





# BMJ Open Does completion of radical hysterectomy improve oncological outcomes of women with clinical early-stage cervical cancer and intraoperative detection of nodal involvement?: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** The management of women with clinical early-stage cervical cancer and lymph node involvement detected intraoperatively is heterogeneous and controversial. This paper presents the protocol of a systematic review and meta-analysis regarding the management of this specific population of patients. This proposed study aims to answer the question: does completion of radical hysterectomy improve the oncological outcomes of women with clinical early-stage cervical cancer and intraoperatively detected nodal involvement?

**Methods and analysis** This protocol is drafted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines, and the proposed study will be conducted in accordance with the standard guidelines of 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' and 'Meta-analysis of Observational Studies in Epidemiology reporting guideline'. Comprehensive literature searches will be performed in PubMed, Embase, Scopus, and Web of Science. The screening of the eligible studies, the extraction of data of interest, and the quality assessment of the included studies will all be independently performed by different members of our team. The primary outcome of this proposed study will be comparing the risk of recurrence or death from cervical cancer and the risk of all-cause death in patients with two different treatments (completion of radical hysterectomy or abandonment of radical hysterectomy); the secondary outcome of this proposed study will be comparing the risk of the grade 3/4 toxicities associated with the two types of management. Given the clinical heterogeneity among the included studies, data on outcomes will be pooled by random-effects models. Heterogeneity will be evaluated using the  $I^2$  statistic. The risk of bias for the included studies will be evaluated using the Newcastle-Ottawa Scale or the Cochrane collaboration's tool. The grade of evidence will

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This proposed study will be the first systematic review and meta-analysis regarding this topic.
- ⇒ This proposed study will be conducted in strict accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
- ⇒ There is a possibility of significant clinical or/and statistical heterogeneity among the eligible studies, the meta-analysis may not be performed.
- ⇒ Most of the included studies will be likely to be retrospective and observational, which will compromise the quality of the evidence.

be evaluated by two independent members of our team using the Grading of Recommendations, Assessment, Development and Evaluations approach.

**Ethics and dissemination** Ethical approval is not required because there will no primary data collected. The findings of this proposed study will be published in an international peer-reviewed journal.

**PROSPERO registration number** CRD42021273527.

## INTRODUCTION

Worldwide, cervical cancer causes about 300 000 deaths per year.<sup>1</sup> Because of the lack of organised screening and human papillomavirus vaccination programmes, nearly 90% of cervical cancers occur in low-income and middle-income countries.<sup>1 2</sup> In developed countries, the incidence and associated mortality of cervical cancer have declined significantly over the past few decades.<sup>1 2</sup>

The management of cervical cancer depends largely on disease stage and locally

available resources. It might consist of surgery or chemotherapy, or a combination of both.<sup>2–4</sup> For women with clinical early-stage cervical cancer, the standard treatment is radical hysterectomy and bilateral pelvic lymphadenectomy.<sup>25</sup> One of the most controversial topics in the management algorithm for women with apparent early-stage cervical cancer is the treatment of patients with intraoperatively identified regional lymph node involvement. This dilemma was quite rare because the patients with grossly enlarged lymph nodes could be identified by preoperative imaging and were referred for definitive concurrent radiochemotherapy. With the development of sentinel lymph node mapping, however, more and more clinical early-stage cases had positive lymph nodes identified intraoperatively.<sup>6</sup> Therefore, this topic is getting more and more attention.

According to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system for cervical cancer, cases with regional nodal metastasis are staged as stage IIIC.<sup>7 8</sup> Most current clinical practice guidelines do not recommend radical surgery for cervical cancer patients with positive lymph nodes.<sup>3 4 9</sup> If nodal involvement is identified intraoperatively, abandoning radical hysterectomy is recommended.<sup>9</sup> However, this recommendation was based mainly on low-quality evidence that was from retrospective studies with small samples.<sup>9</sup> Therefore, the treatment of women with intraoperatively identified nodal metastasis remains controversial and inconsistent.<sup>9 10</sup> For clinical early-stage cervical cancer patients with nodal involvement detected intraoperatively, the most important decision is whether to complete a radical hysterectomy. On one hand, radical surgery is associated with high intraoperative and postoperative morbidity of complications.<sup>11–13</sup> On the other hand, the combination of radical hysterectomy and postoperative adjuvant radiotherapy can also increase the frequency and severity of long-term complications.<sup>14 15</sup> What is more, the survival value of completion of radical hysterectomy for this particular population of patients is still ambiguous. Data on this topic are broadly available, but there are limited and inconsistent data for women in whom radical surgery was abandoned because of intraoperatively identified nodal metastasis.<sup>16–22</sup>

Taken together, we propose this systematic review and meta-analysis to answer this question: does completion of radical hysterectomy improve the oncological survival of women with clinical early-stage cervical cancer and intraoperatively detected nodal involvement?

## METHODS AND ANALYSIS

### Patient and public involvement

Due to the design of the proposed study, there will no patient and/or public get involved.

### Study population

Women with clinical early-stage cervical cancer and regional lymph node metastasis that was detected

intraoperatively will be the study cohort of interest. In this proposed study, clinical early-stage cervical cancer will be defined as follows: the tumour is less than 4 cm, no suspicious involvement of parametrial tissues, no suspicious involvement in the lower third of the vagina, and no signs of advanced disease. The signs of advanced disease include enlarged lymph nodes, suspected metastases of pelvic organ, or distant metastases identified by physical examination or/and preoperative imaging (ultrasound, CT or MRI).

### Question of review

The oncological survival value of completion of radical hysterectomy for women with apparent early-stage cervical cancer and nodal involvement identified intraoperatively.

### Study design and standards

This study will be a systematic review and meta-analysis; it will be carried out in accordance with the standard guidelines of 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses'<sup>23</sup> and 'Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline'.<sup>24</sup> The protocol of this study was drafted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.<sup>25</sup> The PRISMA-P checklist is shown in online supplemental material 1. The study protocol is registered in PROSPERO, the registration number is CRD42021273527. The planned start date of this proposed study is 1 April 2022, and the planned end date will be 1 June 2022.

### Outcomes of interest

In this proposed study, we will compare the effects of the two different managements (completing or abandoning radical hysterectomy) on the oncological survival of women with clinical early-stage cervical cancer and intraoperatively identified nodal metastasis. The survival outcomes of interest in this proposed study include overall survival (OS) and disease-free survival (DFS). OS was defined as the time from the initial treatment for cervical cancer to death from any cause. DFS was defined as the time from the initial treatment for cervical cancer to disease recurrence or death from cervical cancer. Therefore, the primary outcomes of this study will be the pooled risk of recurrence or death from cervical cancer and the pooled risk of all-cause mortality. Pooled HR and 95% CI will be estimated to compare the risk of recurrence or death from cervical cancer and the risk of all-cause mortality for patients who underwent radical hysterectomy to patients who did not receive radical hysterectomy.

In this proposed study, if feasible, we will also compare the risk of the grade 3/4 toxicities of the two different managements (radical hysterectomy plus adjuvant radiochemotherapy or definitive concurrent radiochemotherapy) for women with clinical early-stage cervical cancer and intraoperatively identified nodal metastasis. The grade 3/4 toxicities were identified under the National Cancer Institute Common Terminology Criteria

for Adverse Events (V.5.0).<sup>26</sup> Therefore, the secondary outcomes of this proposed study will be the pooled risk of the grade 3/4 toxicities. Pooled OR and 95% CI will be estimated.

### Search strategy

Comprehensive literature searches will be performed in PubMed, Embase (access via OVID), Scopus, and Web of Science. We will restrict the date of publication of eligible studies to no later than 31 March 2022. Due to the limited resource and the authors' linguistic competence, only the articles published in English will be considered for eligibility.

To ensure that the literature search will be as comprehensive as possible, the keywords for literature searches were informed by medical subject headings (MeSH), and they will be as follows: 'cervical neoplasm', 'cervix neoplasm', 'cancer of the cervix', 'cervical cancer' and 'cervix cancer' for disease; 'lymph node involvement', 'lymph node metastasis', 'nodal involvement', 'nodal metastasis' and 'positive lymph node' will be employed to further define the patient population of interest; 'radical hysterectomy', 'radical surgery', 'radiochemotherapy', 'radiotherapy', 'concurrent radiochemotherapy', 'chemoradiation', 'concurrent chemoradiation' and 'radiation' for intervention. The Boolean logic (AND, OR) will be employed to combine the search terms as necessary. Two members of our team will independently perform the literature searches, and the search strategies will be reviewed by an expert in health informatics based on the Peer Review of Electronic Search Strategies checklist.<sup>27</sup> The precise search strategies for one of the databases (PubMed) are presented in online supplemental material 2. All the reference lists of the included studies will be manually checked to identify any other eligible studies that may have been omitted from the literature searches.

### Study selection

All records identified from the literature searches will be entered into the EndNote reference manager (V.X9), two reviewers of our team will independently conduct the eligibility identification and any disagreement will be arbitrated by a senior reviewer. Studies will be included in this proposed systematic review and meta-analysis if they meet the following inclusion criteria: (1) enrolled adult women (18 years or older) with stage IA2 to IIA1 (based on FIGO 2009 or 2018 staging system for cervical cancer) squamous cell, adenocarcinoma, or adenocarcinoma of the cervix and intraoperatively detected nodal involvement who were treated with either radical surgery followed with adjuvant radiochemotherapy (radiotherapy) or definitive concurrent radiochemotherapy (radiotherapy); (2) compared OS, DFS or progress-free survival (PFS); (3) employed a statistical method of survival analysis that was accounting for censoring and unequal follow-up among groups; (4) attempted to adjust for confounding factors known to alter survival in cancer of the cervix, such as age,

comorbidity, tumour size, postoperative adjuvant therapy, whether or not underwent bilateral pelvic lymphadenectomy, the status of lymphatic vascular space invasion (LVSI), margin status, etc; (5) reported a median duration of follow-up of at least 36 months; (6) being of good quality (had a Newcastle-Ottawa Scale score of 7 points or higher) or low-risk of bias (based on the Cochrane collaboration's tool) and (7) were reported in English. In consideration of the possibility of heterogeneity, we will allow for differences regarding the confounders included in the multivariate analysis among the eligible studies. However, only studies that at least included the following confounders will be eligible for our meta-analysis: postoperative adjuvant therapy, whether or not underwent bilateral pelvic lymphadenectomy, the status of LVSI and margin status.

Studies will be excluded from this study if their results were not reported in a peer-reviewed journal. Studies will also be excluded if they enrolled pregnant women or their study cohort was duplicated in another study. When the latter occurs, we will select the study that had a larger and more diverse sample.

### Data collection

Two of us will independently extract the following data from the eligible studies using a prepiloted and study-specific spreadsheet: (1) the first author and the date of publication, (2) the duration and country of the study, (3) the study design, (4) the size of the sample, (5) the ethnicity of the participants, (6) the age of the participants (the mean or the median), (7) the duration of the follow-up (the mean or the median), (8) the stage of the disease (based on FIGO 2009 or 2018 staging system for cervical cancer), (9) the pathological type of the tumour, (10) the definitions of outcomes (DFS, PFS or OS), (11) the number of death and disease recurrence of the study cohort, (12) the number and the incidence of the grade 3/4 toxicities that were associated with adjuvant treatment or non-surgical definitive treatment, (13) the covariate-adjusted HRs and 95% CIs of OS, DFS or OS among patients undergoing radical hysterectomy followed with postoperative adjuvant radiochemotherapy (radiotherapy) compared with definitive concurrent radiochemotherapy (radiotherapy), (14) the covariate-adjusted ORs and 95% CIs of the grade 3/4 toxicities that were associated with adjuvant treatment or non-surgical definitive treatment, and (15) confounders that were included in the eligible studies to adjust the unbalance between patients.

The data collected will be validated by another of us to make sure integrity and accuracy. Discussion will take place among the team to solve any disagreement if necessary. If the data of interest are not available in some included studies, efforts will be made to contact the first author or the corresponding author to obtain the missing information.



### Risk of bias assessment

The quality assessment for each included study will be conducted by two independent members of our team using the Newcastle-Ottawa Scale (non-randomised studies) or the Cochrane collaboration's tool (randomised clinical studies).<sup>28 29</sup> Any disagreement during this process will be resolved by discussion. The Newcastle-Ottawa Scale assesses study bias based on the following three domains: (1) the selection of participants, (2) the measures of exposure and outcome variables, and (3) the control of confounding.<sup>28</sup> The scale concludes with a quantitative summary score and qualitative categorisation of quality (high, moderate or low) according to the number of points in the three aspects.<sup>28</sup> As is accepted in the published literature,<sup>30–32</sup> the quality of a study is considered high if the Newcastle-Ottawa Scale score is 7 or greater. The Cochrane collaboration's tool<sup>29</sup> evaluates the quality of included studies in the following six key domains: (1) selection bias (random sequence generation and allocation concealment), (2) performance bias (blinding of participants and personnel), (3) detection bias (blinding of outcome assessment), (4) attrition bias (incomplete outcome data), (5) reporting bias (selective reporting), and (6) other bias. A study is judged to be of 'low-risk' of bias if the risk of bias for all the six key domains is low.<sup>29</sup>

If 10 or more studies will be included in this proposed meta-analysis, the publication bias will be assessed using the visual inspection of the funnel plot and the statistical analysis of the Egger test.<sup>33 34</sup> The trim and fill method will be employed to detect and correct for funnel plot asymmetry arising from publication bias, if necessary.<sup>34</sup>

### Data analysis

In consideration of the clinical heterogeneity among the included studies, data on outcomes will be pooled by random-effects models.<sup>35 36</sup> Clinical heterogeneity among the included studies includes, but is not limited to, the following: duration of follow-up, inclusion criteria, disease stage of the tumour, age of the sample and protocol for the adjuvant/definitive radiochemotherapy. Statistical heterogeneity among the eligible studies will be evaluated using the  $I^2$  statistic,<sup>37</sup> and  $I^2$  values of less than 25%, between 25% and 50%, and greater than 50% are considered low, moderate, and high heterogeneity, respectively.<sup>37</sup> Pooled HRs and 95% CIs will be estimated to compare the risk of disease recurrence or death and the risk of all-cause mortality or cancer-associated death for patients treated with radical hysterectomy and adjuvant therapies relative to definitive non-surgical therapies. Pooled ORs and 95% CIs will also be estimated to compare the risk of the grade 3/4 toxicities of the two types of management.

Many sensitivity analyses will be employed to evaluate the robustness of the main results. To check whether any study has a disproportionate influence on the results of the meta-analysis, data will be synthesised after serially excluding each study included in the main analysis. To

evaluate whether the results are sensitive to the employment of the meta-analysis model, a fixed-effects meta-analysis will be conducted.

### Grading of evidence

The grade of the evidence will be evaluated according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.<sup>38 39</sup> Two researchers will independently evaluate the grade of evidence of this proposed study; a third researcher will be consulted in case of disagreements.

### DISCUSSION

For the management of clinical early-stage cervical cancer patients who had intraoperatively identified nodal involvement, current clinical practices are heterogeneous and not based on strong evidence.<sup>3 4 9</sup> Thus, this proposed systematic review and meta-analysis is of high clinical significance. By pooling the data of the original high-quality studies regarding this topic, this proposed study can provide gynaecological oncologists with the current best estimates of the prognostic value of different managements for clinical early-stage cervical cancer patients who had intraoperatively identified nodal involvement, and can assist consultation and shared decision making.

As far as we know, the largest study to date regarding this topic is the ABRAX (ABandoning RADical hysterectomy in cerviX cancer) study.<sup>40</sup> The ABRAX study was an international, multicentre, retrospective cohort study, and the ABRAX consortium was composed of 51 institutions across 19 countries in Europe, Central America and Latin America and was led by the Central and Eastern European Gynecologic Oncology Group (CEEGOG).<sup>40</sup> The ABRAX study enrolled 515 cervical cancer in whom nodal metastasis was identified intraoperatively, of which 361 underwent the planned uterine surgery, and the rest gave up surgical treatment.<sup>40</sup> The ABRAX study did not find significant difference regarding the risks of recurrence (HR 1.154, 95% CI 0.799 to 1.666,  $p=0.45$ ), pelvic recurrence (HR 0.836, 95% CI 0.458 to 1.523,  $p=0.56$ ) or death (HR 1.064, 95% CI 0.690 to 1.641,  $p=0.78$ ) between the two groups.<sup>40</sup> Thus, the authors concluded that completion of radical hysterectomy does not improve survival in patients with intraoperatively detected nodal involvement.<sup>40</sup> Of note, there were some limitations. The first was its retrospective design, so there was inevitably some bias. The second was that it did not evaluate the risk of morbidity and mortality associated with the two types of treatment protocol. The last, the ABRAX did not address the prognostic role of pelvic lymphadenectomy for the clinical early-stage cervical cancer patients who had intraoperatively identified nodal involvement.

This proposed systematic review and meta-analysis may have the following limitations. In consideration of the fact that prospective study regarding this topic in the practical clinical setting is very unlikely, we guess that the majority of the included studies will also be retrospective design;

this will compromise the grade of evidence concluded from this proposed study. Also, there is the possibility that substantial heterogeneity exists among the eligible studies, which will make meta-analysis impossible.

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**Contributors** CH, YX, YD and QL conceived the review topic. YX and YD performed background exploratory searches and drafted the initial search strategy. CH, YX, YD and YJ co-wrote the initial protocol. QZ, YDH and AZ provided critical appraisal and senior oversight of the protocol. For the systematic review, CH, YX, YD, HX, YT, LR, FK, SSC and YJ will perform the searches, data extraction and analysis. AZ and YDH will provide oversight of the searches, data analysis and extraction. QZ, YDH, YT, LR, FK, SSC and AZ will provide critical appraisal and senior oversight of the final manuscript.

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