-Mike K 2013	Excluded, as no multivariate analysis
Atlan D	Looked at only surgical group, no control radiotherapy or chemoradiotherapy group
Bayo 2000	Comparison of neoadjuvant and surgery versus concurrent chemoradiation
Bloss 1992	Comparison of surgery and tailored radiotherapy
Bradbury 2015	No multivariate analysis to control for baseline factors to explain for heterogeneity
Cohn 2014	Review article
Doll 2011	Comparison of radical hysterectomy and radiation in stage IB1 cancer cervix - conference abstract
Doll 2014	Comparison of radical hysterectomy and radiation in stage IB1 cancer cervix - original article
Eifel 1994	Participants who had only radiotherapy were included

Study	Reason for exclusion
Einstein 2011	Cost-effective analysis based on mathematical modelling
Ertas 2013	Conference abstract - we could not obtain original data
Filippeschi 2012	Review article
Gaffney 2012	Review article
Gallion 1985	Combined radiation and surgery
Hopkins1991	Retrospective study comparing radical hysterectomy to radiotherapy with no multivariate analysis for control of baseline factors
Knobel 1987	Combined radiation and surgery
Landoni 1997a	RCT of surgery versus radiotherapy (not chemoradiotherapy)
Landoni 1997b	Comparing class II and class III radical hysterectomy
Landoni 2001	Class II versus class III radical hysterectomy
Landoni 2012	Class I versus class III radical hysterectomy
Micha 2006	No multivariate analysis to control for baseline factors to explain for heterogeneity
Moore 2003	Review article
Morice 2011	Post-chemoradiation RCT - abstract conference
Morice 2011a	Post-chemoradiation RCT - paper
Musaev 2013	Neoadjuvant chemotherapy compared to radical surgery
Rungruang 2012	No multivariate analysis to control for baseline factors to explain for heterogeneity
Ryu 2007	No multivariate analysis to control for baseline factors to explain for heterogeneity
Wen 2011	Evaluation of different preoperative treatments
Yessaian 2004	Not compared to radiotherapy or chemoradiotherapy
Zivanovic 2008a	No multivariate analysis to control for baseline factors to explain for heterogeneity

RCT: randomised controlled trial

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

NCT00039338

Trial name or title	Chemotherapy followed by surgery versus radiotherapy plus chemotherapy in patients with stage IB or II cervical cancer (EORTC-55994)
Methods	Phase 3 RCT

NCT00039338 (Continued)

Participants	Women are stratified according to participating centre, FIGO (International Federation of Gynecology and Obstetrics) stage, age (18 to 50 versus 51 to 75), and histological subtype (adenomatous versus non-adenomatous component) and randomised to 1 of 2 treatment arms
Interventions	<ul style="list-style-type: none"> • Procedure: conventional surgery radical hysterectomy • Procedure: neoadjuvant chemotherapy. Experimental arm: minimal cumulative cisplatin dose of 225 mg/m². Comparator arm: cumulative cisplatin dose of 200 - 240 mg/m² • Radiation: brachytherapy at the end of external radiation. Minimal total dose (external with or without external boost + brachytherapy) of 75 Gy EQD2 (equivalent dose 2) to point A. Overall treatment less than 50 days • Radiation: radiation therapy between 45-50 Gy, in fractions of 1.8 to 2 Gy • Drug: cisplatin minimal cumulative 225 mg/m² (experimental arm). Cumulative 200 - 240 mg/m² (comparator arm) • Experimental: chemotherapy followed by surgery neoadjuvant chemotherapy (cisplatin) followed by surgery (radical hysterectomy). Interventions: conventional surgery; neoadjuvant chemotherapy drug: cisplatin • Active comparator: radiochemotherapy. Concomitant radiotherapy (external radiotherapy combined with external boost or brachytherapy) and chemotherapy (cisplatin). Interventions: neoadjuvant chemotherapy; radiation: brachytherapy radiation, drug: cisplatin
Outcomes	<ul style="list-style-type: none"> • Overall survival • Progression-free survival • Compare the toxicity of the regimes • Quality of life at baseline and at 6, 12, 18, and 24 months
Starting date	March 202
Contact information	EORTC
Notes	

NCT01566240

Trial name or title	Induction chemotherapy plus chemoradiation as first-line treatment for locally advanced cervical cancer (INTERLACE)
Methods	Phase 3 RCT
Participants	Women (aged 18 and over) with histologically confirmed FIGO stage IB2-IVA squamous, adeno or adenosquamous carcinoma of the cervix (except FIGO IIIA). Patients with histologically confirmed FIGO stage IB1 and positive lymph nodes are also eligible
Interventions	<ul style="list-style-type: none"> • Drug: paclitaxel 80 mg/m² (capped at 160 mg maximum total dose) weekly for 6 weeks i.e. on days 1, 8, 15, 22, 29 and 36 • Drug: carboplatin Area Under Curve 2 (capped at 270 mg maximum total dose) weekly for 6 weeks i.e. on day 1, 8, 15, 22, 29 and 36 • Radiation: radiotherapy comprising external beam 40 - 50.4 Gy in 20 - 28 fractions plus intracavity brachytherapy to achieve a minimum total EQD2 dose of 78 - 86 Gy • Drug: cisplatin 40 mg/m² (capped at 70 mg total dose) weekly for five weeks maximum, commencing in the first week of radiotherapy or as soon as blood counts have recovered from induction chemotherapy • Active comparator: chemoradiation. Radiotherapy (external beam and brachytherapy) plus concurrent cisplatin weekly for 5 weeks. Interventions: radiation. radiotherapy, drug: cisplatin

NCT01566240 (Continued)

- Experimental: induction chemotherapy + chemoradiation 6 cycles of weekly paclitaxel and carboplatin followed by chemoradiation as per active comparator interventions. Drug: paclitaxel. Drug: carboplatin. Radiation: radiotherapy, Drug: cisplatin

Outcomes	<ul style="list-style-type: none"> Overall survival Progression-free survival Adverse events, as assessed by the Common Terminology Criteria for Adverse Events v4.03 (time frame: to be assessed at every time point, i.e. baseline; at every chemotherapy cycle, at all follow-up visits) Quality of life (UK and Ireland only), as assessed by EORTC QLQ-C30, QLQ-CX24 and EQ-5D (time frame: patients will fill in the questionnaires at the following time points: baseline, before CRT, during CRT, post-CRT, 3 monthly for 2 years; 6 monthly for 3 years) Patterns of first relapse (local and/or systemic)
Starting date	September 2012
Contact information	Nicola McGowan (ctc.interlace@ucl.ac.uk)
Notes	

ADDITIONAL TABLES
Table 1. Staging of cervical cancer (FIGO 2009)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma, which can be diagnosed only by microscopy with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm
IA1	Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm
IA2	Measured stromal invasion of > 3 mm and not > 5 mm with an extension of not > 7 mm
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2	Clinically visible lesion > 4.0 cm in greatest dimension
II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
IIB	With obvious parametrial invasion
III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney

Table 1. Staging of cervical cancer (FIGO 2009) *(Continued)*

IIIA	Tumour involves lower third of the vagina with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Uterine Cervical Neoplasms] this term only
#2 (cervi* near/5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma*))
#3 #1 or #2
#4 MeSH descriptor: [Hysterectomy] explode all trees
#5 hysterectom*
#6 #4 or #5
#7 #3 and #6

Appendix 2. MEDLINE (Ovid) search strategy

1 Uterine Cervical Neoplasms/
2 (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma*)).mp.
3 1 or 2
4 exp Hysterectomy/
5 hysterectom*.mp.
6 4 or 5
7 3 and 6
8 randomized controlled trial.pt.
9 controlled clinical trial.pt.
10 randomized.ab.
11 placebo.ab.
12 clinical trials as topic.sh.
13 randomly.ab.
14 trial.ti.
15 exp Cohort Studies/
16 (cohort* or prospective* or retrospective*).mp.
17 (case* and series).mp.
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 7 and 18

key:
[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
sh=subject heading

Appendix 3. Embase (Ovid) search strategy

1 exp uterine cervix tumor/
2 (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma*)).mp.
3 1 or 2
4 hysterectomy/
5 hysterectom*.mp.
6 4 or 5

7 3 and 6
8 "controlled clinical trial (topic)"/
9 crossover procedure/
10 double-blind procedure/
11 randomized controlled trial/
12 single-blind procedure/
13 random*.mp.
14 factorial*.mp.
15 (crossover* or cross over* or cross-over*).mp.
16 placebo*.mp.
17 (double* adj blind*).mp.
18 (singl* adj blind*).mp.
19 assign*.mp.
20 allocat*.mp.
21 volunteer*.mp.
22 cohort analysis/
23 (cohort* or prospective* or retrospective*).mp.
24 (case* and series).mp.
25 8 or 9 or 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
26 7 and 25

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

CONTRIBUTIONS OF AUTHORS

Vivek Nama (VN) and Georgios Angelopoulos (GA) searched for relevant studies and individually examined each potentially relevant full-text reference. Data extraction was performed individually by VN, GA and Jeremy Twigg (JT). All differences were agreed between the three authors. VN drafted clinical sections of the protocol and Jo Bailey (JB) and John Murdoch (JM) added expertise. Theresa Lawrie (TL) provided methodological support and helped draft the manuscript.

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DECLARATIONS OF INTEREST

Vivek Nama - none known
Georgios Angelopoulos - none known
Jeremy Twigg - none known
John Murdoch - none known
Jo Bailey - none known
Theresa Lawrie - none known

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not include 'recurrence' as an outcome in the initial protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Chemoradiotherapy; Hysterectomy [*methods]; Neoplasm Staging; Non-Randomized Controlled Trials as Topic; Uterine Cervical Neoplasms [pathology] [*therapy]

MeSH check words

Female; Humans