Published in final edited form as:

Cochrane Database Syst Rev. ; (4): CD008217. doi:10.1002/14651858.CD008217.pub2.

Pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

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Abstract

Background—Cervical cancer is the most common cause of death from gynaecological cancers worldwide. Locally advanced cervical cancer, FIGO stage equal or more than IB1 is treated with chemotherapy and external beam radiotherapy followed by brachytherapy. If there is metastatic para-aortic nodal disease radiotherapy is extended to additionally cover this area. Due to increased morbidity, ideally extended-field radiotherapy is given only when para-aortic nodal disease is proven. Therefore accurate assessment of the extent of the disease is very important for planning the most appropriate treatment.

Objectives—To evaluate the effectiveness and safety of pre-treatment surgical para-aortic lymph node assessment for woman with locally advanced cervical cancer (FIGO stage IB2 to IVA).

Search methods—We searched the Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1), MEDLINE and EMBASE (up to January 2011). We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

Selection criteria—Randomised controlled trials (RCTs) that compared surgical para-aortic lymph node assessment and dissection with radiological staging techniques, in adult women diagnosed with locally advanced cervical cancer.

Data collection and analysis—Two reviewers independently assessed whether potentially relevant trials met the inclusion criteria, abstracted data and assessed risk of bias. One RCT was identified so no meta-analyses were performed.

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Editorial group: Cochrane Gynaecological Cancer Group.

Publication status and date: New, published in Issue 4, 2011.

Review content assessed as up-to-date: 28 February 2011.

Contributions of authors: EB, FK, KR and CP provided clinical expertise, designed the protocol and drafted the clinical sections of the review. AB drafted the methodological sections of the protocol and review. All authors agreed the final version.

Declarations of interest: None

Main results—We found only one trial, which included 61 women, that met our inclusion criteria. This trial reported data on surgical versus clinical staging and an assessment of the two surgical staging techniques; laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging. The clinical staging was either a contrast-enhanced CT scan or MRI scan of the abdomen and pelvis to determine nodal status.

In this trial, clinical staging appeared to significantly prolong overall and progression-free survival compared to surgical staging. There was no statistically significant difference in the number of women who experienced severe (grade 3 or 4) toxicity.

There was no statistically significant difference in the risk of death, disease recurrence or progression, blood loss, severe toxicity and the duration of the operational procedure between LAP and EXP surgical staging techniques.

The strength of the evidence is weak in this review as it is based on one small trial which was at moderate risk of bias.

Authors' conclusions—From the one available RCT we found insufficient evidence that pre-treatment surgical para-aortic lymph node assessment for locally advanced cervical cancer is beneficial, and it may actually have an adverse effect on survival. However this conclusion is based on analysis of a small single trial and therefore definitive guidance or recommendations for clinical practice cannot be made.

Therefore the decision to offer surgical pre-treatment assessment of para-aortic lymph nodes in locally advanced cervical cancer needs to be individualised. The uncertainty regarding any impact on survival from pre-treatment para-aortic lymph node assessment should be discussed openly with the women.

Medical Subject Headings (MeSH)

Aorta, Abdominal; Disease-Free Survival; Lymph Node Excision [adverse effects]; Lymph Nodes [*pathology; surgery]; Lymphatic Metastasis; Magnetic Resonance Imaging; Neoplasm Staging [*methods]; Randomized Controlled Trials as Topic; Tomography, X-Ray Computed; Uterine Cervical Neoplasms [*pathology; radiotherapy; surgery]

MeSH check words

Adult; Aged; Female; Humans; Middle Aged

BACKGROUND

Description of the condition

Cervical cancer is the second most common cancer among women and is the most frequent cause of death from gynaecological cancers worldwide (GLOBOCAN 2002). A woman's risk of developing cervical cancer by age 65 years ranges from 0.8% in developed countries to 1.5% in developing countries (Parkin 2005). In Europe, about 60% of women with cervical cancer are alive 5 years after diagnosis (EUROCARE 2003).

FIGO staging (International Federation of Gynaecology and Obstetrics) for cervical cancer is an assessment of the size of the tumour and its spread to adjacent and distant sites; stage IA1 is the earliest and stage IVB the most advanced. Staging is based on clinical evaluation (Benedet 2000b); although additional investigations and surgical procedures may be useful in treatment planning they must not form part of the assessment of disease stage (Benedet 2000a).

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 5 year survival rate of 92%, while those with cancer spread beyond the true pelvis to adjacent organs (FIGO Stage IVA) have a 5 year survival rate of only 17% (Jemal 2008).

Lymph node status, the presence or absence of metastatic cancer in the lymph nodes within the pelvis and abdominal cavity, does not contribute to FIGO staging. However, stage for stage, lymph node status at presentation impacts on survival. Five year survival rates for women with FIGO Stage IB and IIA disease is 95% if node negative but only 78% with positive lymph nodes (Kim 2000). Stage IB is microscopic disease greater than 5mm in depth or 7mm in width or clinical lesions confined to the cervix, stage IIA disease is when the cancer has spread beyond the cervix into the upper two thirds of the vagina. It is estimated that para-aortic lymph node metastasis is present in 21% of women with stage IIB disease (cancer extending into the soft tissue adjacent to the cervix but not to the pelvic side wall), 31% of those with stage III (extension of the cancer to the pelvic side wall or lower third of the vagina) and 13% of those with stage IVA disease (extension of the cancer to the lining of the bladder or rectum) at presentation (Heller 1990). The para-aortic nodes are those lying adjacent to the major abdominal vessels.

Description of the intervention

For women with locally advanced disease (stage IB2 to IVA) radiation of the primary tumour and pelvic lymph nodes, with concurrent chemotherapy is the treatment of choice, where available (Moore 2008). Accurate detection of involved para-aortic nodes does not alter staging, but may result in modification of treatment plans. Additionally, it is recognised that stage for stage, women with metastatic para-aortic lymph nodes at presentation have a lower progression free and overall survival than those who are para-aortic node negative at presentation (Carl 1993). Prophylactic extended field radiation to include the para-aortic nodes for all women with locally advanced disease is not proven to improve survival rates, but does increase morbidity (side effects and complications of treatment) (Haie 1988). Accurate knowledge regarding para-aortic nodal status enables treatment planning such that only those women with confirmed involved para-aortic nodes are given extended field radiotherapy, with its individualised benefits but concurrent risks (Gold 2008). The best method by which to detect involved para-aortic nodes remains uncertain.

Non-invasive radiological methods for detection of para-aortic nodal involvement remain unsatisfactory; Magnet Resonance Imaging (MRI) and Computerised Tomography (CT) have a similar diagnostic accuracy with reported false negative rates of 20% to 50% to detect those women with macroscopic lymph node metastasis (Choi 2006; Subak 1995).

Positron Emission Tomography (PET), which is a form of functional imaging, seems to be more successful at detecting involved para-aortic nodes; however reported sensitivities range from as low as 38% and up to 86% (Gold 2008).

Surgical staging is when an operation is performed to remove the lymph nodes which then allows microscopic examination of tissue to assess the extent of disease involvement. Surgical staging, either laparotomy (open) or laparoscopy (key hole surgery), for all women with locally advanced cervical cancer has been considered. Initially open transperitoneal surgical staging was employed (Piver 1974). This involves operating to remove the lymph nodes by opening up the abdominal cavity. However when followed by radiotherapy this approach results in a significant increase in morbidity with up to 30% of women requiring a second surgical procedure for small bowel complications (Berman 1977). More recently laparoscopic staging has been proposed (Benedetti-Panici 1999). Laparoscopy is recognised to be associated with reduced trauma to the abdominal wall and abdominal-pelvic organs, a shorter hospital stay and earlier return to normal activity when compared to laparotomy (Cuschieri 1999). The feasibility to recognise and remove all positive para-aortic lymph nodes laparoscopically has been documented (Fowler 1993).

Why it is important to do this review

The benefit of surgical para-aortic lymph node assessment and dissection for women with locally advanced cervical cancer prior to treatment remains debated, with no current consensus in international literature. We were not aware of any previous systematic review in this area.

This review examined the role of surgical para-aortic lymph node assessment versus no pre-treatment surgical nodal assessment for locally advanced cervical cancer (FIGO stage IB2-IVA). The review aimed to look at each FIGO stage separately. Additionally an assessment of the impact of the route of the surgical approach: laparoscopic or open was made.

OBJECTIVES

To evaluate the effectiveness and safety of pre-treatment surgical para-aortic lymph node assessment for locally advanced cervical cancer (FIGO stage IB2-IVA).

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

Types of participants—Women with histologically confirmed carcinoma of the cervix, of which at least 80% was squamous cell in histological type, who had FIGO stage IB2 to IVA disease. No exclusion criteria on age or co-morbidities.

Types of interventions

Intervention

- Surgical para-aortic lymph node assessment and dissection
 - Laparoscopy
 - Open para-aortic lymphadenectomy
 - Other surgical staging approach

Comparison

- Non-surgical pre-treatment assessment of lymph node status (e.g. Radiographic)

The laparoscopic surgical approach was either trans or retroperitoneal. The grade or prior training of the surgeon did not need to be explicitly stated. We also considered direct comparisons of surgical staging methods (e.g. laparoscopic approach versus open para-aortic lymphadenectomy).

Types of outcome measures

Primary outcomes: 1. Overall survival (OS): survival until death from all causes. Survival was assessed from the time when women were enrolled in the trial.

Secondary outcomes:

1. Progression-free survival (PFS)
2. Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
3. Adverse events classified according to CTCAE 2006:
 - i. Intra-operative complications (death, significant visceral injury)
 - ii. Post operative complications (death within 30 days, infection, fistula, bowel obstruction, lymphocyst, lymphoedema, thromboembolism)
 - iii. Recovery: delayed discharge, unscheduled readmission
 - iv. Other

Search methods for identification of studies

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

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

The following electronic databases were searched:

- The Cochrane Gynaecological Cancer Review Group's Trial Register
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1)

- MEDLINE up to January 2011
- EMBASE up to January 2011

The Medline, Embase and Central search strategies based on terms related to the review topic are presented in Appendix 1, Appendix 2 and Appendix 3 respectively.

Databases were searched from 1950 until January 2011.

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

Searching other resources

Unpublished and Grey literature: Metaregister, Physicians Data Query, www.controlled-trials.com/mrct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials were searched for ongoing trials. We contacted the authors of one ongoing trial (Ramirez 2010) to request additional trial details (see Results of the search for additional details).

Handsearching: Reports of conferences were hand searched in the following sources:

- British Journal of Cancer
- British Cancer Research Meeting
- Annual Meeting of British Gynaecological Cancer Society
- Annual Meeting of European Society of Gynaecological Oncology
- Annual Meeting of the International Gynecologic Cancer Society
- Annual Meeting of the American Society of Gynecologic Oncologist
- Annual Meeting of the American Society of Clinical Oncology

Reference lists and Correspondence: The citation lists of included studies were checked and experts in the field contacted to identify further reports of trials.

Data collection and analysis

Selection of studies—All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote, duplicates were removed and the remaining references were examined by two review authors (EB, FK) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers were assessed independently by two review authors (EB, FK). Disagreements were resolved by discussion between the two review authors or by appeal to a third review author (AB) when necessary. Reasons for exclusion are documented.

Data extraction and management—For included studies, data were abstracted as recommended in Chapter 7 of the Cochrane Handbook 2008. This included 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
 - Patient characteristics
 - Age
 - Previous gynaecological cancer (diagnosis and treatment)
 - Co-morbidities
 - Performance status
- Cervical cancer details at diagnosis
 - FIGO stage
 - Histological cell type
 - Tumour grade
- Intervention details
 - Details of surgical procedure
 - ◇ Conversion to laparotomy (for laparoscopy, if required)
 - ◇ Transperitoneal or retroperitoneal (for laparoscopic procedure)
 - ◇ Grade or prior training of surgeon
 - ◇ Length of the operative procedure.
- Comparison details
 - Details of non-surgical procedure
- Details of treatment after surgical nodal assessment
 - Surgery
 - Chemotherapy
 - Radiotherapy and/or extended field radiation
 - Other
- Risk of bias in study (see below)

- Duration of follow-up
- Outcomes: OS, PFS, QOL and 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
 - The time points at which outcomes were collected and reported will be noted.

Data on outcomes were extracted as below:

- For time to event (OS and PFS) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. duration of operation for surgical staging procedures), we extracted the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in groups to which they were assigned.

Data were abstracted independently by two review authors (EB, AB) onto a data abstraction form specially designed for the review. Differences between review authors were resolved by discussion.

Assessment of risk of bias in included studies—The risk of bias in included RCTs was assessed using the Cochrane Collaboration's tool and the criteria specified in chapter 8 of the Cochrane Handbook 2008. This included assessment of:

- sequence generation
- allocation concealment
- blinding (of participants, healthcare providers and outcome assessors)

- incomplete outcome data:
 - We recorded the proportion of participants whose outcomes were not reported at the end of the study. We coded the satisfactory level of loss to follow-up for each outcome as:
 - ◇ Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
 - ◇ No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms
 - ◇ Unclear if loss to follow-up was not reported
- selective reporting of outcomes
- other possible sources of bias

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

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

- For time to event data, we used the HR, when possible.
- For dichotomous outcomes, we used the RR.
- For continuous outcomes, we used the mean difference between treatment arms.

Dealing with missing data—We did not impute missing outcome data for the primary outcome.

Data synthesis—We were unable to pool the results in meta-analyses as there was only one trial that met our inclusion criteria. Therefore it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup or sensitivity analyses.

RESULTS

Description of studies

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

Results of the search

The search strategy identified 1678 references in Medline, 1145 in Embase, 109 in Central and 69 in the specialised register. When the search results were merged into Endnote and duplicates were removed there were 2288 unique references. The title and abstract screening

of these references identified nine references as potentially eligible for the review. The full text screening of the nine references excluded eight for the reasons described in the table Characteristics of excluded studies. The remaining one reference was a report of a relevant RCT which met our inclusion criteria and is described in the table Characteristics of included studies. Searches of the grey literature identified one possible additional trial, but personal communication with the author confirmed that this in fact did not meet our inclusion criteria (Ramirez 2010).

Included studies

The one included trial (Lai 2003) randomised 61 women, of whom all 61 were assessed. Fifty-three of the 61 women received protocol treatment, but analysis was on an intention-to-treat basis.

This was a single centre two-step prospective randomised trial. The trial included women aged 18 to 70 with untreated, histologically confirmed FIGO stage IIB to IVA cervical cancer. These women had no medical or surgical contraindication to a surgical staging procedure and definitive radiotherapy, with or without concurrent chemotherapy. Women with small cell carcinoma, bulky (≥ 3 cm) pelvic lymph nodes on imaging, CT guided aspiration or biopsy proven para-aortic nodal metastasis or proven distant metastasis to liver, lung, supraclavicular nodes or bone were excluded.

Sixty-one patients were randomised to either clinical staging ($n = 29$), with a contrast-enhanced CT scan or MRI scan of the abdomen and pelvis to determine nodal status, or surgical staging ($n = 32$). Patient characteristics were similar in the two arms. The majority had squamous cell carcinoma (SCC) (93% in the clinical staging group and 84% in the surgical staging group) and the rest had adenocarcinoma/adenosquamous carcinoma (AD/AS) (7% versus 16% respectively). The women in the surgical staging arm were then randomised to either laparoscopic ($n = 15$) or extraperitoneal approach ($n = 17$). At surgery any enlarged or suspicious nodes were excised, or biopsied if unresectable. Nodal tissue from the common iliac bifurcation to inferior mesenteric artery was excised.

The extraperitoneal surgical approach was either via a midline vertical or lateral J incision. The retroperitoneum was exposed by rolling the peritoneum medially until the psoas muscle and iliac vessels were visualized. Dissection above the level of the inferior mesenteric artery was done in the cases with palpable suspicious nodes only. The laparoscopic surgical approach used standard laparoscopic techniques with a similar extent to the lymph node dissection as for the extraperitoneal approach.

All women received 44 to 45 gray (Gy) whole pelvic irradiation after staging. Para-aortic nodes were included only if documented metastasis. The parametria was boosted to 54 to 58 Gy and women had 6 fractions of intracavity brachytherapy, 4.3 Gy per fraction. Time to starting radiotherapy from randomisation in the surgical arm was significantly longer than that in clinical staging arm, however there was no difference of time to starting radiotherapy or total radiotherapy time between survivors and non-survivors. Women with documented para-aortic lymph node metastasis received concurrent and postradiation adjuvant chemotherapy. Those with pelvic but not para-aortic lymph node metastasis had concurrent

chemotherapy with pelvic radiotherapy and women with no nodal metastasis had concurrent chemotherapy with pelvic radiotherapy or radiotherapy alone. Chemotherapy regimes were either cisplatin, mitomycin and 5-fluorouracil or cisplatin, vincristine and bleomycin or carboplatin and ifosfamide. The duration of follow-up was 96 months from first patient enrolment. The median follow-up time of the surviving patients was 58 months. The primary end point of this trial was percent improvement in para-aortic node metastasis detection. Secondary outcomes included feasibility and efficacy of both surgical staging methods (operation time, blood loss, and lymph node yield), overall (OS) and progression-free survival (PFS), and complications. The trial used hazard ratios for time to event (survival) data that correctly accounted for censoring. Toxicity and survival of extended-field radiation plus chemotherapy in the management of surgical staging documented para-aortic lymph node metastasis was also evaluated. Acute and late toxic effects were scored by the RTOG (Radiation Therapy Oncology Group) and EORTC (European Organization for Research and Treatment of Cancer) criteria.

At interim analysis patients in the surgical staging arm had worse PFS and OS than those in the clinical staging arm, so the trial was terminated according to the early stopping rules.

Excluded studies

Nine references were excluded, after obtaining the full text, for the following reasons:

- One reference (Gold 2008) presents results from three RCTs (Rose 1999; Whitney 1999; Lanciano 2005). Gold 2008 retrospectively grouped together women from one of the randomisation arms in each of the contributing trials. Women were not randomised in terms of surgical para-aortic lymph node assessment, so selection bias is likely to be a significant problem. None of the three contributing trials to the Gold 2008 paper meet our inclusion criteria.
- Two references (Cosin 1998; Marnitz 2005) were retrospective case series of pre-treatment surgical lymph node assessment with no comparison group.
- Two references (Berman 1977; LaPolla 1986) were retrospective cohort studies of two surgical methods for pretreatment para-aortic lymph node assessment; the two surgical methods were not studied concurrently.
- Two reports (Podczaski 1989; Weiser 1989) were of cohort studies comparing two surgical methods for pre-treatment para-aortic lymph node assessment. It was not reported how patients were allocated, so it was not possible to ascertain if they were RCTs.
- One study (Leblanc 2007) was a case series of pre-treatment surgical lymph node assessment; 147 of the 184 women had presurgical radiological lymph node assessment, but this was not a concurrent comparison group.
- The grey literature search identified one scientific meeting abstract (Ramirez 2010). Personal communication with the author confirmed that this was a prospective comparison study of radiological and surgical findings in the same patients. There was no separate comparison group.

For further details of all the excluded studies see the Characteristics of excluded studies.

Risk of bias in included studies

The one included trial (Lai 2003) was at moderate risk of bias as it satisfied three criteria used to assess risk of bias (see Figure 1).

The trial reported that tumour size (break point at 6 cm) was used as a stratification factor which is an adequate method of treatment allocation, but it was not reported whether an effort was made to conceal this allocation sequence from patients and healthcare professionals involved in the trial. It was not reported whether the patients, health care professionals or outcome assessors were blinded. No patients were lost to follow up and it seemed unlikely that outcomes had been selectively reported as the authors provided overall and progression-free survival and used appropriate statistical techniques. They also reported several other pertinent outcomes. It was unclear if any other bias may have been present.

Effects of interventions

We found only one trial (Lai 2003) which included 61 women that met our inclusion criteria and this trial reported data on surgical versus clinical staging and an assessment of the two staging techniques used for surgical staging (Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging).

Surgical versus clinical staging

Overall survival: (see Analysis 1.1)

The trial of Lai 2003 found that women who underwent surgical staging for pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer had a significantly higher risk of death than women who underwent clinical staging (HR = 1.50, 95% CI: 1.04 to 2.17).

Progression-free survival: (see Analysis 1.2)

The trial of Lai 2003 found that women who underwent surgical staging for pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer had a significantly higher risk of relapse or disease progression than women who underwent clinical staging (HR = 1.71, 95% CI: 1.17 to 2.49).

Severe (grade 3 or 4) toxicity: (see Analysis 1.3)

There was no statistically significant difference in the risk of severe toxicity in women who underwent surgical and clinical staging for pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer (RR = 0.84; 95% CI: 0.46 to 1.53).

Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging

Overall survival—(see Analysis 2.1)

There was no statistically significant difference in the risk of death in women who underwent LAP and EXP surgical staging for pretreatment surgical para-aortic lymph node assessment in locally advanced cervical cancer (HR = 1.21; 95% CI: 0.78 to 1.85).

Progression-free survival—(see Analysis 2.2)

There was no statistically significant difference in the risk of relapse or disease progression in women who underwent LAP and EXP surgical staging for pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer (HR = 1.28; 95% CI: 0.83 to 1.96).

Blood loss—(see Analysis 2.3)

There was no statistically significant difference in the risk of blood loss in women who underwent LAP and EXP surgical staging for pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer (MD = -35.00; 95% CI: -225.56 to 155.56).

Severe (grade 3 or 4) toxicity—(see Analysis 2.4)

There was no statistically significant difference in the risk of severe toxicity in women who underwent LAP and EXP surgical staging for pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer (RR = 1.59; 95% CI: 0.64 to 3.96).

Duration of operation—(see Analysis 2.5)

There was no statistically significant difference in the duration of the operational procedure in women who underwent LAP and EXP surgical staging for pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer (MD = -23.00; 95% CI: -51.49 to 5.49).

DISCUSSION

Summary of main results

We found one RCT (Lai 2003) addressing the question of pretreatment para-aortic lymph node assessment in locally advanced cervical cancer. This trial aimed to compare clinical staging of locally advanced cervical cancer; CT or MRI to determine para-aortic nodal status, with surgical staging. The surgical approach was either laparoscopic or extraperitoneal for para-aortic nodal assessment. The trial found that women who underwent surgical staging had a significantly higher risk of death and persistent or recurrent disease than women who underwent clinical staging (The HR for death and persistent or recurrent disease, for surgical vs clinical staging, was 1.50 (95% CI: 1.04 to 2.17) and 1.71 (95% CI: 1.17 to 2.49) respectively). There was no significant difference between the number of women who experienced severe toxicity in the two staging groups. Overall and progression-free survival, operating time, blood loss, duration of operation and lymph node yield was not significantly different in the laparoscopic versus extraperitoneal surgical approach arms.

This RCT suggests that pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer is detrimental to patient survival. However, there are a number of factors which may have influenced the results and therefore potentially downgrade the value of this evidence. Apart from time from randomisation to starting radiotherapy, there were no statistically significant baseline imbalances between the clinical and surgical staging groups for any known prognostic factors. However, a higher proportion of patients with poor prognostic pre-treatment features were in the surgical compared to the clinical staging arm; 17/32 (53%) in the surgical staging arm had FIGO stage III disease, compared to 11/29 (38%) in the clinical staging arm. In the surgical arm 8/32 (25%) had a primary tumour > 6cm, in the clinical arm this was 5/29 (18%). Adenocarcinomas occurred more in the surgical arm; 5/32 (16%) versus 2/29 (7%) in the clinical arm. Although only histology (adenosquamous versus squamous carcinoma) had a significant impact on overall survival when prognostic factors were investigated by the trial authors.

The longer time from randomisation to starting radiotherapy in the surgical versus the clinical staging arm (median 20 days, range 10 to 46 days in the surgical arm versus a median of 11 days, range 2 to 52 days in the clinical staging arm) may have had an effect on outcomes. However, although there was a significant difference between the two groups at baseline, the authors state that there was no significant difference in time to starting radiotherapy between survivors and non survivors ($p = 0.90$, exact numbers for this analysis not given). The fact that a smaller, non-significant percentage of patients in the surgical arm received concurrent chemotherapy with their radiotherapy may have influenced the progression-free and overall survival data; 15/32 (47%) women in the surgical arm had concurrent chemotherapy versus 19/29 (65%) in the clinical staging arm.

The para-aortic lymph node yield was relatively low: mean of 6.1 with standard deviation (SD) of 2.2 for those staged via the laparoscopic route and 5.9 with SD of 2.9 for those in the extraperitoneal arm. It may be that the node dissection was incomplete and therefore insufficient to exert a positive effect on survival data. Overall the results of this one RCT are not sufficient alone to confirm or refute that there is a survival benefit from pre-treatment para-aortic lymph node assessment in locally advanced cervical cancer.

Overall completeness and applicability of evidence

Overall, the quality of the evidence was low (GRADE Working Group). We only identified one RCT that met our inclusion criteria and no good quality non-randomised studies with concurrent comparison groups to test the robustness of findings from this one trial; we have identified insufficient evidence to address the objectives of the review. The overall conclusions of the review are weak and there is no external validity. However, we recognise that within clinical practice the findings from a number of non-randomised case series on surgical staging of para-aortic nodal disease in advanced cervical cancer will continue to influence practice. Although we specified quality of life (QoL) as an outcome of interest, this was not reported in the RCT identified, nor in any of the excluded non-randomised trials. QoL after cancer treatment is an extremely important outcome; treatment related morbidity often degrades the quality of a patient's remaining time alive.

Quality of the evidence

The one RCT identified analysed the outcome of 61 women. Women were assigned to staging groups using an appropriate method of sequence generation (although it was unclear whether the allocation had been concealed). Eight women had a protocol violation; one woman randomised to the clinical staging arm had an extraperitoneal lymph node assessment. One woman randomised to have laparoscopic surgical staging in-fact had an extraperitoneal approach. In each arm there were two women who had no or incomplete radiotherapy. Two women with documented para-aortic node metastasis did not receive a radiation field covering the para-aortic nodes. However, analyses were based on an intention-to-treat basis which generally is less biased than the per protocol approach. There was no loss to follow up.

Although this RCT suggests that the pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer is detrimental to patient survival, the number of patients studied was small and, as identified above, there are a number of confounding factors which may have influenced the results.

The trial was at a moderate risk of bias, since it did not report adequate concealment of the randomisation sequence from healthcare providers and patients, or blinding of outcome assessors. Inadequate concealment of allocation and lack of blinding are often associated with an exaggeration of the effects of treatment (Moher 1998; Schulz 1995). The evidence on overall survival is more robust than that for progression-free survival, since blinding of outcome assessors is of less relevance for death than for disease progression.

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

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature and all studies were sifted and data extracted by at least two review authors independently. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias i.e. studies that did not find pretreatment surgical para-aortic lymph node assessment in locally advanced cervical cancer to have been effective may not have been published. We were unable to assess this possibility.

Agreements and disagreements with other studies or reviews

Pre-treatment assessment of para-aortic nodal status in locally advanced cervical cancer allows the option of tailoring the radiotherapy field to include the para-aortic nodal tissue or not. Prophylactic extended field radiotherapy for all those with advanced stage disease has not conclusively been shown to confer a survival advantage, but does significantly increase treatment related morbidity, particularly gastrointestinal complications (Chatani

1995; Haie 1988; Rotman 1995; Small 2007). Therefore, being able to accurately identify those women who do have para-aortic nodal disease and tailoring extended field radiotherapy to this sub-group of women with locally advanced cervical cancer is an attractive proposition.

Non-invasive radiological methods for detection of para-aortic nodal involvement remain unsatisfactory. Magnet Resonance Imaging (MRI) and Computerised Tomography (CT) have a similar diagnostic accuracy with reported false negative rates of 20% to 50% to detect those women with macroscopic lymph node metastasis (Choi 2006; Subak 1995). Positron Emission Tomography (PET) seems to be more successful at detecting involved para-aortic nodes; however reported sensitivities range from as low as 38% and up to 86% (Gold 2008). A recent conference report confirmed the poor sensitivity of PET at detection of small volume node disease; 22% if histologically confirmed para-aortic nodal metastasis was less than 5mm in size (Leblanc 2010). Additionally the improved detection of extra-pelvic metastatic disease by PET over MRI may not be translated into a survival advantage (Tsai 2010). A recent meta-analysis involving data on lymph node status in 5042 women with cervical cancer found that the pooled positive likelihood ratios (and 95% CI) were 15.3 (7.9 to 29.6) for PET, 6.4 (4.9 to 8.3) for MRI and 4.3 (3.0 to 6.2) for CT. The pooled negative likelihood ratios (and 95% CIs) were 0.27 (0.11 to 0.66) for PET, 0.50 (0.39 to 0.64) for MRI and 0.58 (0.48 to 0.70) for CT (Selman 2008).

Sentinel lymph node (SN) biopsy may be a minimally invasive, accurate assessment of lymph nodes status. A systematic review of the diagnostic performance of SN detection for assessing the nodal status in early stage cervical carcinoma showed that the combination of ^{99m}Tc and a blue dye for SN biopsy in these cases is a reliable method to detect lymph node metastases (Van De Lande 2007). No studies have looked at the potential role of sentinel lymph node assessment in advanced cervical cancer. Therefore using a surgical pre-treatment assessment of para-aortic nodal status remains of interest, despite the potential detrimental effects of surgical staging observed in the trial of Lai 2003. A number of case series report on the safety and feasibility of surgical lymph node assessment which then allows tailored external beam radiotherapy (Berman 1977; Chu 1997; Cosin 1998; Goff 1999; Hertel 2002; Holcomb 1999; LaPolla 1986; Leblanc 2007; Marnitz 2005; Podczaski 1989; Sonoda 2003; Weiser 1989). None of these case series included a concurrent comparison group so would not have met the inclusion criteria for this review even if non-randomised studies been included.

Initial reports on the use of surgical staging for the purpose of defining the need for extended field radiation identified that 2.5 to 6.8% of patients undergoing pretreatment staging laparotomy for cervical cancer will have a survival benefit as a consequence of radiotherapy treatment modifications based on surgical findings (LaPolla 1986; Tewfik 1982). However this was at the expense of significant morbidity. Reports in the 1970s and 1980s looked at the use of extraperitoneal staging to minimise the risk of enteric morbidity. A study in the 1970s compared 33 women who had transperitoneal approach to 40 who had a retroperitoneal approach to operative evaluation, including para-aortic lymphadenectomy, prior to radiation therapy (Berman 1977). The extraperitoneal approach resulted in a greater mean number of pelvic and para-aortic lymph nodes sampled; 23.1 versus 11.4. Those who

had a transperitoneal approach had a 30% small bowel complication rate following radiotherapy, all of which required surgical correction. In comparison, for those with the retroperitoneal approach the small bowel related morbidity rate was only 2.5%. The two surgical approaches were not studied concurrently; the transperitoneal approach was the earlier operative technique applied. Similarly, the authors of LaPolla *et al* in their retrospective cohort study of two surgical methods for pre-treatment evaluation of para-aortic nodes observed a higher rate of small bowel complications following radiotherapy that required surgical correction for women who had a transperitoneal surgical exploration versus those who had an extraperitoneal surgical assessment; 9% versus 0% (LaPolla 1986).

Weiser 1989 compared 128 women who had extraperitoneal surgical staging, including selective para-aortic lymphadenopathy followed by pelvic irradiation, with or without para-aortic irradiation with 156 women who had transperitoneal surgical staging. Those with confirmed para-aortic metastasis or thought to be at risk of undetected occult para-aortic metastasis received radiation to the para-aortic area. Surgical complications and pelvic complications secondary to radiotherapy were similar in each group. In agreement with other studies, bowel obstruction and non-obstructive enteric injuries were observed significantly more often in those who had transperitoneal staging compared to those who had extraperitoneal surgical staging; 18/156 (11.5%) versus 5/128 (3.9%), $p = 0.03$.

With the published evidence, as outlined above, suggesting that extraperitoneal surgical staging minimised morbidity, the shift within published literature was then to establish whether such an approach to pre-treatment assessment in locally advanced cervical cancer affords a survival benefit.

Cosin 1998 reported the results of a retrospective review of 266 women with stage IB to IV cervical carcinoma whom all had an extraperitoneal pelvic and para-aortic lymphadenectomy prior to receiving radiotherapy. Patients were divided into groups based on their lymph node status. Group A had negative lymph nodes; Group B had resected, microscopic lymph node metastases; Group C had macroscopically positive lymph nodes that were resectable at the time of surgery; and Group D had unresectable lymph nodes. All patients received standard pelvic radiotherapy. Patients with lymph node metastases received extended field irradiation. The use of concurrent and adjuvant chemotherapy increased over the time of this review. Although there was no survival difference between women in group C who received chemotherapy and those who did not. 133/266 (50%) women had histologically confirmed lymph node metastasis. Overall survival rates were not reported. The disease-free survival at ten years was 68% for group A, 35% group B, 46% group C and 0% (by 3 years) for group D. These data suggest that actually removing macroscopically involved lymph nodes confers a survival advantage. Whether this is due to removing the bulk of the disease, and/or ensuring the radiation field includes confirmed nodal disease is unclear.

The aim of Holcomb 1999s retrospective review of 274 women with stage IIB-IVA cervical cancer was to determine the effect of pretreatment surgical staging on survival. 89 women had pretreatment staging laparotomy and 172 patients underwent clinical staging. Para-aortic metastases were identified in 11/89 (12.3%) and intra-abdominal metastases were found in

4/89 (4.5%) women who had a staging laparotomy. Extended field radiotherapy and or systemic chemotherapy were given in these cases. The median survival of women who had a staging laparotomy was longer than that of women who had clinical staging; 29 months vs 19 months ($p = 0.01$). Multivariate analysis controlling for both stage and age showed pretreatment staging laparotomy to be a significant predictor of survival in this study ($p = 0.03$).

The retrospective single institute case series by Goff 1999 reported on the impact of surgical staging over a 5 year period for 98 women with locally advanced cervical cancer. 86/98 patients underwent surgical staging with removal of pelvic lymph nodes followed by removal of common iliac and, or para-aortic lymph nodes. The highest lymph nodes removed were sent for frozen section, and if positive for metastatic disease, scalene node dissection was performed through a separate incision. The surgical approach was retroperitoneal for 61/86 (69%) women, laparoscopic for 18/86 (21%) and intraperitoneal for 7/86 (10%) women. Based on the results of surgical staging, 37/86 (43%) women had a modification to the plan for standard pelvic radiation; 27/86 (32%) received extended field radiation. The authors did not report the factors which determined the use of extended field radiation for these 27 women. Of significance, the type of radiotherapy, pelvic versus extended field did not affect survival. Ten from 86 (11%) women surgically staged were identified for palliative treatment only, due to scalene metastasis or ovarian metastasis with extensive intraperitoneal disease. They were therefore spared the side effects of aggressive treatment with no chance of cure. So although this study did not show any survival benefit with the information obtained from surgical pre-treatment assessment of para-aortic node, it did identify a possible role of surgical staging in ensuring that women are not inappropriately treated with curative intent.

In order to potentially further reduce surgical related morbidity, laparoscopic para-aortic nodal assessment has now come to the forefront of research on the pretreatment assessment of para-aortic lymph node status in locally advanced cervical cancer (Hertel 2002; Leblanc 2007; Marnitz 2005; Querleu 1993; Sonoda 2003; Vergote 2002).

Hertel 2002 reported their single institute case series on laparoscopic surgical staging of 109 women with stage IB2 or higher stage cervical cancer. 101 women had para-aortic lymphadenectomy with mean of 10.4 (range 1 to 50) lymph nodes removed. 21/101 (20.8%) had positive para-aortic lymph nodes. 4/101 (3.7%) women had an intraoperative complication; two vascular injuries and two ureteric injuries. 2/101 (1.8%) required an intra-operative blood transfusion. 2/101 (1.8%) patients had post-operative complications; one retroperitoneal lymphocoele and one retroperitoneal hematoma. False-negative or false-positive results of MRI and CT imaging were identified on the basis of laparoscopic findings in 24/101 (22%) patients and led to a change in treatment plans. Ten women had false positive imaging for para-aortic lymph node metastasis, extended field radiotherapy had been planned; eight of these were treated with radical hysterectomy and two had pelvic radiotherapy. Planned operative management was changed to adjuvant chemotherapy in 14 women; in two patients due to intraperitoneal metastases (palliative setting) and to combined radiochemotherapy in 12 patients (positive para-aortic lymph nodes which had been

negative by imaging techniques). Thus for these patients extensive surgery was avoided. No overall or progression-free survival data were reported.

Marnitz 2005 reported on a retrospective case series of 84 women with locally advanced cervical cancer who had transperitoneal laparoscopic surgical staging, including right sided para-aortic lymphadenectomy and infra-mesenteric left-sided para-aortic lymphadenectomy (and then para-aortic lymphadenectomy up to infrarenal level if these lymph nodes contained metastasis on frozen section) prior to treatment with chemoradiotherapy. There were no intra-operative complications. 13/84 (15.5%) women developed post-operative lymphocysts >5cm, eight of whom required laparoscopic drainage. 32/84 (38%) women had histologically confirmed para-aortic nodal disease. The authors made no comment on how or whether nodal involvement was assessed preoperatively. 36/84 (43%) women were upstaged according to the histological findings following laparoscopic staging. Downstaging was not necessary in any patient following laparoscopic evaluation. Multivariate analysis identified that removal of more than five positive para-aortic lymph nodes was associated with significant improvement in overall survival compared with those who had less than five positive nodes removed ($p=0.01$). Removal of five or more involved pelvic or para-aortic lymph nodes took survival back to that for those with histologically negative nodes. The laparoscopic extraperitoneal approach potentially combines the benefits of an extraperitoneal approach with those of minimally invasive surgery. This was confirmed by the single institute case series of 111 women with FIGO stage IB2 to IVA cervical cancer who had laparoscopic extraperitoneal surgical staging (Sonoda 2003). They had no radiologically enlarged para-aortic lymph nodes. The mean operative time was 157 (SD = 46) minutes. The mean lymph node count was 19 (SD = 12). There were no intra-operative complications. 14/111 (13%) women had a postoperative complication, of which five required a second procedure under anaesthesia. 30/101 (27%) women who were confirmed to have lymph node metastasis. After an average (unclear whether this was mean or median) follow-up of 16.5 months, mean survival for the node-negative group was 38.6 months compared to 26.5 months for the node-positive group. 6/30 (20%) node-positive patients developed distant metastasis, compared to 5/81 (6%) node-negative women ($p = 0.05$).

Leblanc 2007 reported a single centre case series of 184 women with stage IB2-IVA cervical cancer who had pretreatment laparoscopic staging procedure, including transperitoneal abdominopelvic exploration and extraperitoneal bilateral infrarenal para-aortic lymph node dissection. They had no evidence of extrapelvic disease on pre-operative imaging; MRI and/or CT. Patients were then treated with definitive radiotherapy tailored according to the staging results; those with negative para-aortic lymph nodes were managed with external beam radiotherapy to the pelvis followed by intracavitary brachytherapy with intent to cure. Women with metastatic disease to para-aortic lymph nodes received extended-field external beam radiotherapy followed by intracavitary brachytherapy, with intent to cure. The study ran from 1997 to 2004, where from 1999 women also received concurrent platinum-based chemotherapy. Those with carcinomatosis were given platinum-based chemotherapy with palliative radiotherapy. 3/184 women had peritoneal carcinomatosis at the initial diagnostic laparoscopy so did not proceed to lymphadenectomy. Lymphadenectomy was abandoned in eight women; five due to macroscopically positive fixed nodes and three due to obesity. 4/181 (2.2%) had intra-operative complications and

19/181 (10.5%) had post-operative complications. Fourteen of these were symptomatic lymphocysts in the first 104 patients. Therefore the surgical technique was amended to include the creation of a transperitoneal opening in the left paracolic gutter for the final 77 women; with a reduction in lymphocyst formation to 3/77 (3.8%). 44/181 (24.3%) women had histologically confirmed para-aortic nodal disease. Histological findings from pretreatment staging affected the therapeutic approach taken in 96/184 (52.1%) women. Three women with stage II-IV patients, identified to have peritoneal carcinomatosis, were managed with full dose chemotherapy and pelvic irradiation. Of the 67 women with stages IB2 and IIA disease who would have received pelvic radiation only, 14 (20.8%) had positive para-aortic nodes and therefore received extended-field radiation. These women would have been under-treated if treatment planning was based on clinical staging alone. Conversely, 79/109 (72.4%) women with stages IIB-IVA disease had negative para-aortic lymph nodes and therefore received only pelvic radiotherapy. These women would have been over-treated with prophylactic extended field radiation if treatment planning was based on clinical staging. In this series, overall and disease-free survival was 58.3% (95% CI: 48.3 to 68.3) and 56.3% (95% CI: 46.9 to 65.7) respectively at 5 years. A Cox proportional hazards model revealed that survival was significantly worse when tumour size was >5 cm ($p = 0.007$) and when para-aortic nodes were positive ($p = 0.02$). There was no survival difference between those with node-negative disease who received a pelvic treatment alone and patients with microscopic nodal disease (≤ 5 mm) managed with definitive extended-field (chemo)radiation therapy; this suggests a therapeutic benefit in para-aortic node dissection.

Additionally, Occelli 2000 demonstrated in a porcine study, decreased formation of adhesions after the laparoscopic extraperitoneal approach when compared to the transperitoneal laparoscopic approach. Of note, the majority of adhesions formed after the extraperitoneal approach were located outside the para-aortic external radiation field. Intraabdominal adhesion formation is a major causative factor for radiation induced small-bowel injury after surgical staging, so means of reducing adhesion formation are likely to impact on reducing morbidity associated with pretreatment surgical staging for locally advanced cervical cancer. Gold 2008 reported the combined results of three RCTs retrospectively, using women from one of the randomisation arms in each of the contributing studies. Women with cervical cancer who had negative para-aortic lymph nodes as identified by pretreatment surgical staging were compared with those who had radiographic exclusion of para-aortic lymph node metastases before they received treatment with pelvic radiation and brachytherapy plus cisplatin based chemotherapy. The women were pooled from three Gynecologic Oncology Group (GOG) RCTs (Rose 1999; Whitney 1999; Lanciano 2005). GOG 85 (Rose 1999) was a randomised trial of radiotherapy in combination with three concurrent chemotherapy regimens; cisplatin alone; cisplatin, fluorouracil, and hydroxyurea; and hydroxyurea alone; in patients with locally advanced cervical cancer. All patients were required to have undergone extraperitoneal para-aortic lymphadenectomy. GOG 120 (Whitney 1999) compared primary radiation therapy plus hydroxyurea to irradiation plus fluorouracil and cisplatin for patients with locally advanced cervical carcinoma. All women underwent para-aortic lymphadenectomy via a retroperitoneal approach. GOG 165 (Lanciano 2005) was a comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation for

women with advanced cervical cancer. Surgical para-aortic lymph node assessment was optional, no information was given by the authors on how women were selected for surgical nodal assessment. The Gold 2008 study analysed data from 685 patients; 177 from GOG 85 in the radiotherapy and cisplatin plus 5-FU arm; 176 from GOG 120 in the radiotherapy and cisplatin arm or radiotherapy and cisplatin with 5-FU plus hydroxyurea arm; and 159 from GOG 165 in the radiotherapy plus cisplatin arm. Staging was completed surgically in 555 patients (including 29 patients on GOG 165 in which the procedure was optional) and radiographically in 130 patients. Patients in the radiological assessment group had better performance status ($p < 0.01$), less advanced stage ($p = 0.023$), and smaller tumour size ($p = 0.004$) compared with those in the surgical assessment group. Women with stage III and IV disease in the surgical group had better 4-year progression-free survival (48.9% versus 36.3%) and overall survival (54.3% versus 40%) compared with those in the radiological group. Actual numbers for the survival data were not reported. Overall, those in the radiological evaluation group had a poorer prognosis than those in the surgical assessment group; the hazard ratio for disease progression was 1.35 (95% CI: 1.01 to 1.81) and the hazard ratio for death was 1.46 (95% CI: 1.08 to 1.99). However, as women were not randomised in terms of surgical para-aortic lymph node assessment, selection bias is likely to be a significant problem and therefore the validity of these results in respect to the objectives of this review is low.

The non-RCT published data, as discussed above, suggests that laparoscopic pre-treatment staging and assessment of para-aortic lymph nodes in locally advanced cervical cancer is more accurate than currently available imaging modalities. It is safe with low intra and post operative morbidity; evidence suggests that the laparoscopic approach can eliminate major post operative complications, with an overall complication rate for laparoscopic staging less than 3% compared to 10 to 15% following transperitoneal laparotomy (Hertel 2002; Sonoda 2003; Leblanc 2007; LaPolla 1986; Sonoda 2003). However, the included RCT in this review did not find any significant difference in the postoperative morbidity between these two techniques. The laparoscopic approach results in fewer postoperative adhesion formation, and therefore less bowel related complications if the woman goes on to receive extended field radiotherapy compared to transperitoneal laparotomy. Laparoscopic staging appears to be comparable to laparotomy techniques in terms of node count and results in treatment modification 22 to 58% of the time. (Goff 1999; Hertel 2002; Lai 2003; Leblanc 2007). Complete debulking of involved para-aortic lymph nodes appears to translate into a survival advantage compared to when no nodal debulking is performed. Surgical pre-treatment assessment of para-aortic lymph nodes in locally advanced cervical cancer results in treatment modifications for 22 to 58% of women; although it is not proven that this results in a positive impact on survival.

AUTHORS' CONCLUSIONS

Implications for practice

From the one available RCT we found insufficient evidence that pre-treatment surgical para-aortic lymph node assessment for locally advanced cervical cancer is beneficial, and it may actually have an adverse effect on survival. However this conclusion is based on analysis of

a small single trial and therefore definitive recommendations for clinical practice cannot currently be made. Until further RCTs of sufficient size and quality are available to guide clinical practice, the body of non-RCT data as outlined above will continue to influence practice.

Therefore the decision to offer surgical pre-treatment assessment of para-aortic lymph nodes in locally advanced cervical cancer needs to be individualised. If embarked on it should be done laparoscopically, with the intent of complete debulking of any involved nodes. The uncertainty regarding any impact on survival from pre-treatment para-aortic lymph node assessment should be discussed openly with the women.

Implications for research

Good quality prospective multi-centre RCTs are required to assess the effectiveness and safety of pre-treatment surgical para-aortic lymph node assessment for locally advanced cervical cancer. Noninvasive radiological and minimally invasive surgical techniques need to be compared in such RCTs. Patient outcomes and health service costs should be assessed. QoL outcome data, using appropriate validated scales, and adverse event outcomes should also be reported within such trial settings.

Acknowledgments

We thank Chris Williams for clinical and editorial advice, Jane Hayes for designing the search strategy and Gail Quinn and Clare Jess for their contribution to the editorial process. We also thank Heather Dickinson for many helpful suggestions and being a coauthor in the protocol.

Sources of support

Internal sources

- Department of Gynaecological Oncology, St Bartholomews Hospital, Barts and The London NHS Trust, London, UK.

External sources

- Department of Health, UK.

NHS Cochrane Collaboration programme Grant Scheme CPG-506

CHARACTERISTICS OF STUDIES

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

Lai 2003

Methods	Two-step prospective randomised controlled trial comparing clinical and surgical staging in previously untreated locally advanced cervical carcinoma Step one: Clinical staging (arm A) versus surgical staging (arm B) Step two: Laparoscopic (LAP) versus the extraperitoneal (EXP) approach Single centre Trial in Taiwan.
Participants	61 women with histologically confirmed FIGO stage IIB to IVA cervical cancer. 29 in clinical staging arm, 32 in surgical staging of which 17 in extraperitoneal arm and 15 in laparoscopic arm In the clinical staging arm the median age was 53 years, range 33 to 70. In the surgical staging arm it was 56 years, range 36 to 69 years

FIGO stage in the clinically staged arm was; IIB: 18 (62%) women, IIIA: 1 (3%), IIIB: 10 (35%). In the surgical staged arm it was; IIB: 15 (47%), IIIA: 2 (6%) and IIIB: 15 (47%)

The primary cervical tumour was >6cm in 5/29 (17%) of those in the clinically staged arm and 8/32 (25%) in the surgically staged arm

27 (93%) of the women in clinical staging arm and 27 (84%) in the surgical staging arm had squamous cell carcinoma. The remaining women in each arm had adenocarcinoma or adenosquamous carcinoma

Tumour grade was not reported.

All women had a performance status (PS) of 0 to 2, but numbers for each PS was not reported by treatment arm

Interventions	Interventions:
	<ul style="list-style-type: none"> • Clinical staging (tumour size and FIGO stage was measured by pelvic examination, with either a contrast enhanced CT scan or an MRI scan to determine nodal status) • Surgical staging (extraperitoneal (EXP) or laparoscopic (LAP) approach) <ul style="list-style-type: none"> ○ Further randomised comparison of EXP with LAP approach in the surgical staging group. <ul style="list-style-type: none"> ◇ The skin incision could be either midline vertical or lateral "J," and so on. The retroperitoneum was exposed by rolling the peritoneum medially till the psoas muscle and iliac vessels were visualised. The bifurcation of the aorta, the inferior vena cava, the ovarian vessels, inferior mesenteric artery, and the ureters were identified. Any enlarged or suspicious nodes were excised, or biopsied if unresectable. The nodal tissue from the level of common iliac bifurcation to the inferior mesenteric artery was removed. Lymph nodes submitted for pathology were separately submitted by location (para-aortic or pelvic) and laterality. Dissection above the level of the inferior mesenteric artery was restricted to those cases with palpable suspicious nodes. The caudal and cephalic extent of lymph node dissection and unresectable nodes were outlined with clips. Sampling of lower pelvic nodes could be performed if indicated or at the discretion of the responsible surgeon (if lateral J incision was used, only unilateral pelvic nodes were assessed). Intraperitoneal lavage cytology was performed via a small opening after completion of the staging procedures. ◇ LAP: The patient was placed in the supine position in the Trendelenburg position. Pneumoperitoneum was obtained with a Veress needle insertion at the midpoint between the umbilicus and xyphoid process; a 5-trocar technique was used. Intraperitoneal lavage cytology and biopsy of any suspicious area was done after initial laparoscopic overview of the whole abdomen. The extent of lymph node dissection was similar to that of EXP.
Outcomes	<ul style="list-style-type: none"> • Overall survival. • Progression free survival.

All patients randomised to receive LAP staging were operated on under the collaboration of attending surgeons from the Divisions of Gynecologic Oncology and Gynecologic Endoscopy, Department of Obstetrics and Gynecology. EXP staging procedures were performed by fellows under supervision or by attending gynaecologic oncologists

- Percent improvement in para-aortic node metastasis detection.
- Feasibility and efficacy of both surgical staging methods; operation time, blood loss and lymph node yield.
- Toxicity and survival of extended-field radiation plus chemotherapy in the management of surgical staging documented para-aortic lymph node metastasis.

The median follow-up time of surviving patients was 58 months

Notes

Patient accrual was stopped after interim analysis due to significantly worse progression free survival in the surgical staging arm. Data was analysed after a further 24 months follow up. The research team planned to randomise 120 patients, to ensure a > 80% power to detect a 20% improvement in detecting paraaortic lymph node metastasis. The interim analysis was after enrolment of 61 women

There was no significant difference between the clinical and surgical staging groups in terms of women who received concurrent chemotherapy (15/32 = (47%) versus 19/ 29 = (65%), $p = 0.198$) but the time from randomisation to starting radiotherapy was significantly longer for surgical staging (median = 20 days (range 10 to 46 days) versus 11 days (range 2 to 52 days), $P = 0.001$)

Paraaortic lymph node metastasis were identified in 11 of the 32 women in the surgical staging group; 6 of 15 (40%) in the laparoscopic staging group and 5 of 17 (29%) in the extraperitoneal staging group

grade 3 treatment related toxicities occurred in 13/29 (45%) women in the clinical staging group and 12/32 of those in the surgical staging group (laparoscopic 7/15 (47%) and extraperitoneal 5/17 (29%))

Two women in the surgical staging group and one in the clinical staging group died of treatment related complications without recurrent or persistent disease

Recurrent or persistent disease occurred in 10/29 (34%) of those clinically staged and 21/32 (66%) women who were surgically staged ($p = 0.021$). Local pelvic recurrence occurred in 5/29 (17%) women who were staged clinically and 12/32 (38%) of those staged surgically. Distant recurrence, with or without pelvic recurrence occurred in 5/29 (17%) of those staged clinically and 9/32 (28%) of those staged surgically

Median time to recurrence was 14.3 months (range 6.2 to 23.9 months) for those clinically staged and 6.1 months (range 1.4 to 45.9 months) for those staged surgically

At 96 months from 1st enrolment, 11/29 (38%) of the women in the clinical staging arm and 22/32 (69%) in the surgical staging arm had died

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Those who were eligible and had signed informed consent were at first randomized to receive either arm A or arm B, then patients on arm B were randomized between LAP and EXP. Stratification factor was tumor size (break point at 6 cm)"
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed: 61/61 (100%)
Free of selective reporting?	Yes	Trial appears to have reported all pertinent outcome data types. Although it would have been beneficial to have reported QoL it seemed very unlikely that this would have been selectively reported
Free of other bias?	Unclear	Insufficient information to assess whether an additional source of bias may have been present

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Berman 1977	Not an RCT: a retrospective cohort study of two surgical methods for pre-treatment paraaortic lymph node assessment; the two surgical methods were not studied concurrently
Cosin 1998	Not an RCT: A retrospective case series of pre-treatment surgical lymph node assessment with no comparison group
Gold 2008	Not an RCT: Results from three randomised controlled trials retrospectively grouped together using women from one of the randomisation arms in each of the contributing studies. Women were not randomised in terms of surgical para-aortic lymph node assessment, so selection bias was likely to be a significant problem
LaPolla 1986	Not a RCT: A retrospective cohort study of two surgical methods for pre-treatment paraaortic lymph node assessment; the two surgical methods were not studied concurrently
Leblanc 2007	Not an RCT: A case series of pre-treatment surgical lymph node assessment with no concurrent comparison group
Marnitz 2005	Not an RCT: A retrospective case series of pre-treatment surgical lymph node assessment with no comparison group
Podczaski 1989	A cohort study of two surgical methods for pre-treatment paraaortic lymph node assessment. It was not reported how patients were allocated, so it was not possible to ascertain if this was an RCT, nor if they were studied concurrently
Ramirez 2010	Not an RCT: A prospective comparison study of radiological and surgical findings in the same patients. There was no separate comparison group
Weiser 1989	A cohort study of two surgical methods for pre-treatment paraaortic lymph node assessment. It was not reported how patients were allocated, so it was not possible to ascertain if this was an RCT, nor if they were studied concurrently

Data and analyses

Comparison 1 Surgical versus clinical staging

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

Comparison 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
2 Progression-free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
3 Blood loss	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Severe (grade 3 or 4) toxicity	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Duration of operation	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 1.1

Comparison 1 Surgical versus clinical staging, Outcome 1 Overall survival

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 1 Surgical versus clinical staging

Outcome: 1 Overall survival

Analysis 1.2

Comparison 1 Surgical versus clinical staging, Outcome 2 Progression-free survival

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 1 Surgical versus clinical staging

Outcome: 2 Progression-free survival

Analysis 1.3

Comparison 1 Surgical versus clinical staging, Outcome 3 Severe (grade 3 or 4) toxicity

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 1 Surgical versus clinical staging

Outcome: 3 Severe (grade 3 or 4) toxicity

Analysis 2.1

Comparison 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging, Outcome 1 Overall survival

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging

Outcome: 1 Overall survival

Analysis 2.2

Comparison 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging, Outcome 2 Progression-free survival

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging

Outcome: 2 Progression-free survival

Analysis 2.3

Comparison 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging, Outcome 3 Blood loss

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging

Outcome: 3 Blood loss

Analysis 2.4

Comparison 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging, Outcome 4 Severe (grade 3 or 4) toxicity

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging

Outcome: 4 Severe (grade 3 or 4) toxicity

Analysis 2.5

Comparison 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging, Outcome 5 Duration of operation

Review: pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer

Comparison: 2 Laparoscopic (LAP) versus extraperitoneal (EXP) surgical staging

Outcome: 5 Duration of operation

Appendix 1. MEDLINE search strategy

Medline Ovid 1950 to January week 2 2011

1. exp Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. exp Lymph Node Excision/
5. (lymph node adj5 (excision or dissection)).mp.
6. lymphadenectomy.mp.
7. 4 or 5 or 6
8. exp Lymph Nodes/
9. (lymph adj node*).mp.
10. exp Lymphatic Metastasis/
11. (lymph* adj5 metasta*).mp.
12. 8 or 9 or 10 or 11
13. exp Surgical Procedures, Operative/
14. surg*.mp.
15. "surgery".fs.
16. exp Laparoscopy/
17. laparoscop*.mp.
18. exp Laparotomy/
19. laparotomy.mp.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 12 and 20
22. 7 or 21
23. 3 and 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomized.ab.
27. randomly.ab.
28. trial.ab.
29. groups.ab.

30. exp Cohort Studies/
31. cohort*.mp.
32. exp Retrospective studies/
33. (case* and series).mp.
34. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 23 and 34

key: mp=title, original title, abstract, name of substance word, subject heading word

pt=publication type

fs=floating subheading

Appendix 2. Embase search strategy

Embase Ovid 1980 to 2011 week 03

1. exp uterine cervix tumor/
2. (cervi* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. exp lymphadenectomy/
5. (lymph node* adj5 (excis* or dissect*)).mp.
6. lymphadenectomy.mp.
7. 4 or 5 or 6
8. exp lymph node/
9. (lymph adj node*).mp.
10. exp lymph node metastasis/
11. (lymph* adj5 metasta*).mp.
12. 8 or 9 or 10 or 11
13. exp surgery/
14. surg*.mp.
15. su.fs.
16. exp laparoscopy/
17. laparoscop*.mp.
18. exp laparotomy/
19. laparotomy.mp.

20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 12 and 20
22. 7 or 21
23. 3 and 22
24. exp controlled clinical trial/
25. randomized.ab.
26. randomly.ab.
27. trial.ab.
28. groups.ab.
29. exp cohort analysis/
30. cohort*.mp.
31. exp retrospective study/
32. exp prospective study/
33. (case* and series).mp.
34. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 23 and 34

key:

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

ab=abstract

fs=floating subheading

Appendix 3. Central search strategy

CENTRAL Issue 1 2011

1. MeSH descriptor Uterine Cervical Neoplasms explode all trees
2. cervi* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)
3. (#1 OR #2)
4. MeSH descriptor Lymph Node Excision explode all trees
5. lymph node* near/5 (excis* or dissect*)
6. lymphadenectomy
7. (#4 OR #5 OR #6)

8. MeSH descriptor Lymph Nodes explode all trees
9. lymph node*
10. MeSH descriptor Lymphatic Metastasis explode all trees
11. lymph near/5 metasta*
12. (#8 OR #9 OR #10 OR #11)
13. MeSH descriptor Surgical Procedures, Operative explode all trees
14. surg*
15. Any MeSH descriptor with qualifier: SU
16. MeSH descriptor Laparoscopy explode all trees
17. laparoscop*
18. MeSH descriptor Laparotomy explode all trees
19. laparotomy
20. (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
21. (#12 AND #20)
22. (#7 OR #21)
23. (#3 AND #22)

History

Protocol first published: Issue 1, 2010

Review first published: Issue 4, 2011

Differences between protocol and review

Restriction to RCTs

The search strategy identified one RCT that met our inclusion criteria and although we specified that we would also include non-randomised studies of sufficient quality we decided to restrict the review to RCTs as they provide the best level of evidence. In the protocol we had stated the following:

“Since we expected to find few RCTs of surgical interventions (Johnson 2008), non-randomised studies with concurrent comparison groups will be included:

- Quasi-randomised trials, non-randomised trials, prospective and retrospective cohort studies, and case series of 30 or more patients.

Case-control studies and case series of fewer than 30 patients will be excluded”

Searches

In the protocol, we stated:

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

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

Data extraction

The included trial did not report adjusted results, so we were unable to extract these. In the protocol we had stated the following:

“Both unadjusted and adjusted statistics will be extracted, if reported. If adjusted statistics are reported, we will record the variables used in adjustment.”

Risk of bias

In the protocol, we stated that “We coded satisfactory level of loss to follow-up for each outcome”. We were unable to do this as loss to follow-up was not reported separately for each outcome in the included papers.

Risk of bias was not examined in non-randomised studies as the review was restricted to RCTs. In the protocol we stated the following:

“The risk of bias in non-randomised studies will be assessed in accordance with four additional criteria:

Cohort selection

1. Were relevant details of criteria for assignment of patients to treatments provided?
 - i. Yes
 - ii. No
 - iii. Unclear
2. Was the group of women who received the experimental intervention (Surgical para-aortic lymph node assessment and dissection) representative?
 - i. Yes, if they were representative of women with cervical cancer of FIGO stage IB2 to IV
 - ii. No, if group of patients was selected
 - iii. Unclear, if selection of group was not described
3. Was the group of women who received the comparison intervention (Alternative surgical procedure or no surgical pre-treatment lymph node assessment) representative?

- i. Yes, if drawn from the same population as the intervention group
- ii. No, if drawn from a different source
- iii. Unclear, if selection of group not described

Comparability of treatment groups

1. Were there no differences between the two groups or differences controlled for, in particular with reference to age, FIGO stage, histological type, histological grade, performance status, grade of operating surgeon (if direct comparison of surgical interventions)?
 - i. Yes, if at least two out of six of these characteristics were reported and any reported differences were controlled for
 - ii. No, if the two groups differed and differences were not controlled for.
 - iii. Unclear, if fewer than two of these characteristics were reported even if there were no other differences between the groups, and other characteristics had been controlled for.

Dealing with missing data

In the protocol, we stated:

“If data were missing or only imputed data were reported we contacted trial authors to request data on the outcomes only among participants who were assessed.”

This was not done, as the trial did not impute missing data.

Data synthesis

We were unable to pool the results in meta-analyses as there was only one included trial. Therefore it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup analyses or sensitivity analyses. The following sections of the protocol were therefore removed:

“Assessment of heterogeneity

Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which 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 sub-group analyses (see below). If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects such as publication bias. If these plots suggest

that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, further meta-analyses will be performed using fixed effects models.

Data synthesis

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

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

If any trials had multiple treatment groups, the 'shared' comparison group was divided into the number of treatment groups and comparisons between each treatment group and the split comparison group was treated as independent comparisons.

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

Where possible, indirect comparisons, using the methods of Bucher 1997 were used to compare competing interventions that had not been compared directly with each other.

Subgroup analysis and investigation of heterogeneity

Sub-group analyses were performed, grouping the trials by:

- Histological grade; high or low grade.
- FIGO stage (Stage I, II, III, IV).
- Route of surgery

Factors such as age, performance status, length of follow-up, adjusted/unadjusted analysis were considered in interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analyses were performed (i) excluding non-randomised studies (ii) excluding studies at high risk of bias and (iii) using unadjusted results".

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

The role of surgical assessment of lymph nodes before treatment for women with locally advanced cervical cancer

Cervical cancer arises from the neck of the womb (cervix). Cervical screening programmes have decreased the rate of advanced cervical cancer. However, a significant number of cases still present with locally advanced disease that involves large cervical tumours (> 4cm) or tumours that extend to the upper vagina. The larger the primary tumour, the greater the likelihood of metastasis (spread of cancer to other areas of the body). Cervical cancer spreads to the lymph nodes in the pelvis and around the aorta (one of the major blood vessels in the abdomen). Stage is a standardised assessment of the size of the cancer and if it has spread to adjacent or distant sites. Stage for stage, women with para-aortic lymph node metastases at presentation have a lower survival than those who do not have para-aortic metastases at presentation.

Accurate detection of involved para-aortic lymph nodes helps to tailor radiotherapy so that it includes this area (extended field radiotherapy). It also provides prognostic information. Different methods have been used to detect para-aortic lymph node metastases including surgical and radiological (various types of x-rays) techniques, however it is unclear which is more accurate.

The purpose of this review was to assess the available literature on the effectiveness and safety of pre-treatment surgical para-aortic lymph node assessment for locally advanced cervical cancer. We found only one randomised controlled trial (RCT) that assessed nonsurgical staging versus surgical staging. We found limited evidence that suggested that clinical staging may offer a survival benefit (in terms of overall and progression-free survival) compared with surgical staging, but the strength of the evidence from this small trial is weak and the trial was at moderate risk of bias. There was no statistically significant difference in any of the reported outcomes between two surgical staging techniques examined in the trial.

Due to the small number of patients with locally advanced cervical cancer in only one included trial there was insufficient evidence to conclude that any of the staging techniques are superior to each other. This review highlights the need for future good quality, well designed trials which report not only survival and severe adverse event outcomes but also examine quality of life (QoL) outcome data.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Lai 2003	+	?	?	+	+	?

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