

Rundle S, Halvorsrud K, Bizzarri N, Ratnavelu NDG, Fisher AD, Ang C, Bryant A, Naik R, Kucukmetin A. [Sentinel node biopsy for diagnosis of pelvic lymph node involvement in early stage cervical cancer](#). *Cochrane Database of Systematic Reviews* 2017, 2017(12).

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DOI link to article:

<https://doi.org/10.1002/14651858.CD007925.pub2>

Date deposited:

11/01/2018

Embargo release date:

18 December 2018



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Sentinel node biopsy for diagnosis of pelvic lymph node involvement in early stage cervical cancer.
Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD007925.
DOI: 10.1002/14651858.CD007925.pub2.

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Sentinel node biopsy for diagnosis of pelvic lymph node involvement in early stage cervical cancer

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

Publication status and date: Edited (no change to conclusions), published in Issue 12, 2017.

Citation: Rundle S, Halvorsrud K, Bizzarri N, Ratnavelu NDG, Fisher AD, Ang C, Bryant A, Naik R, Kucukmetin A. Sentinel node biopsy for diagnosis of pelvic lymph node involvement in early stage cervical cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD007925. DOI: 10.1002/14651858.CD007925.pub2.

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ABSTRACT

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

To assess the diagnostic accuracy of sentinel lymph node biopsy in the identification of lymph node involvement in patients with early stage cervical cancer (Stage IA2 to IIA).

We will first explore the impact of major factors for heterogeneity such as tumour size, FIGO stage and timing between application, detection of tracers, tracer substance used, surgical approach, experience of the operator and use of histological ultra-staging techniques. Then, we may consider other factors such as previous treatment to the cervix (including conisation), patient age and body mass index, as these have previously been suggested as possible factors associated with success or failure of sentinel node identification ([Sinno 2014](#); [Tanner 2015](#); [Wuntakal 2015](#)).

BACKGROUND

Target condition being diagnosed

Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases and 266,000 deaths attributed to cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths ([GLOBOCAN 2012](#)). A large majority (around 85%) of the global burden occurs in less-developed regions, where it accounts for almost 12% of all female cancers. Cervical cancer remains the most common

cancer in women in Eastern and Middle Africa. This fact reflects the differences in the availability of effective Human Papilloma Virus (HPV) vaccination and cervical screening programmes as well as effective treatments. In Europe, approximately 60% of women with cervical cancer are alive five years after diagnosis ([EUROCARE 5a](#)).

Cervical cancer is staged according to the FIGO system ([Benedet 2003](#)), which is based on findings from clinical examination ([Table 1](#)). Stage I disease is confined to the cervix. This is subdivided into stage IA and IB. Stage IA can only be seen with a microscope, while IB can usually be seen with the naked eye. Stage IA is further

divided into Stage IA1 and stage IA2. Stage IA1 means the cancer has invaded less than 3 mm into the cervical tissue and it is less than 7 mm wide. Stage IA2 means that the cancer has invaded between 3 mm and 5 mm deep but is still less than 7 mm wide. If the cancer is bigger than Stage IA2, but still confined to the cervix, it would be classified as stage IB. Stage IB again can be divided into IB1 and IB2 where IB1 represents cancers that are less than 4 cm across while IB2 are tumours larger than 4 cm.

For Stage II disease, the tumour has spread to the upper part of the vagina (stage IIA) or to the tissues around the cervix, but not reaching the pelvic side wall (stage IIB). Stage III represents disease that has reached the lower part of the vagina (IIIA) or the pelvic side wall (IIIB) and Stage IV represents disease that has spread to the other organs such as the bladder or the bowel. Although lymph node involvement does not contribute to the FIGO staging, it is one of the most important factors in prognosis and determining treatment. For early disease (stage IB to IIA), about 95% of women can expect to be alive after five years (Kim 2000). However, if the tumour had spread to the lymph glands in the pelvis, the expected survival at five years drops to about 78%. Furthermore, data suggest that extra-pelvic lymph node metastases further impacts on survival (Kim 2000). In this review, women with FIGO stage IA2 to IIA cervical cancer will be the population of interest as this group of women would usually be candidates for systematic pelvic lymphadenectomy as part of the surgical treatment of their cervical cancers (Rationale).

Index test(s)

The detection of the sentinel node in cervical cancer involves subepithelial injection of a radioactive tracer substance e.g. ^{99m}Tc (technetium) -labelled colloid, blue dye (e.g. Patent Blue or methylene blue) or indocyanine green (ICG) into the cervix before the operation. The spread of the tracer substance would mimic the cancer cells and follow the lymphatic drainage around the cervix. The tracer substance would localise to the lymph nodes that represent the first lymph nodes in the lymphatic chain to which cancer cells would spread. If radioactive tracer substance is used, the total radioactive dose varies between 10 MBq to 111 MBq, depending on the time interval between injection and surgery (Lantzsch 2001; Rhim 2002), and a scan to look at the lymphatic system (lymphoscintigraphy) may be performed after injection of the radioactive tracer to map the location of the sentinel lymph nodes (Bats 2007; Darai 2007). Preoperative lymphoscintigraphy gives some guidance to the surgeons with regard to the location of the sentinel lymph nodes. If blue dye or ICG are used, the tracer substance is injected into the cervix at the beginning of surgery. Intraoperatively, blue dye stained lymph nodes can be visualised after opening the retroperitoneum, and nodes with radioactive

uptake can be detected with a gamma camera. ICG is visualised using near-infrared fluorescence (NIR) and can be detected transperitoneally prior to opening the retroperitoneum. Lymph nodes that are stained with ICG or blue dye or nodes and are radioactive are then removed as sentinel lymph nodes (Schneider 2007). The sentinel node is then submitted for histological analysis. Histological analysis may include ultra-staging techniques to improve the detection of smaller cancer cell deposits (Cibula 2012). If cancer cells are present, the node is considered as positive. Intraoperative frozen section histological analysis of sentinel lymph nodes has previously been described. This technique, however, has been shown to be less reliable for the diagnosis of lymph node metastases than analysis of fixed histological specimens (Bats 2011). Prospective and retrospective data suggest that sentinel lymph node assessment can achieve a greater than 90% sensitivity and 100% specificity in predicting lymph node status in women with cervical cancer (Cibula 2012; Kadkhodayan 2015; Lecuru 2011; Selman 2008; Tax 2015; Wang 2015). However, if the procedure only includes the injection of blue dye without the use of a radioactive tracer or vice versa, the detection rate and sensitivity are significantly reduced when compared to the combined technique (Van de Lande 2007). Currently, the technique of sentinel lymph node detection is mainly confined to clinical trials, though reports of this technique being incorporated into standard practice in early stage disease are emerging (Devaja 2012; Gortzak-Uzan 2010; Niikura 2012; Wuntakal 2015). In clinical trials, regardless of the status of the sentinel node, a systematic lymphadenectomy would still be carried out in order to avoid wrong clinical management in the case of a false-negative result. Ideally, if sentinel node assessment is accurate, it can replace the need for a systematic lymphadenectomy and its associated risks (see Rationale). However, in the situation where there is a false-negative result (i.e. when there were positive lymph nodes but the sentinel lymph node was negative), omission of a systematic lymphadenectomy would mean that the positive lymph nodes would remain in the woman and she would be falsely diagnosed as "lymph node negative". This would lead to omission of chemo-irradiation as part of her treatment and might lead to a significant negative impact on her overall prognosis.

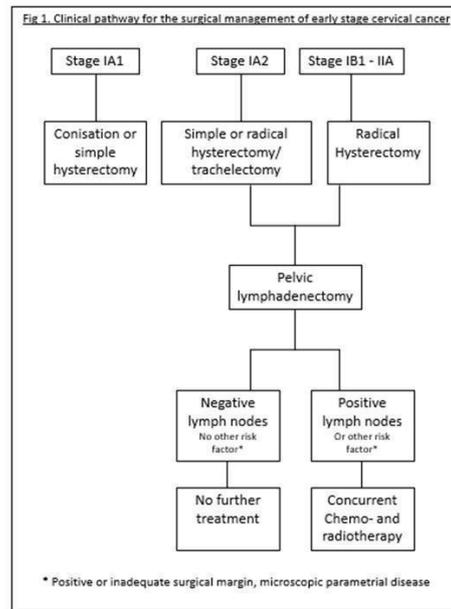
Role of the index test

The role of the index test is to predict accurately lymph node metastases in women with early stage cervical cancer so that the need for further treatment can be determined whilst the extent of surgery can be reduced.

Clinical pathway

Clinical pathway for women with early stage cervical cancer (Figure 1)

Figure 1.



Alternative test(s)

Radiological Imaging techniques have been used to assess lymph node status before primary surgery. These have the advantage of being non-invasive, but their sensitivities appeared to be limited. Computer tomography (CT) and magnetic resonance imaging (MRI) rely on size and morphological criteria to recognise lymph node metastasis, and small metastatic nodes may be missed (Boss 2000; Hricak 1993; Schneider 2007; Yang 2000). A systematic review of 57 articles between 1985 and 2002 showed sensitivities for lymph node involvement in women with cervical cancer for MRI and CT of 60% and 43%, respectively (Bipat 2003). Positron emission tomography (PET) gives functional imaging of cancer cells. Used alone or in combination with CT, it has been applied in the staging assessment of various gynaecological cancers. High sensitivity and specificity in detection of para-aortic metastases in advanced or recurrent cervical cancer have been reported (Rose 1999), but its role in predicting pelvic node involvement in early disease of gynaecological cancers in general is still uncertain (Lai 2007). A meta-analysis involving 445 women with primary cervical cancer in eight studies showed that the sensitivity of PET in predicting lymph node status was 74.7% and the specificity was 97.6% (Selman 2008). The sensitivities for imaging techniques in the detection of the sentinel nodes in cervical cancer are not high enough to be clinically useful.

Rationale

For early disease (Stage I to Stage IIA), surgery is the most common treatment method. In very early disease (IA1 and IA2), this can be limited to removal of the part of the cervix affected by cancer or by a simple, or standard hysterectomy (Bouchard-Fortier 2014). For Stage IB disease or above, a radical hysterectomy which involves a hysterectomy together with removal of tissues around the cervix is the traditional treatment of choice and this may be either as an open abdominal or as a key-hole operation (Kucukmetin 2013). Radical hysterectomy may be followed by radiotherapy or a combination of chemotherapy and radiotherapy for women with stage IB to IIA cervical cancer, though the impact of this adjuvant treatment on overall survival is thought to be limited (Rogers 2012). For higher stages (Stage IIB or above), the main treatment would be chemo-irradiation instead of surgery. Lymph node metastasis has been found in less than 1% of FIGO Stage IA1 disease (Elliott 2000), but this increases to 9% in Stage IA2 disease (Takeshima 1999). As there is a higher chance of lymph node metastasis in Stage IA2 or above, pelvic lymph node dissection forms part of the standard treatment for Stage IA2 to IIA cervical cancer. The current reference standard for determining lymph node spread is by a systematic lymphadenectomy where all the lymph nodes along the major vessels in the pelvis are removed for histological assessment. However, such dissection is associated with potential morbidities such as formation of lymphocysts and lymphoedema in up to 20% of women (Ryan 2003), and the risk of these morbidities may be significantly reduced if sentinel lymph node excision were to replace systematic lymphadenectomy (Achouri 2013).

Considering the low incidence of lymph node involvement, most women, particularly those with very early disease, would have undergone a systematic dissection, with its associated risks, unnecessarily. Furthermore, in situations where lymph nodes are histologically confirmed to be involved, chemo-irradiation would be offered. In these patients, systematic node dissection is of uncertain additional benefit. Therefore, different ways of assessing lymph node involvement have been explored.

Imaging techniques such as CT scans, MRI and PET are non-invasive methods that can be used to detect enlarged lymph nodes. However, these methods cannot accurately determine whether the enlarged nodes are due to cancer involvement or due to a reactive response to local infection or an inflammatory response to the malignant lesion. Alternatively, the concept of sentinel node assessment has been investigated. The sentinel lymph node is the first lymph node to which the tumour cells would spread via the lymphatics. The histological status of the sentinel node is presumed to be representative of all other lymph nodes draining the same anatomical site: that is, if this sentinel node is negative histologically; the remaining lymph nodes draining the same region are assumed to be also negative. Since there is a possibility for sentinel node biopsy to replace a systematic lymphadenectomy in clinical practice (whereas the various imaging techniques are unlikely to do so), this review will concentrate on assessing the diagnostic accuracy of sentinel node biopsy alone.

OBJECTIVES

To assess the diagnostic accuracy of sentinel lymph node biopsy in the identification of lymph node involvement in patients with early stage cervical cancer (Stage IA2 to IIA).

Secondary objectives

We will first explore the impact of major factors for heterogeneity such as tumour size, FIGO stage and timing between application, detection of tracers, tracer substance used, surgical approach, experience of the operator and use of histological ultra-staging techniques. Then, we may consider other factors such as previous treatment to the cervix (including conisation), patient age and body mass index, as these have previously been suggested as possible factors associated with success or failure of sentinel node identification (Sinno 2014; Tanner 2015; Wuntakal 2015).

METHODS

Criteria for considering studies for this review

Types of studies

Included studies may be either prospective or retrospective designs comparing sentinel node biopsy with the reference standard. We will exclude studies reporting insufficient data for accurate identification of the target population or for the construction of a two-by-two table, and case-control studies. We will also exclude studies with fewer than 10 cases.

Participants

Women diagnosed with early stage (IA2 to IIA) cervical cancer on the basis of loop biopsy (for microscopic disease) or examination under anaesthesia and biopsy with or without cystoscopy. We will consider all settings and all ages in this review. We will include studies that include at least 80% of women with early stage disease, as it is expected that some studies will have small percentages of women with Stage IIB, III and IV disease.

Index tests

Sentinel lymph node biopsy. Studies should specify the technique used, including:

- whether radioactive tracer, blue dye, ICG or a combination of these were used;
- technique of injection of tracer substance, including timing of injection, amount of tracer used and location of injection;
- exact technique of detection of tracer substance (e.g. whether a preoperative scintigram was done, whether the intraoperative detection was done via an open, laparoscopic or robotic approach and for studies which use ICG, which near-infrared fluorescence (NIR) system was used to detect the lymph node);
- definition of what is regarded as a sentinel node;
- the histological method of assessment of the sentinel node including details of any ultra-staging techniques used.

A sentinel node should be defined as a lymph node sending a radioactive signal with an activity higher than 10-fold above background radiation level, a node that appears blue intraoperatively or, in the case of ICG-NIR, a node that appears to fluoresce when specialised near-infrared equipment is used for detection. The sentinel node identified should be removed and submitted for histological examination with at least haematoxylin and eosin (H & E) staining, including those at extra-pelvic sites. If the sentinel node is found to be malignant by histological examination, it is defined as a positive sentinel node. If a sentinel node is detected but histologically did not show any malignancy, it may be subjected to ultra-staging techniques. If no malignancy is detected in the lymph node, it is defined as a negative node. Results of the studies need to report whether sentinel nodes are detected unilaterally or bilaterally. If a sentinel node cannot be identified by the tracer substance used, then it is defined as 'failure to detect sentinel nodes'. In the case of failure to detect sentinel nodes either unilaterally

or bilaterally, the studies should report whether a side-specific or bilateral systematic pelvic lymphadenectomy was undertaken.

In the situation where lymph node metastases is detected by systematic lymphadenectomy and not by a sentinel lymph node, it should be specified whether the positive lymph nodes identified by systematic lymphadenectomy are on the side that no sentinel node was detected; or that a sentinel node was identified on that side and was negative. We would take these situations into account in conducting the analysis, as they may have important implications on the true accuracy of the test.

Target conditions

Pelvic lymph node metastases in early stage cervical cancer (IA2 to IIA).

Reference standards

Systematic pelvic lymphadenectomy, laparoscopic or open, followed by standard histological assessment of surgical specimen. Systematic pelvic lymphadenectomy should include removal of all the obturator, internal and external iliac and common iliac nodes, with or without para-aortic nodes. The removed surgical specimen would be subjected to standard histological assessment with at least H & E staining. If any of the removed nodes showed cancer metastasis histologically, the reference standard is considered positive. Studies should specify how many lymph nodes at each of the above sites were removed. Studies should also specify whether the reference standard result is positive for one side or both sides of the pelvis.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases.

- MEDLINE (OvidSP) (1946-current)
- Embase (OvidSP) (1980-current)

We will use the search strategy specified in [Appendix 1](#) to search MEDLINE, which reflects the key concepts of the review to include recent reports that incorporate ICG-NIR technology: index test (sentinel lymph node biopsy) AND target condition (pelvic lymph node metastases in early stage cervical cancer). We will design a similarly structured search strategy using search terms appropriate for Embase.

We will not apply language restrictions to the electronic searches and we will arrange for translations, where possible, if relevant studies are found in languages other than English.

Searching other resources

We will check the reference lists of all studies deemed to be relevant from the electronic searches for additional potentially relevant studies.

We will also search the following databases for related systematic reviews, and we will check the reference lists of those that are relevant for additional studies.

- DARE (Database of Abstracts of Reviews of Effects)
www.york.ac.uk/inst/crd/crddatabases.htm#DARE
- MEDION (Meta-Analyses van Diagnostisch Onderzoek)
www.mediondatabase.nl
- HTA Database (Health Technology Assessments Database)
www.york.ac.uk/inst/crd/crddatabases.htm#HTA
- ARIF (Aggressive Research Intelligence Facility)
www.arif.bham.ac.uk

We will use all studies identified as relevant as seeds in PubMed to search for additional studies using the related articles feature.

We will also use the relevant studies as seeds in the Science Citation Index (ISI Web of Knowledge) and Google Scholar (www.scholar.google.com) to determine whether articles citing these studies are also relevant.

We will handsearch abstract books of meetings of the International Gynaecological Cancer Society, the European Society of Gynaecological Oncology and the Society of Gynecologic Oncologists from 2000 to latest edition to identify unpublished studies.

Where necessary, we will contact the main investigators of relevant ongoing studies for further information.

If necessary, we will also contact authors of relevant studies to ask if they know of further data which may or may not have been published.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to the reference management database Endnote. We will remove duplicates and two review authors (SR, NB) will independently examine the remaining references. We will exclude those studies which clearly do not meet the inclusion criteria, and obtain copies of the full text of potentially relevant references. Two review authors (SR, NB) will assess the eligibility of retrieved papers independently. We will resolve disagreements, if possible, between SR and NB, and, if necessary, involve a third review author (NR, AK, or RN). We will document reasons for exclusion.

Data extraction and management

We will extract data on the following items.

- Author, year of publication and journal (including language).
 - Country.
 - Settings.
 - Inclusion and exclusion criteria.
 - Study design.
 - Study population.
 - Number of patients.
 - Definition of cervical pathology (by punch biopsy, loop biopsy etc).
 - Any triage or add-on tests done in addition to the index test.
 - Experience of the operator.
 - Cervical cancer details:
 - FIGO stage;
 - size of tumour;
 - histological cell type;
 - lymphovascular space involvement;
 - previous treatment details such as loop biopsy, laser treatment etc.
- Reference standard and performance of the reference standard:
 - laparoscopic or open;
 - lymph node yield (and site);
 - histological assessment method.
- Performance of the index test:
 - for sentinel lymph node biopsy:
 - ◇ tracer substance used, amount and dilution;
 - ◇ method of application;
 - ◇ timing of application;
 - ◇ method of detection;
 - ◇ histological assessment method.
- Reporting of results:
 - sentinel lymph node detection rate for unilateral and bilateral nodes;
 - in false-negative cases, are the positive nodes by reference standard on the side where there is failure to detect sentinel nodes?
 - any adverse effect arising from the index test;
 - any adverse effect arising from the reference standard.
- QUADAS-2 items (see below).
- Data for two-by-two table.

Two review authors (SR, NB) will extract data independently onto a data abstraction spreadsheet specially designed for the review. We will resolve differences between review authors by discussion or by appeal to a third review author (NR, AKM, or RN) if necessary. We will use two primary diagnostic studies to pilot the data abstraction spreadsheet (including the quality assessment).

Assessment of methodological quality

Two review authors (SR and NB) will independently perform the quality assessment. In case of disagreement, a consensus meeting will be held. In case of persisting disagreement, we will refer the issue to a third review author (NR, AKM, RN or KH). We will assess study quality using the QUADAS-2 list (Whiting 2011). We will report the results in detail in tabular and graphical form, and summarise them in the text. We will report methodological quality graphically by showing the percentage of studies that did or did not fulfil each item. We will also produce tables showing the results of each quality item for all individual studies. We will assess the quality items derived from the QUADAS-2 tool using the methodology stated in Table 2. The QUADAS-2 tool, tailored specifically for use in this review omits the core quality questions “was a case-control design avoided?” and “if a threshold was used, was it pre-specified?”. These quality items are of limited applicability to this review due to the proposed inclusion of all study designs prior to quality assessment and the dichotomous nature of the index test and reference standard result. Additional QUADAS-2 quality questions were included within the index test domain: “Did the study provide clear information about which cases were considered to be a ‘failure to detect sentinel nodes?’” and “Had test operators had appropriate training?”. These signalling questions represent important quality assessments for the performance and interpretation of the index test result.

Statistical analysis and data synthesis

We will input data from two-by-two tables into Review Manager 2014 (5.3.5) for the calculations of sensitivity and specificity for each study. We will present individual study results graphically by plotting estimates of sensitivities and specificities in receiver operating characteristic (ROC) space. If more than one threshold is reported, we will choose the two-by-two table for the threshold most widely reported in the included studies to incorporate in the meta-analysis. We will use the statistical package Stata 14.1 (College Station, TX: StataCorp, 2015) to meta-analyse pairs of sensitivity and specificity using a bivariate random-effects approach (Reitsma 2005). As we anticipate little variation in thresholds between studies (since the histological confirmation of the presence or absence of lymph node metastases yields a dichotomous result), we will calculate summary estimates of sensitivity and specificity, while correctly dealing with any correlation that might exist between sensitivity and specificity. Co-variables can be incorporated in the bivariate model in order to examine the effect of potential sources of heterogeneity on sensitivity and specificity. The results of the bivariate model will be used to calculate likelihood ratios. To illustrate the findings, the negative predictive value will be presented for a range of plausible values of the prevalence of pelvic lymph node involvement; e.g. the median and inter-quartile range of prevalence in included studies. It is not anticipated that a false-positive result will be encountered

as a positive result in the index test is regarded as a true-positive result, even in the case where the reference test yields a negative result. This arises from the assumption that a positive sentinel lymph node would have been included in the lymphadenectomy specimen (reference test) had the sentinel lymph node procedure (index test) not been carried out. Therefore, positive predictive values will not be calculated.

We will treat extra-pelvic sentinel node involvement (e.g. in the para-aortic region) in the same way as for pelvic sentinel nodes, i.e. removed and sent for histological assessment. Therefore, we will include extra-pelvic sentinel nodes in the statistical analysis as part of the overall sentinel node yield.

Investigations of heterogeneity

We will investigate heterogeneity by visual examination of forest plots of sensitivities and specificities and through a visual examination of the ROC plot of the raw data. We will use bivariate models to estimate imprecision by which sensitivity and specificity have been measured within each study and variation beyond chance in sensitivity and specificity between studies. We expect the results of the index test to vary according to (i) the sentinel node procedure (use of radioactive tracer, blue dye, ICG or a combination of these), and (ii) whether the approach was open laparoscopic or robotic, (iii) whether ultra-staging techniques were used in the histological analysis of the sentinel lymph nodes.

We will investigate this by including these factors as a co-variate in meta-regression in Stata 14.1 (College Station, TX: StataCorp, 2015), where we will test for differences between groups and obtain relative measures of test accuracy such as relative diagnostic odds ratios. We will therefore interpret our findings in the light of possible heterogeneity between different methods of detection

and between different subgroups of patients as specified above (see [Secondary objectives](#)). Any unexplained variability between studies will be interpreted using clinical judgement.

Sensitivity analyses

If sufficient data are available, we will explore possible sources of bias by undertaking sensitivity analyses based on the overall quality assessment (QUADAS-2). We will omit studies that did not satisfy quality criteria and scored 'no' or 'unclear' for all QUADAS-2 domains in sensitivity analyses. If permitted by the variability of included studies, we will also conduct sensitivity analysis based on the type of study design, for example whether retrospective or prospective.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Karen KL Chan and Javier Zamora who contributed to the authorship of the previous version of this protocol ([Chan 2009](#)).

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

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

ADDITIONAL TABLES**Table 1. FIGO stage classifications**

<i>FIGO classification for cervical cancer</i>	
STAGE	CHARACTERISTICS
I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)

Table 1. FIGO stage classifications (Continued)

IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not > 7.0 mm. Depth of invasion should not be > 5.0 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging
IA₁	Measured stromal invasion of not > 3.0 mm in depth and extension of not > 7.0 mm
IA₂	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm
IB	Clinical lesions confined to the cervix or preclinical lesions > IA
IB₁	Clinical lesions not > 4 cm in size.
IB₂	Clinical lesions > 4 cm in size.
II	The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall; the carcinoma involves the vagina, but not as far as the lower third
IIA	No obvious parametrial involvement.
IIB	With parametrial involvement.
III	The carcinoma has extended onto the pelvic wall; on rectal examination there is no cancer-free space between the tumour and the pelvic wall; the tumour involves the lower third of the vagina; all cases with a hydronephrosis or non-functioning kidney should be included, unless they are known to be due to other causes
IIIA	No extension onto the pelvic wall, but involvement of the lower third of the vagina
IIIB	Extension onto the pelvic wall or hydronephrosis or nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.

Table 2. QUADAS-2 classifications

Domain	Signalling question	Signalling question	Signalling question	Signalling question	Signalling question	Risk of bias	Concerns for applicability
1. Patient selection	1. Was a consecutive or random sample of patients enrolled?	2. Did the study avoid inappropriate exclusions?	-	-	-	Could the selection of patients have introduced bias?	Is there concern that the included patients are not representative?

Table 2. QUADAS-2 classifications (Continued)

							tive of the patients who will receive the test in practice?
	Yes: The study enrolled randomly sampled or consecutive patients with clinically determined FIGO stage 1A2 to IIA cervical cancer No: The study enrolled selected patients. Unclear: This was not clear from the report.	Yes: All patients with clinically determined FIGO stage 1A2 to IIA cervical cancer were included in the analysis No: Patients were excluded following additional triage tests such as computed tomography or magnetic resonance scan imaging Unclear: This was not clear from the report.	-	-	-	Low risk: 'yes' for all signalling questions. High risk: 'no' or 'unclear' for signalling question 1 or 'no' for signalling question 2 Unclear: 'unclear' for signalling question 2.	Low concern: the selected patients represent the patients in whom the tests will be used in clinical practice (please see diagnostic pathway, Figure 1) High concern: patient selection was performed in such a way that the included participants did not represent patients in whom the tests will be used in clinical practice
2. Index Test (Sentinel node detection and analysis)	1. Were the index test results interpreted without knowledge of the results of the reference standard? (Reference standard results blinded)	2. Did the study provide a clear definition of what was considered to be a "positive" and result?	3. Did the study provide clear information about which cases were considered to be a "failure to detect sentinel nodes"?	4. Had test operators had appropriate training?	-	Could the conduct or interpretation of the index test have introduced bias?	Is there concern that the index test, its conduct or interpretation differs from the review question?
	Yes: histological analysis of sentinel node was car-	Yes: clear definition for diagnosing sen-	Yes: clear definition of "failure to	Yes: clear information regarding test	-	Low risk: 'yes' for all signalling ques-	Low concern: the index test is conducted

Table 2. QUADAS-2 classifications (Continued)

	ried out without the knowledge of the histological analysis of the pelvic lymphadenectomy specimen No: histological analysis of sentinel node was carried out with the knowledge of the histological analysis of the pelvic lymphadenectomy specimen Unclear: it is unclear whether histological analysis of sentinel node was carried out with or without the knowledge of the histological analysis of the pelvic lymphadenectomy specimen	tinel lymph node metastasis is given No: criteria for diagnosis of sentinel lymph node metastases were not pre-specified Unclear: insufficient information regarding whether criteria used were specified before the study was started	detect sentinel nodes” is given No: no clear definition of “failure to detect sentinel nodes” is given Unclear: Insufficient information regarding the criteria used to determine “failure to detect sentinel nodes” is specified	operator training is given No: test operator training is not detailed Unclear: insufficient information regarding test operator training is given		tions. High risk: ‘no’ or ‘unclear’ for any one of signalling questions 1, 2 or 3 Unclear: ‘no’ or ‘unclear’ for signalling question 4	and interpreted in the way it is likely to be used in clinical practice High concern: the conduct or interpretation of the index test differs from the way it is likely to be used in clinical practice
3. Reference standard (Pelvic lymph node analysis)	1. Is the reference standard likely to correctly classify the target condition	2. Were the reference standard results interpreted without knowledge of the results of the index test? (Index test results blinded)	3. Did the study provide a clear definition of what was considered to be a “positive” result?	-	-	Could the reference standard, its conduct, or its interpretation have introduced bias?	Are there concerns that the target condition as defined by the reference standard does not match the review question?

Table 2. QUADAS-2 classifications (Continued)

	<p>Yes: all the patients received standard pelvic lymphadenectomy</p> <p>No: some or no patients received standard pelvic lymphadenectomy</p> <p>Unclear: surgical extent of lymphadenectomy is not reported or could not be clearly distinguished</p>	<p>Yes: histological analysis of the pelvic lymphadenectomy specimen was carried out without the knowledge of the histological analysis of sentinel node</p> <p>No: histological analysis of the pelvic lymphadenectomy specimen was carried out with the knowledge of the histological analysis of sentinel node</p> <p>Unclear: it is unclear whether the histological analysis of the pelvic lymphadenectomy specimen was carried out with or without the knowledge of histological analysis of sentinel node</p>	<p>Yes: clear definition for diagnosing lymph node metastasis is given</p> <p>No: criteria for diagnosis of lymph node metastases were not pre-specified</p> <p>Unclear: insufficient information regarding whether criteria used were specified before the study was started</p>	-	-	<p>Low risk: 'yes' for all signalling questions.</p> <p>High risk: 'no' for signalling questions 1 or 2. 'No' or 'unclear' for signalling question 3</p> <p>Unclear: 'unclear' for signalling questions 1 or 2.</p>	<p>Low concern: the reference standard is conducted and interpreted in the way it is used in clinical practice</p> <p>High concern: the conduct or interpretation of the index test differs from the way it is used in clinical practice</p>
4. Flow and Timing	1. Was there an appropriate interval between index test and reference standard?	3. Did all patients receive a reference standard?	3. Did patients receive the same reference standard?	4. Were all patients included in the analysis?	5. Were withdrawals from the study explained?	Could the patient flow have introduced bias?	-

Table 2. QUADAS-2 classifications (Continued)

	<p>Yes: less than or equal to four weeks between index test and reference standard</p> <p>No: more than four weeks between index test and reference standard</p> <p>Unclear: not reported, variable or could not be clearly determined</p>	<p>Yes: whole population received reference standard.</p> <p>No: reference standard not carried out in the whole population</p> <p>Unclear: no clear information on what proportion of population received reference standard</p>	<p>Yes: all the patients received same reference standard regardless of index test results</p> <p>No: not all the patients received same reference standard regardless of index test results</p> <p>Unclear: it is unclear whether all the patients received same reference standard regardless of index test results</p>	<p>Yes: all enrolled patients were included in the analysis.</p> <p>No: not all enrolled patients were included in the analysis</p> <p>Unclear: it is unclear if all enrolled patients were included in the analysis</p>	<p>Yes: all withdrawals from study were explained.</p> <p>No: not all withdrawals from study were explained.</p> <p>Unclear: it is not clear if all withdrawals were explained.</p>	<p>Low risk: 'yes' for all signalling questions.</p> <p>High risk: 'no' for any one of signalling questions 1 to 5. 'Unclear' for signalling questions 4 or 5</p> <p>Unclear: 'unclear' for signalling questions 1, 2 or 3</p>	-
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APPENDICES

Appendix I. MEDLINE search strategy

1. exp Lymph Nodes/
2. (lymph* adj (node* or nodal)).ti,ab.
3. (lymph* adj3 (mapping or spread* or staging)).ti,ab.
4. lymphadenopath*.ti,ab.
5. or/1-4
6. Pelvis/
7. (pelvic or pelvis).ti,ab.
8. Cervix Uteri/
9. (cervix or cervical or cervico*).ti,ab.
10. or/6-9
11. 5 and 10
12. Lymphatic Metastasis/ or (lymph* adj3 (metasta* or micrometasta*)).ti,ab.
13. 12 and 10
14. (neoplas* or cancer* or carcinoma* or malignan* or metasta* or micrometasta* or carcinogen* or adenocarcinoma* or carcinosarcoma* or adenosquamous).ti,ab.
15. Neoplasm Staging/ or Neoplasm Invasiveness/ or Neoplasm Micrometastasis/
16. 14 or 15

17. 16 and 11
18. Uterine Cervical Neoplasms/
19. exp Uterine Cervical Dysplasia/
20. Cervical Intraepithelial Neoplasia/
21. or/18-20
22. 21 and (5 or 12)
23. 22 or 17 or 13
24. Sentinel Lymph Node Biopsy/
25. (sentin?l adj3 node*).ti,ab.
26. (lymphoscintigraph* or lymphoscintigram*).ti,ab.
27. Lymphography/
28. scintiphotograph*.ti,ab.
29. (scintigraph* or scintigram*).ti,ab.
30. (gamma camera adj imag*).ti,ab.
31. (radioisotope* adj scan*).ti,ab.
32. gamma probe.ti,ab.
33. (radioactive adj3 (tracer* or isotope*)).ti,ab.
34. (near infrared adj3 (fluorescen* or imag* or endoscop* or spectroscop*)).ti,ab.
35. (NIR adj3 (fluorescen* or imag* or endoscop* or spectroscop*)).ti,ab.
36. Spectroscopy, Near-Infrared/
37. Indocyanine Green/
38. (Technetium or Tc 99m or 99mTC or blue dye* or patent blue or indocyanine green or methylene blue or isosulfan or iso sulfan or lymphazurin blue or radiocolloid or fluorescen* dye*).ti,ab,nm.
39. Technetium Tc 99m Sulfur Colloid/
40. Rosaniline Dyes/
41. Coloring Agents/
42. Methylene Blue/
43. Fluorescent Dyes/
44. Gamma Cameras/
45. or/24-44
46. 23 and 45
47. exp animals/ not humans.sh.
48. 46 not 47

Appendix 2. Embase search strategy

- 1 pelvis lymph node/
- 2 lymph node/ or sentinel lymph node/
- 3 (lymph* adj (node* or nodal)).ti,ab.
- 4 (lymph* adj3 (mapping or spread*or staging)).ti,ab.
- 5 lymphadenopath*.ti,ab.
- 6 or/2-5
- 7 pelvis/
- 8 (pelvic or pelvis).ti,ab.
- 9 exp Uterine Cervix/
- 10 (cervix or cervical or cervico*).ti,ab.
- 11 or/7-10
- 12 6 and 11
- 13 1 or 12
- 14 exp lymph node metastasis/ or (lymph* adj3 (metasta* or micrometasta*)).ti,ab.
- 15 14 and 11

16 (neoplas* or cancer* or carcinoma* or malignan* or metasta* or micrometasta* or carcinogen* or adenocarcinoma* or carcinosarcoma* or adenosquamous).ti,ab.
 17 Cancer Staging/ or Tumor Invasion/
 18 or/16-17
 19 18 and 13
 20 exp uterine cervix tumor/
 21 exp uterine cervix dysplasia/
 22 or/20-21
 23 22 and (1 or 6 or 14)
 24 23 or 13 or 15
 25 sentinel lymph node biopsy/ or (sentin?l adj3 node* adj3 biops*).ti,ab.
 26 lymphoscintigraphy/
 27 lymphography/
 28 scintillation camera/ or gamma camera/
 29 exp tumor scintiscanning/
 30 (lymphoscintigraph* or lymphoscintigram*).ti,ab.
 31 scintiphograph*.ti,ab.
 32 (scintigraph* or scintigram*).ti,ab.
 33 (gamma camera adj imag*).ti,ab.
 34 (radioisotope* adj scan*).ti,ab.
 35 gamma probe.ti,ab.
 36 (radioactive adj3 (tracer* or isotope*)).ti,ab.
 37 (Technetium or Tc 99m or 99mTC or blue dye* or patent blue or indocyanine green or methylene blue or disulfine blue or isosulfan or iso sulfan or lymphazurin blue or radiocolloid or fluorescen* dye*).ti,ab.
 38 (near infrared adj3 (fluorescen* or imag* or endoscop* or spectroscop*)).ti,ab.
 39 (NIR adj3 (fluorescen* or imag* or endoscop* or spectroscop*)).ti,ab.
 40 Near infrared spectroscopy/ or fluorescence spectroscopy/ or fluorescence imaging/
 41 indocyanine green/
 42 technetium sulfur colloid tc 99m/
 43 methylene blue/
 44 disulfine blue/
 45 fluorescent dye/
 46 coloring agent/
 47 fuchsine/
 48 or/25-47
 49 24 and 48
 50 (animal.hw. or nonhuman/) not human/
 51 (veterinary or animal or animals or feline or canine or tierheilkunde).jw.
 52 (cat or cats or dog or dogs or beagle or beagles or rat or rats or rodent or rodents or mouse or mice or murine or rabbit or rabbits or pig or pigs or bitch or bitches or feline or canine or swine or porcine or sheep or hamster or hamsters or cattle or bovine or monkey or monkeys or macaque or macaques).ti.
 53 or/50-52
 54 49 not 53

WHAT'S NEW

Date	Event	Description
14 November 2017	Amended	A new team of authors updated the text of the protocol adding new citations and a reference to Quadas-2 quality assessment criteria
14 November 2017	New citation required and minor changes	Update of clinical descriptive sections following local review and revisions to DTA methods

CONTRIBUTIONS OF AUTHORS

All of the review authors contributed to the conception and design of the study, acquisition and interpretation of the data, and drafting and revising of the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.
NHS Cochrane Collaboration programme Grant Scheme CPG-506