Neoadjuvant chemotherapy and surgery versus chemoradiotherapy for locally advanced cervical cancer (Protocol)

Athanasiou A, Bowden SJ, Paraskevaidis E, Shylasree TS, Lathouras K, Kyrgiou M

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[Intervention Protocol]

**Neoadjuvant chemotherapy and surgery versus chemoradiotherapy for locally advanced cervical cancer**

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**ABSTRACT**

**Objectives**

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

The aim of this review is to compare neoadjuvant chemotherapy (NACT) followed by radical surgery (RS) versus chemoradiotherapy (CRT) for locally advanced cervical cancer.
BACKGROUND

Description of the condition

Cervical cancer is almost always caused by high risk types of human papillomavirus (HPV), which is a very common sexually transmitted infection. Risk factors for cervical cancer include a large number of sexual partners, early onset of sexual intercourse, smoking and a weak immune system (Franco 2001). Most people will be exposed to HPV infection and in most this regresses spontaneously within 12 to 24 months. In a minority of women the infection persists and can lead to the development of low- or high-grade pre-invasive cervical lesions, or even cancer, if left untreated. The interval between the initial HPV infection and progression to cancer might be longer than 10 years (de Sanjose 2018). Pre-invasive or very early invasive cervical disease is usually asymptomatic and can be detected through cervical screening; more advanced disease can cause post-coital or spontaneous vaginal bleeding, vaginal discharge, and pelvic or back pain (Petignat 2007).

Cervical cancer is the fourth most common female malignancy globally, mainly due to the absence of screening in low-resource settings (Arbyn 2020). Cervical cancer age-standardised incidence varies from less than 10 cases per 100,000 women in many high-resource countries to more than 40 cases per 100,000 women in some low-resource countries (GLOBOCAN 2018 incidence). Similarly, cervical cancer age-standardised mortality varies from less than three deaths per 100,000 women in many high-resource countries to more than 30 deaths per 100,000 women in some low-resource countries (GLOBOCAN 2018 mortality). With the advent of national screening programmes in developed countries, the majority of invasive cancers are prevented, whilst many women with invasion are diagnosed with early small-volume disease (Cancer Research UK 2010-2014). In the absence of organised screening, many of these tumours present with symptoms and locally advanced cervical cancer (LACC) at diagnosis WHO 2018 (i.e. FIGO 2018 stage IB3/IA2/IB/IIA-B/IVA (Bhatla 2019; Table 1) or FIGO 2009 stage IB2/IA2/IIB/IIB-B/IVA (Pecorelli 2009; Table 1)) with poor prognosis (Office for National Statistics 2013-2017).

Description of the intervention

Radiotherapy (RT) had been the mainstay of treatment for LACC, although primary radical surgery (RS) has been practiced in some centres for selected IB3/IA tumours as per 2018 FIGO staging (IB2/ IIA as per FIGO 2009 criteria) (Park 2012). In 1999, the National Cancer Institute (NCI) issued a clinical alert (Josefson 1999) that chemoradiotherapy (CRT) improves survival when compared to RT alone based on the results of five randomised clinical trials (RCTs) (Keys 1999; Morris 1999; Peters 2000; Rose 1999; Whitney 1999). A systematic review and meta-analysis also reported that CRT improved overall survival by 7.5% compared to RT alone for treatment of LACC (Datta 2017). Platinum-based CRT has since become the standard of care for LACC globally (Chuang 2016; Cibula 2018; Marth 2018), even for stage IIIB (Shrivastava 2018).

Despite the improved outcomes with the combination of chemotherapy and radiotherapy, a significant number of women experience relapse and many of these develop distant metastases (25% to 40%) (CRT for Cervical Cancer Meta-Analysis). Toxicity of radical RT also remains a significant problem for women treated for LACC, particularly since a substantial number experience gastrointestinal and urogenital side effects, as well as ovarian failure (Morris 2015; Viswanathan 2014), which might be further aggravated by the combination of chemotherapy and RT (Datta 2017).

Alternative regimens that could further improve survival, reduce the risk of distant metastases and further reduce toxicity have been proposed, although their oncological safety has not been extensively studied. The administration of neoadjuvant chemotherapy to include a combination of platinum and taxane followed by radical hysterectomy in LACC has also been proposed (Schwab 2014). These advocates support that chemotherapy could reduce tumour size to permit surgery and reduce systemic failures by treating distant micrometastases. However, opponents express concerns that taxanes have little survival benefit over platinum alone (Veerasar 2007), whilst survival may be inferior without radiotherapy in these highly radiosensitive tumours.

How the intervention might work

Neoadjuvant chemotherapy (NACT) prior to RS or RT for cervical cancer was first proposed in the 1980s and has the potential to shrink tumour size, control micro-metastases and enhance tumour radiosensitivity by increasing tumour vasculature and improving tumour cell oxygenation (Lapresa 2015). A 2012 Cochrane systematic review of individual participant data from RCTs found that NACT followed by RS improved overall survival compared to RS alone in both early and locally advanced cervical tumours (Rydzewska 2012). Two further meta-analyses of RCTs comparing NACT followed by RS also reported improved overall survival compared to RT alone in women with LACC (NACT for LACC Meta-analysis Collaboration; Osman 2016). More recently, NACT has also been used experimentally prior to fertility-sparing surgery (FSS: trachelectomy or conisation) to shrink bulky (>2cm) early cervical tumours below the 2 cm cut-off of eligibility for FSS (Kobayashi 2006; Maneo 2008; Wang 2013).

The standard-of-care for LACC is CRT. However, the high toxicity of pelvic RT is a major concern (Morris 2015). As such, NACT prior to RS might be a more attractive alternative over CRT since RT is avoided. Furthermore, given that over 90% of cervical cancers are diagnosed in low- and middle-income countries, NACT followed by RS could permit access to treatment in low-resource settings with minimal infrastructure for RT (Cohen 2019). Drawbacks of NACT include the possibility of non-response to chemotherapy, which could be as high as 25% (Minig 2013); in these cases, definitive treatment is delayed unnecessarily, which may compromise survival. Additionally, high-risk patients (such as patients with lymphovascular space invasion) might still need adjuvant RT with its related toxicity. Finally, chemotherapy-induced radio-resistance remains a concern due to cross-resistance between RT and some chemotherapeutic agents (González-Martin 2008).

Why it is important to do this review

Although NACT followed by RS has been found to offer survival benefit over RS or RT alone, the comparative outcomes over the current standard of care (CRT) remains unclear. Although scarce observational data reported comparable or even better survival for NACT+RS when compared to CRT in LACC (Minig 2013; Yin 2011), this was refuted by an RCT reporting better survival for CRT when compared to NACT+RS at the cost of increased late toxicity (Gupta 2018). The populations across studies differed; the studies included
different distribution of disease stages and rates of patients with radiologically suspicious lymph nodes ahead of treatment.

Given the lack of clarity in the existing evidence base, a systematic review is required to systematically and critically appraise the existing evidence base.

**OBJECTIVES**

The aim of this review is to compare neoadjuvant chemotherapy (NACT) followed by radical surgery (RS) versus chemoradiotherapy (CRT) for locally advanced cervical cancer.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomised controlled trials (RCTs) comparing neoadjuvant chemotherapy (NACT) + radical surgery (RS) with chemoradiotherapy (CRT) for treatment of locally advanced cervical cancer (LACC), i.e. of stage IB2/IA2/IIA-B/IVA according to FIGO 2009 staging, or stage IB3/IA2/IIA-B/IVA according to FIGO 2018 staging (Table 1). We will include studies which have included either all or a subset of LACC stages. We will use the FIGO 2018 staging and convert, if needed, FIGO 2009 stages to FIGO 2018 stages (e.g. IB2 FIGO 2009 will be converted to IB3 FIGO 2018). However, if this is not feasible and the majority of studies have used FIGO 2009 staging, we will use the older FIGO staging.

**Types of participants**

Women aged 18 years or older with locally advanced cervical cancer (LACC).

**Types of interventions**

Experimental arm: neoadjuvant chemotherapy (NACT) + radical surgery (RS) (i.e. radical hysterectomy), Standard of care: chemotherapy (CRT) plus external beam radiotherapy (EBRT) and brachytherapy (BT).

**Types of outcome measures**

We will assess outcomes regarding both efficacy and toxicity.

**Primary outcomes**

- Overall survival (OS): interval between randomisation and death of any cause.
- Disease-free survival (DFS): interval between randomisation and recurrence (local, regional or distant).

**Secondary outcomes**

- Recurrence: Local, regional or distant.
- Toxicity: acute toxicity (gastrointestinal (e.g. acute diarrhoea), urological (e.g. acute cystitis), gynaecological (e.g. acute vaginal mucositis), haematological (e.g. anaemia), skin (e.g. skin erythema), lymphoedema), late toxicity (gastrointestinal (e.g. chronic diarrhoea), urological (e.g. urge incontinence), gynaecological (e.g. vaginal stenosis), lymphoedema). Overall toxicity will include both acute and late toxicity of any grade (grade 1 (mild), grade 2 (moderate), grade 3 (severe/medically significant), grade 4 (life-threatening) or grade 5 (death) (NCI 2017)). The definition of acute/late toxicity is known to differ across studies i.e. cut-offs of 42, 60 or 90 days have been used (Kirwan 2003); which cut-off we will use will depend on the cut-offs used by individual eligible studies. Analyses will be conducted for acute and late toxicity and by grade (1/2 vs 3/4/5) separately if possible.

- Quality of Life (QoL) scales, such as QLC-C30 (for any cancer) and QLQ-CX24 (for cervical cancer only) developed by EORTC (European Organization for Research and Treatment of Cancer (EORTC)). We will preferably use QLQ-CX24, since this scale has been developed specifically for cervical cancer patients.

**Search methods for identification of studies**

The literature search will be designed and executed by experienced Cochrane Information Specialists. There will be no time, place or language restrictions. If publications other than English are identified, they will be translated into English.

**Electronic searches**

We will search the following electronic databases from inception:

- MEDLINE;
- Embase;
- Cochrane Central Register of controlled trials (CENTRAL).

The MEDLINE search algorithm is presented in Appendix 1. Searches in other databases will be adjusted accordingly.

**Searching other resources**

We will search https://www.clinicaltrials.gov/ to identify ongoing RCTs and we will contact the principal investigator for further information. In order to identify RCTs that were possibly missed by electronic searches, we will handsearch references of included studies and we will also ask experts in the field. Furthermore, we will handsearch relevant conference abstracts including European Society of Gynaecological Oncology (ESGO), European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and Society of Gynaecologic Oncology (SGO).

Both published and unpublished studies will be included if inclusion criteria are met.

**Data collection and analysis**

**Selection of studies**

Studies identified by electronic searches will be put through the RCT classifier, software developed by Cochrane to refine the search and automatically exclude non-randomised studies. Remaining studies will be imported into a reference management programme (covidence.org) Covidence and they will be screened by title and abstract, excluding those that clearly do not fulfil criteria for inclusion in the review. Full texts of the remaining publications will be retrieved and assessed for eligibility, documenting reasons for exclusion. Screening of studies will be independently performed by two review authors (AA; SB). Differences will be resolved through discussion and, if necessary, by involvement of a third review author (MK).
Data extraction and management

Independently two review authors (AA; SB) will extract study characteristics and outcome data from included studies on to a piloted data collection form. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (MK). One review author (AA) will transfer data into the Review Manager file (Review Manager 2014). We will double-check that data have been entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SB) will 'spot-check' the accuracy of the study characteristics against the trial report. For included studies, we will extract the following data:

- author;
- year of publication;
- country;
- study design;
- inclusion and exclusion criteria;
- cancer stage;
- intervention details (scheme, duration, dose);
- follow-up duration;
- definition of outcomes;
- outcome measures;
- risk of bias measures;
- proportion of patients in the NACT group not proceeding to surgery;
- proportion of patients in the NACT group receiving radiotherapy (definitive or adjuvant).

Differences will be resolved through discussion and, if necessary, by involvement of a third review author. If data are missing, we will contact the corresponding author for further information.

Results will be extracted as follows.

- For time to event data (survival and disease progression), we will extract the log of the hazard ratio \( \log(\text{HR}) \) and its standard error from trial reports. If these are not reported, we will attempt to estimate the \( \log(\text{HR}) \) and its standard error using the methods of Parmar 1998.

- For dichotomous outcomes (e.g. adverse events or deaths, if it is not possible to use a hazard ratio) we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).

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

If reported, we will extract both unadjusted and adjusted statistics. Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants will be analysed in the groups to which they were assigned. We will note the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

Risk of bias will be assessed through RoB2 tool for RCTs (Sterne 2019). The following domains will be assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition data), selective reporting (reporting bias). Risk of bias will be assessed by two authors independently. Differences will be resolved through discussion and, if necessary, by involvement of a third review author.

Measures of treatment effect

We will report hazard ratio (HR) for OS, DFS and progression-free survival (PFS), MD for QoL, and RR for all other outcomes.

Unit of analysis issues

If cluster-randomised trials not adjusting for clustering are identified, we will attempt to adjust for clustering by multiplying the standard error of this study by the square root of the design effect, or by diving number of events and sample size by the design effect, as described in Cochrane Handbook version 6 (Cochrane Handbook). If ICC (intra-correlation coefficient) is not reported (thus design effect cannot be calculated), we will use ICC from an external source (e.g. similar trial) and we will perform a sensitivity analysis where we will exclude cluster-randomised trials for which ICC from an external source was used. We will exclude cluster-randomised trials not adjusting for clustering and not reporting ICC for which no suitable external source can be identified.

Dealing with missing data

If data can be assumed to be missing at random, we will analyse only the available data. However, if there is a valid reason to suspect that data are not missing at random, we will use replacement values through an appropriate imputation method according to trial setting and experts' opinion, e.g. assuming all women lost to follow-up had a poor outcome, or assuming that the last value being observed before dropping out would also be observed if any women had not dropped out (last observation carried forward). If imputation is used, we will perform a sensitivity analysis where we will exclude trials with imputed data.

Assessment of heterogeneity

Heterogeneity will be assessed through Chi\(^2\) (Cochran's Q) test and I\(^2\) (Cochrane Handbook). Heterogeneity will be considered to be important if the I\(^2\) = 0% to 40%, moderate if I\(^2\) = 40% to 60%, substantial if I\(^2\) = 60% to 90% and considerable if I\(^2\) = 90% to 100% (Cochrane Handbook). We will also visually inspect forest plots to assess heterogeneity.

Assessment of reporting biases

If there is a sufficient number of studies (at least 10), we will produce and visually inspect funnel plots. If there is asymmetry in the funnel plots, we will attempt to explain it by exploring for publication bias or inflated effect estimates in smaller studies at high risk of bias (small-study effects). If we suspect small-study effects, we will compare the results of random-effects and fixed-effect meta-analysis (since the weight of smaller studies is bigger in random-effects than in fixed-effect meta-analysis) and we will also perform sensitivity analyses by excluding smaller studies.
If at least 10 studies are available, we will also check for asymmetry by applying Egger test for asymmetry.

**Data synthesis**

We will perform a random-effects meta-analysis using the inverse-variance method in order to account for the heterogeneity amongst different studies (e.g. surgeon’s experience or chemotherapy regimen might vary across different centres). Meta-analyses will be performed where appropriate, i.e. only if clinically and morphologically criteria are sufficiently similar. Different outcome types will not be pooled together (e.g. in the analysis for OS we will not include studies which report DFS but not OS).

**Subgroup analysis and investigation of heterogeneity**

We will perform subgroup analyses according to age, performance status, stage of cervical cancer and lymph node status.

**Sensitivity analysis**

We will perform sensitivity analyses according to risk of bias (i.e. exclusion of studies at high risk of bias), country/continent, chemotherapy regimen [e.g. cycle length, dose intensity, total dose and agent used (single agent or combination)], adjuvant treatment [e.g. radiotherapy or chemoradiotherapy after surgery] and centre experience (if this can be inferred). If missing data was not assumed to be at random and we used an imputation method, we will perform a sensitivity analysis by excluding studies with imputed data. If cluster-randomised trials with an external source for ICC were included, we will perform a sensitivity analysis where these will be excluded. Finally, if we suspect small-study effects, we will perform a sensitivity analyses where small studies will be excluded.

**Summary of findings and assessment of the certainty of the evidence**

We will present the overall certainty of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013; Schünemann 2011). We will create a summary of findings table (Appendix 2) based on the methods described the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and using GRADEPro GDT 2014. We will use the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We will downgrade the evidence from ‘high’ certainty by one level for serious (or by two for very serious) concerns for each limitation:

- **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.

**ACKNOWLEDGEMENTS**

We thank Jo Morrison for clinical and editorial advice, Gail Quinn, Clare Jess and Tracey Harrison for their contribution to the editorial process and Jo Platt for designing the search strategy.

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The authors and Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Team, are grateful to the following peer reviewers for their time and comments; Andrew Bryant, Junzo Chino, Mary Lunnen, Mary McCormack and Alexandra Taylor.
Additional references

Arbyn 2020

Bhatla 2019

Cancer Research UK 2010-2014

Chuang 2016

Cibula 2018

Cochrane Handbook

Cohen 2019

Covidence [Computer program]

CRT for Cervical Cancer Meta-Analysis

Datta 2017

de Sanjosé 2018

EORTC

Franco 2001

GLOBOCAN 2018_incidence
GLOBOCAN. Estimated age-standardized incidence rates (World) in 2018, cervix uteri, females, all ages. https://gco.iarc.fr/today/online-analysis-map?v=2018&mode=population&mode_population=continents&population=900&%5B%5D=ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_d earth&color_palette=default&map_scale=quantile&map_nb_colors=5&continent%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_d earth&color_palette=default&map_scale=quantile&map_nb_colors=5&continent%5B%5D=10%252C0%25250%2525D 2018.

GLOBOCAN 2018_mortality
GLOBOCAN. Estimated age-standardized mortality rates (World) in 2018, cervix uteri, females, all ages. https://gco.iarc.fr/today/online-analysis-map?v=2018&mode=population&mode_population=continents&population=900&%5B%5D=ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_d earth&color_palette=default&map_scale=quantile&map_nb_colors=5&continent%5B%5D=20.25%252C3.35%25250%2525D 2018.

González-Martín 2008

GRADEPro GDT 2014 [Computer program]
GRADE Working Group, McMaster University, Hamilton (ON) GRADEpro Guideline Development Tool (GDT) [www.gradepro.org]. Version [insert date of use]. GRADE Working Group, McMaster University, Hamilton (ON), 2014.

Gupta 2018
Higgins 2011

Josefson 1999

Keys 1999

Kirwan 2003

Kobayashi 2006

Langendam 2013

Lapresa 2015

Maneo 2008

Marth 2018

Meader 2014

Minig 2013

Morris 1999

Morris 2015

NACT for LACC Meta-analysis Collaboration

NCI 2017

Office for National Statistics 2013-2017

Osman 2016

Park 2012

Parmar 1998

Pecorelli 2009
**Table 1. FIGO 2009 and FIGO 2018 staging for cervical cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>FIGO 2009</th>
<th>FIGO 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>confined to uterus (cervix +/- corpus)</td>
<td>confined to uterus (cervix +/- corpus)</td>
</tr>
<tr>
<td>IA</td>
<td>diagnosed only by microscopy; stromal invasion ≤5 mm and largest dimension ≤7 mm</td>
<td>diagnosed only by microscopy; stromal invasion &lt;5 mm</td>
</tr>
<tr>
<td>IA1</td>
<td>stromal invasion ≤3 mm</td>
<td>stromal invasion &lt;3 mm</td>
</tr>
<tr>
<td>Stage</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>IA2</td>
<td>stromal invasion ≥3 mm but ≤5 mm</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>clinically visible tumour confined to uterus, or microscopic dimensions larger than stage IA</td>
<td></td>
</tr>
<tr>
<td>IB1</td>
<td>greatest dimension ≤4 cm</td>
<td></td>
</tr>
<tr>
<td>IB2</td>
<td>greatest dimension &gt;4 cm</td>
<td></td>
</tr>
<tr>
<td>IB3</td>
<td>greatest dimension ≥4 cm</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>invasion beyond uterus, but not to lower third of vagina or pelvic wall</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>no parametrial invasion</td>
<td></td>
</tr>
<tr>
<td>IIA1</td>
<td>greatest dimension ≤4 cm</td>
<td></td>
</tr>
<tr>
<td>IIA2</td>
<td>greatest dimension &gt;4 cm</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>parametrial invasion</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>extension to lower third of vagina or pelvic wall, or tumour causing hydronephrosis or non-functioning kidney</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>extension to lower third of vagina</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>extension to pelvic wall, or tumour causing hydronephrosis or non-functioning kidney</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>involvement of pelvic and/or para-aortic lymph nodes</td>
<td></td>
</tr>
<tr>
<td>IIIC1</td>
<td>involvement of pelvic lymph nodes only</td>
<td></td>
</tr>
<tr>
<td>IIIC2</td>
<td>involvement of para-aortic lymph nodes</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>extension beyond the true pelvic or involvement of the mucosa of bladder or rectum</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>spread to adjacent organs</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>spread to distant organs</td>
<td></td>
</tr>
</tbody>
</table>

**Appendices**

**Appendix 1. MEDLINE search algorithm**

1. exp Uterine Cervical Neoplasms/
2. (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. exp Antineoplastic Agents/
5. Antineoplastic Combined Chemotherapy Protocols/
6. chemotherapy.mp.
Title: Neoadjuvant chemotherapy and surgery versus chemoradiotherapy for locally advanced cervical cancer

Participant or population: Women with locally advanced cervical cancer (LACC).

Settings: Hospital

Intervention: Experimental arm: neoadjuvant chemotherapy (NACT) + radical surgery (RS)

Comparison: Standard of care: chemotherapy (CRT) plus external beam radiotherapy (EBRT) and brachytherapy (BT)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks*</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of evidence (GRADE)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease free survival</td>
<td></td>
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<tr>
<td>Recurrence</td>
<td></td>
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<tr>
<td>Toxicity</td>
<td></td>
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<tr>
<td>QoL</td>
<td></td>
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</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Abbreviations: CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio
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.

CONTRIBUTIONS OF AUTHORS

The study was conceived by MK and EP. The protocol was drafted by AA, SB and MK, with significant contributions from TS and KL. The final draft was reviewed by all authors.

DECLARATIONS OF INTEREST

Antonios Athanasiou: none known
Sarah J Bowden: none known
Evangelos Paraskevaidis: none known
TS Shylasree: none known
Kostas Lathouras: none known
Maria Kyrgiou: none known

SOURCES OF SUPPORT

Internal sources
- New Source of support, Other

External sources
- National Institute for Health Research, UK, Other