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Abstract

Positron emission tomography/computerised tomography imaging in detecting and managing recurrent cervical cancer: systematic review of evidence, elicitation of subjective probabilities and economic modelling

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Background: Cancer of the uterine cervix is a common cause of mortality in women. After initial treatment women may be symptom free, but the cancer may recur within a few years. It is uncertain whether it is more clinically effective to survey asymptomatic women for signs of recurrence or to await symptoms or signs before using imaging.

Objectives: This project compared the diagnostic accuracy of imaging using positron emission tomography/computerised tomography (PET-CT) with that of imaging using CT or magnetic resonance imaging (MRI) alone and evaluated the cost-effectiveness of adding PET-CT as an adjunct to standard practice.

Data sources: Standard systematic review methods were used to obtain and evaluate relevant test accuracy and effectiveness studies. Databases searched included MEDLINE, EMBASE, Science Citation Index and The Cochrane Library. All databases were searched from inception to May 2010.

Review methods: Study quality was assessed using appropriately modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria. Included were any studies of PET-CT, MRI or CT compared with the reference standard of histopathological findings or clinical follow-up in symptomatic women suspected of having recurrent or persistent cervical cancer and in asymptomatic women a minimum of 3 months after completion of primary treatment. Subjective elicitation of expert opinion was used to supplement diagnostic information needed for the economic evaluation. The effectiveness of treatment with chemotherapy, radiotherapy, chemoradiotherapy, radical hysterectomy and pelvic exenteration was

systematically reviewed. Meta-analysis was carried out in RevMan 5.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 11 (StataCorp LP, College Station, Texas, USA). A Markov model was developed to compare the relative cost-effectiveness using TreeAge Pro software version 2011 (TreeAge Software Inc., Evanston, IL, USA).

Results: For the diagnostic review, a total of 7524 citations were identified, of which 12 test accuracy studies were included in the review: six studies evaluated PET-CT, two evaluated MRI, three evaluated CT and one evaluated both MRI and CT. All studies were small and the majority evaluated imaging in women in whom recurrence was suspected on the basis of symptoms. The PET-CT studies evaluated local and distant recurrence and most used methods similar to current practice, whereas five of the six CT and MRI studies evaluated local recurrence only and not all employed currently used methods. Meta-analysis of PET-CT studies gave a sensitivity of 92.2% [95% confidence interval (CI) 85.1% to 96.0%] and a specificity of 88.1% (95% CI 77.9% to 93.9%). MRI sensitivities and specificities varied between 82% and 100% and between 78% and 100%, respectively, and CT sensitivities and specificities varied between 78% and 93% and between 0% and 95%, respectively. One small study directly compared PET-CT with older imaging methods and showed more true-positives and fewer false-negatives with PET-CT. The subjective elicitation from 21 clinical experts gave test accuracy results for asymptomatic and symptomatic women and the results for symptomatic women were similar to those from the published literature. Their combined opinions also suggested that the mean elicited increase in accuracy from the addition of PET-CT to MRI and/or CT was less than the elicited minimum important difference in accuracy required to justify the routine addition of PET-CT for the investigation of women after completion of primary treatment. For the effectiveness review, a total of 24,943 citations were identified, of which 62 studies were included (chemotherapy, 19 randomised controlled trials; radiotherapy or chemoradiotherapy, 16 case series; radical hysterectomy and pelvic exenteration, 27 case series). None provided the effectiveness of cisplatin monotherapy, the most commonly used chemotherapeutic agent in the NHS, compared with supportive care in a background of other treatment such as radiotherapy in recurrent and persistent cervical cancer. The model results showed that adding PET-CT to the current treatment strategy of clinical examination, MRI and/or CT scan was significantly more costly with only a minimal increase in effectiveness, with incremental cost-effectiveness ratios for all models being > £1M per quality-adjusted life-year (QALY) and the additional cost per additional case of recurrence being in the region of £600,000.

Limitations: There was considerable uncertainty in many of the parameters used because of a lack of good-quality evidence in recurrent or persistent cervical cancer. The evidence on diagnostic and therapeutic impact incorporated in the economic model was poor and there was little information on surveillance of asymptomatic women.

Conclusions: Given the current evidence available, the addition of PET-CT to standard practice was not found to be cost-effective in the diagnosis of recurrent or persistent cervical cancer. However, although probabilistic sensitivity analysis showed that the main conclusion about cost-ineffectiveness of PET-CT was firm given the range of assumptions made, should more reliable information become available on accuracy, therapeutic impact and effectiveness, and the cost of PET-CT reduce, this conclusion may need revision. Current guidelines recommending imaging for diagnosis using expensive methods such as PET-CT need to be reconsidered in the light of the above.

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Contents

List of abbreviations

ADM	adriamycin
BEMP	bleomycin, vindesine, mitomycin and cisplatin
BPI	Brief Pain Inventory
CBDCA	carboplatin
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHIP	iproplatin
CI	confidence interval
CT	computerised tomography
DARE	Database of Abstracts of Reviews of Effects
DDP	*cis*-diamminedichloroplatinum(II)
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life-5 Dimensions
EVPI	expected value of perfect information
FACT-Cx TOI	Functional Assessment of Cancer Therapy–Cervix Trial Outcome Index
FACT-G	Functional Assessment of Cancer Therapy – General
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity four-item scale
^{18}F-FDG	^{18}F-fluorodeoxyglucose
FIGO	Federation of Gynaecology and Obstetrics
GOG	Gynecologic Oncology Group
HPV	human papillomavirus
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
MeSH	medical subject heading
MRI	magnetic resonance imaging
MVAC	methotrexate, vinblastine, doxorubicin and cisplatin
MVBC	mitomycin C, vincristine, bleomycin and cisplatin
NCI CTC	National Cancer Institute Common Toxicity Criteria
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
PET	positron emission tomography
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomised controlled trial

RR	relative risk
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SROC	summary receiver operating characteristic
TPE	total pelvic exenteration
VOI	value of information

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Cancer of the uterine cervix is a common cause of mortality in women. After initial treatment women may be symptom free, but the cancer may recur within a few years. It is uncertain whether it is more clinically effective to survey asymptomatic women for signs of recurrence or to await symptoms or signs before using imaging. This project compared the diagnostic accuracy of imaging using positron emission tomography/computerised tomography (PET-CT) with that of imaging using CT or magnetic resonance imaging (MRI) alone and evaluated the cost-effectiveness of adding PET-CT as an adjunct to standard practice.

Methods

Standard systematic review methods were used to obtain and evaluate relevant test accuracy and effectiveness studies. Databases searched included MEDLINE, EMBASE, Science Citation Index and The Cochrane Library. All databases were searched from inception to May 2010. Study quality was assessed using appropriately modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria. Included were any studies of PET-CT, MRI or CT compared with the reference standard of histopathological findings or clinical follow-up in symptomatic women suspected of having recurrent or persistent cervical cancer and in asymptomatic women a minimum of 3 months after completion of primary treatment. Subjective elicitation of expert opinions was used to supplement diagnostic information needed for the economic evaluation. The effectiveness of treatment with chemotherapy, radiotherapy, chemoradiotherapy, radical hysterectomy and pelvic exenteration was systematically reviewed. Meta-analysis was carried out in RevMan 5.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 11 (StataCorp LP, College Station, TX, USA). A Markov model was developed to compare the relative cost-effectiveness using TreeAge Pro software version 2011 (TreeAge Software, Inc., Evanston, IL, USA).

Results

From 7524 citations retrieved, 12 test accuracy studies were found: six studies evaluated PET-CT, two evaluated MRI, three evaluated CT and one evaluated both MRI and CT. All studies were underpowered and the majority evaluated imaging in women in whom recurrence was suspected on the basis of symptoms. The PET-CT studies evaluated local and distant recurrence and most used methods similar to current practice, whereas five of the six CT and MRI studies evaluated local recurrence only and were published between 1981 and 2000, and not all employed currently used methods.

Meta-analysis of PET-CT studies gave a sensitivity of 92.2% [95% confidence interval (CI) 85.1% to 96.0%] and a specificity of 88.1% (95% CI 77.9% to 93.9%). MRI sensitivities and specificities varied between 82% and 100% and 78% and 100%, respectively, and CT sensitivities and specificities varied between 78% and 93% and 0% and 95% respectively. One small study directly compared PET-CT with older imaging methods and showed more true-positives and fewer false-negatives with PET-CT.

The subjective elicitation from 21 clinical experts gave test accuracy results for asymptomatic and symptomatic women and the results for symptomatic women were similar to those from the published literature. Their combined opinions also suggested that the mean elicited increase in accuracy from the addition of PET-CT to MRI and/or CT was less than the elicited minimum important difference in accuracy

required to justify the routine addition of PET-CT for the investigation of women after completion of primary treatment.

From 24,943 citations, 62 effectiveness studies were included (chemotherapy, 19 randomised controlled trials; radiotherapy or chemoradiotherapy, 16 case series; radical hysterectomy and pelvic exenteration, 27 case series). None provided the effectiveness of cisplatin monotherapy, the most commonly used chemotherapeutic agent in the NHS, compared with supportive care in a background of other treatment such as radiotherapy in recurrent and persistent cervical cancer. The model results showed that adding PET-CT to the current treatment strategy of clinical examination, MRI and/or CT scan was significantly more costly with only a minimal increase in effectiveness, with incremental cost-effectiveness ratios for all models being > £1M per quality-adjusted life-year (QALY) and the additional cost per additional case of recurrence being in the region of £600,000.

Conclusion

Given the current evidence available, the addition of PET-CT to standard practice was not found to be cost-effective in the diagnosis of recurrent or persistent cervical cancer. There was considerable uncertainty in many of the parameters used because of a lack of good-quality evidence in recurrent or persistent cervical cancer. The evidence on diagnostic and therapeutic impact incorporated in the economic model was poor and there was little information on surveillance of asymptomatic women. Although probabilistic sensitivity analysis showed that the main conclusion about cost-ineffectiveness of PET-CT was firm given the range of assumptions made, should more reliable information become available on accuracy, therapeutic impact and effectiveness, and the cost of PET-CT reduce, this conclusion may need revision. Current guidelines recommending imaging for diagnosis using expensive methods such as PET-CT need to be reconsidered in the light of the above.

Funding

The National Institute for Health Research Health Technology Assessment programme.

Chapter 1 Aims of the report

The aims of this project were as follows:

1. To evaluate, through systematic review of the literature, the diagnostic accuracy of adding positron emission tomography/computerised tomography (PET-CT) to CT and/or magnetic resonance imaging (MRI) compared with the diagnostic accuracy of CT and/or MRI alone in women with suspected recurrent or persistent cervical cancer in identifying local recurrence, regional recurrence and nodal and distant metastases.
2. To evaluate, through systematic review of the literature, the diagnostic and therapeutic impact of the addition of PET-CT to CT and/or MRI compared with CT and/or MRI alone on recurrent and persistent cervical cancer.
3. To assess, through systematic review of the literature, the effectiveness of various interventions and combinations of interventions (surgery, radiotherapy, chemotherapy and chemoradiotherapy) for mortality, morbidity and quality of life in the management of recurrent and persistent cervical cancer.
4. To evaluate, using decision-analytic modelling, including value of information analysis, the cost-effectiveness of adding PET-CT imaging to CT and/or MRI compared with CT and/or MRI alone, and with different follow-up strategies, for the detection and work-up of recurrent and persistent cervical cancer.

The original protocol for this report is provided in *Appendix 1*.

Chapter 2 Background

Description of the underlying health problem

Cervical cancer is a malignancy originating in the female uterine cervix. Cervical cancer usually originates in the transformation zone of the cervix where the squamous epithelial cells of the ectocervix meet the columnar epithelium of the endocervix. Approximately 80% of cervical cancers are squamous cell carcinomas. This type of cancer originates in the thin, flat squamous cells on the surface of the ectocervix, the part of the cervix that is next to the vagina. Another 10% of cervical cancers are of the adenocarcinoma type. This cancer originates in the mucus-producing cells of the inner or endocervix, near the body of the uterus. Occasionally, the cancer may have characteristics of both types and is called adenosquamous carcinoma or mixed carcinoma. Cervical cancers can be locally invasive and also spread by metastases. Pelvic recurrence can be central at the cervix or vaginal vault and in the lymph nodes of the pelvic side wall. Distant metastases can be to supraclavicular lymph nodes, para-aortic lymph nodes and the lungs.

Staging of cervical cancer can use the tumour, node, and metastases parameters (*Box 1*), but much more often uses the Federation of Gynaecology and Obstetrics (FIGO) criteria[1] (*Table 1*).

Aetiology

Human papillomavirus (HPV) infection of the cervix is a sexually transmitted infection that is necessary for the development of cervical cancer.[2] However, only a relatively small proportion of women who encounter persistent infection from high-risk genotypes (HPV 16 and 18, and some other strains) go on to develop cervical cancer.[3] When HPV is detected, around 17% of women go on to develop cervical intraepithelial

BOX 1 TNM classification for disease staging

T: size or direct extent of the primary tumour

Tx: tumour cannot be evaluated
Tis: carcinoma in situ
T0: no signs of tumour
T1, T2, T3, T4: size and/or extension of the primary tumour

N: degree of spread to regional lymph nodes

Nx: lymph nodes cannot be evaluated
N0: tumour cells absent from regional lymph nodes
N1: regional lymph node metastasis present (at some sites, tumour spread to closest or small number of regional lymph nodes)
N2: tumour spread to an extent between N1 and N3 (N2 is not used at all sites)
N3: tumour spread to more distant or numerous regional lymph nodes (N3 is not used at all sites)

M: presence of metastasis

Mx: distant metastasis cannot be evaluated
M0: no distant metastasis
M1: metastasis to distant organs (beyond regional lymph nodes)

TABLE 1 Revised FIGO criteria for disease staging

Stage	Characteristic
Stage I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus would be disregarded)
	Stage IA: invasive carcinoma that can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm
	Stage IA1: measured stromal invasion of ≤ 3 mm in depth and extension of ≤ 7 mm
	Stage IA2: measured stromal invasion > 3 mm and not > 5 mm with an extension of ≤ 7 mm
	Stage IB: clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA[a]
	Stage IB1: clinically visible lesion ≤ 4 cm in greatest dimension
	Stage 1B2: clinically visible lesions > 4 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
	Stage IIA: without parametrial invasion
	Stage IIA1: clinically visible lesion ≤ 4 cm in greatest dimension
	Stage IIA2: clinically visible lesions > 4 cm in greatest dimension
	Stage IIB: with obvious parametrial invasion
Stage III	The tumour extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney[b]
	Stage IIIA: tumour involves lower third of the vagina, with no extension onto the pelvic wall
	Stage IIIB: extension to the pelvic wall and/or causes hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
	Stage IVA: spread of the growth to adjacent organs
	Stage IVB: spread to distant organs

a All macroscopically visible lesions – even with superficial invasion – are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5 mm and a horizontal extension of ≤ 7 mm. Depth of invasion should be ≤ 5 mm taken from the base of the epithelium of the original tissue – superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with 'early (minimal) stromal invasion' (~1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.

b On rectal examination there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non- functioning kidney are included, unless they are known to be due to another cause.

neoplasia grade II+ within 3 years.[2] HPV infection is very common; it is estimated that 20% of sexually active girls will contract the virus by the age of 18 years.[4] The risk of infection increases with the age at first sexual intercourse.[5]

There are a number of factors that can increase or decrease the risk of developing cervical cancer:

- Age. Cervical cancer is rare before the age of 20 years but the incidence increases rapidly with age, giving a peak incidence of around 17 per 100,000 between the ages of 30 and 39 years.[6] Cervical cancer mortality rates generally increase with age, so that only about 7% of cervical cancer deaths occur in women under 35 years, with the highest rates in women over 70 years.[7] Squamous cell tumours are more common, but the rates of both squamous cell tumours and adenocarcinomas rise sharply from age 20–40 years, after which they plateau until age 80 years.[8]
- Sexual behaviour. There is an increased risk of invasive cervical cancer with early age at first sexual intercourse,[5,9] early pregnancy[5] and current use of hormonal contraceptives.[10]
- Smoking. Current smoking intensity is an independent risk factor for high-grade cervical intraepithelial neoplasia in young women, after controlling statistically for cervical HPV infection,[11] and may be a risk factor for developing cervical cancer.[12]
- HIV infection. HIV infection leads to an increased risk of advanced and early cervical pathology.[13]

- Socioeconomic status. Women living in the most deprived areas in the UK have cervical cancer rates that are more than three times as high as those women in the least deprived areas. Data from a longitudinal study, representing 1% of the population from England and Wales, showed that cervical cancer incidence is considerably higher among women of working age in manual occupations than among women in non-manual occupations.[14]

Epidemiology

Cervical cancer is a common gynaecological malignancy, with an estimated 31,400 new cases diagnosed each year in the European Union.[15] In the UK, approximately 2800 patients are diagnosed with cervical cancer per year, accounting for around 2% of all female cancer cases.[6] In England, carcinoma of the cervix is rare in women <20 years of age.[6] Cancer of the cervix is a leading cause of cancer death in women. In 2008, there were 1110 deaths from cervical cancer in the UK, giving a European age-standardised death rate of 2.7 per 100,000 person-years.[15] In the UK population, the 5-year disease-free survival rate for treated stage IA disease is almost 100%, whereas it is 50–70% for stage IB2 and IIB, 30–50% for stage III and 5–15% for stage IV disease.[16] It is estimated that the median survival for stage IVB disease is around 9–10 months, with 30% of patients surviving 1 year and 2–5% surviving 2 years.[17]

Initial treatment of cervical cancer

When patients are initially diagnosed with cervical cancer they can be treated with surgery, a combination of chemotherapy and radiotherapy (chemoradiotherapy) or with palliative care. The treatment chosen is based on stage of tumour, fitness of the woman and tumour characteristics, for example greater than one-third stromal invasion, capillary lymphatic space involvement and large tumour diameter.[18] Surgery is usually radical hysterectomy but can also be trachelectomy (if the tumour is small), which is the removal of the cervix only rather than the whole uterus and can be performed in younger women with early cervical cancer who wish to retain their fertility.[3] Approximately 20–30% of women undergoing surgery also receive adjuvant postoperative chemoradiotherapy for positive tumour margins or positive lymph nodes or because of the tumour size, volume, lymphovascular space invasion or stromal invasion.[19]

Recurrent or persistent cervical cancer

Patients can be cured by initial treatment and approximately 70–80% of initially treated cases are cured with surgery. If surgery is not appropriate because of tumour characteristics or lack of fitness in the patient, chemoradiotherapy can be given. However, the initial treatment may not affect a cure and in approximately 15% of patients disease is detected 3 months after treatment, which is called persistent cervical cancer (rather than recurrent). Recurrence is more common within the first 24 months after the initial diagnosis, but can happen up to 15 years after initial treatment.[20]

The Scottish Intercollegiate Guidelines Network (SIGN) guideline[3] found the rates of recurrence from the three studies reviewed in the guideline to be 13%,[21] 18.2%[22] and 29%.[23] In another study, the proportion with recurrence in early-stage cervical cancer was 6%;[24] a further study of locally advanced cervical cancer reported 30% recurrence.[25] Recurrences are more common within the first 24 months after the initial diagnosis – the median disease-free interval was 17 months for symptomatic patients and 16 months for asymptomatic patients in one cohort[21] and the median time from surgery to recurrence in another cohort was 17.6 months.[22] The percentage recurrence was higher after radiotherapy (17%) than after surgery (13%),[21] but none of the studies compared recurrence after chemoradiotherapy with recurrence after surgery. The proportions of asymptomatic to symptomatic recurrences were 19 : 114[21] and 2 : 5.[22]

Patients with pelvic recurrence usually present with one or more of vaginal bleeding, discharge, pelvic pain and sciatic pain. Patients with disseminated recurrence eventually develop systemic symptoms associated with cachexia.

Risk factors for recurrence include disease stage, number of positive lymph nodes, parametrial involvement and depth of invasion of the tumour.[24] The squamous cell carcinoma antigen is elevated in 28–88% of patients with cervical cancer and can precede clinical diagnosis of relapse in 46–92% of cases.[26]

Patients with recurrence or persistence are described according to the stage they were when they were diagnosed originally, along with some further information on whether or not and how much the cancer has progressed since the original diagnosis. For example, a woman who presented with a stage IIA cancer who now has distant metastases does not become a stage IVB cancer, but is described as a stage IIA cancer with metastases. Occasionally, a new stage can be assigned in addition if the cancer has recurred, particularly in trials, in which case it will be described with a lower case r in front of the new staging, for example stage rIVB.[27]

Prognosis

Survival with recurrent or persistent disease is poor – from 6 months to 2 years.[3] Also, patients frequently experience substantial morbidity from local recurrence and distant spread.[3] It is unclear whether or not earlier detection of recurrence (from clinical follow-up or scanning) leads to increased survival rates, but this is a reasonable assumption to make. Worse survival is associated with shorter disease-free interval, being symptomatic and poorer prognostic factors.[28]

Imaging to detect recurrence

This project investigates three imaging techniques: CT, MRI and PET-CT. These techniques allow non-invasive visualisation of anatomical structures and physiological functions of the body.

Computerised tomography and magnetic resonance imaging scanning

Computerised tomography scanning was introduced in the 1970s and is now widely used in the NHS. A CT scan is a series of tomographic radiographic images used to visualise two-dimensional 'slices' through the body. Because the X-ray beam emission and the receiving film-intensifying screen are both revolving around a focal point in the body, this focal point can be visualised much more clearly than in a standard radiography film. A very large number of focal points are visualised consecutively and then a computer is used to mathematically reconstruct a two-dimensional matrix to give a digital image of the part of the body being scanned. CT scanning is painless and takes 15–30 minutes. It is non-invasive unless contrast medium is being used. For most whole-body CT scans, intravenous iodinated contrast is now used and there is the risk of allergic reactions. The main disadvantage, however, is the dose of radiation that is absorbed during the scanning. It has been estimated that 40% of all diagnostic radiation exposure in patients comes from CT scanning.[29] CT scanning can also produce artefacts that impede interpretation of the images. These artefacts can come from motion (e.g. patients have to hold their breath when the chest is being scanned) and from high-density objects such as tooth fillings and orthopaedic hardware.

Magnetic resonance imaging scanning was introduced in the 1980s and is now also widely used in major centres in the NHS. It is also a tomographic imaging technique but uses the ability of hydrogen atoms to absorb and emit radio waves (at a similar frequency to FM radio) when placed in a strong magnetic field. Visualisation of tissues can occur because of the different concentrations of hydrogen atoms in different tissues and the characteristics of the atoms in different complex biochemical environments. MRI uses characteristics such as the density of hydrogen atoms, the speed at which they become magnetised and lose their magnetisation and the presence of flow or motion in a tissue. MRI does not use ionising radiation, which is an advantage compared with CT. However, patients are placed in a magnetic field and so metal objects inside and outside the body will be affected. Patients with pacemakers, cochlear implants, shotgun fragments, etc. should not have a MRI scan. The energy generated inside the body can cause hyperthermia, particularly in obese people. The size of the trolley and aperture (MRI machines are longer than CT machines and fit the whole body inside) mean that people who weigh >20 stone (127 kg) are unlikely to fit inside the machine. The machine is also noisy and a small proportion of patients have anxiety-related reactions. MRI scans can give false-positive results from motion artefacts, interfaces between fat and water and distortions due to magnetic objects inside the body.

Computerised tomography and MRI are high-resolution anatomical imaging techniques that are commonly used in cancer to detect potential tumours. MRI and CT are currently considered first when recurrence is suspected.[17] Whole-body CT and MRI scanning are now rarely performed; imaging for cervical cancer is frequently limited to the pelvis only. CT and MRI have limitations in differentiating recurrent tumours from postradiotherapy or surgical fibrosis and also have limitations in accurately identifying the extent of recurrence as small volume nodal metastasis. If CT or MRI of the pelvic area only is carried out, distant recurrence may not be identified. They can also be unreliable in determining the presence or absence of recurrent disease in the pelvis after radiotherapy, as radiotherapy-induced fibrosis makes tissues indurated and thus potentially conceals recurrent disease.

Positron emission tomography/computerised tomography scanning

Positron emission tomography is an imaging method that can be used to establish the functional parameters of tissue, allowing detection of metabolically active areas in tissues such as tumours.[30] ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most widely used radiotracer and is intravenously injected 1–2 hours before imaging. It is a glucose analogue and is taken up and actively trapped in the enhanced glycolytic pathway of hypermetabolic areas, demonstrated by high-energy photons emitted as a result of annihilation of positrons emitted by the radioisotope, with nearby negatively charged electrons. PET provides anatomical image resolution of the order of 4–6 mm, significantly better than conventional gamma cameras but inferior to the 1- to 2-mm resolution of CT or MRI. The size of lesion that can be detected by PET is limited by several factors, including the physics of positron emission, the spatial resolution of the scanner (typically 4.5–6.0 mm in the centre of the axial field) and the safe dosing limits of ^{18}F-FDG.[30]

Positron emission tomography/computerised tomography is a combination of PET scanning and CT scanning on the same machine. It precisely aligns and combines metabolic PET imagines with anatomical CT images obtained immediately and consecutively without patient movement, and is being increasingly preferred over PET scanning alone as it allows more precise localisation of active disease sites than either technology separately. The CT scan usually has a lower radiation dose than standard CT scans and contrast media are rarely used. PET-CT in suspected recurrent or persistent cervical cancer can detect metabolically active metastatic lesions in normal-sized nodes and in postsurgical or radiotherapy fibrosis. PET-CT in the follow-up of cervical cancer patients can be used to identify recurrent or persistent disease, assess local tumour extension, evaluate pelvic nodal involvement, detect distant metastases (e.g. lung, supraclavicular lymph nodes and para-aortic lymph nodes), plan radiotherapy and assess response to therapy.[31]

There are several disadvantages to PET-CT scanning. First, the machine is very expensive (approximately £2M). Second, ^{18}F-FDG has a short half-life of around 2 hours and therefore can cause throughput difficulties. False-positives are relatively common because the technique is looking for metabolically active regions and not all are cancerous, for example sepsis and inflammation following surgery and radiotherapy may mimic metastases. False-negatives can also occur soon after chemotherapy because the drugs may slow the metabolism of the metastases but not eliminate them altogether. Therefore, PET-CT to find secondary spread is not recommended within 3 months of surgery and radiotherapy and within 6 weeks of chemotherapy.

Current guidelines on imaging strategies in recurrent cervical cancer

The SIGN guidelines[3] state that evidence for the effectiveness of post-treatment surveillance is inconsistent and that there is no evidence to suggest that prior radiotherapy or chemotherapy alters the sensitivity of detection of recurrence. They suggest that patients should be followed up every 4 months for at least 2 years. In asymptomatic patients, a PET-CT scan is recommended at 9 months' follow-up in women who have had chemoradiotherapy. If positive, pelvic MRI should be considered for surgical planning if pelvic exenteration is appropriate. In symptomatic women, MRI or CT should be considered to assess potential clinical recurrence. If positive, a whole-body PET or PET-CT scan should be performed in patients in whom salvage therapy (pelvic exenteration or radiotherapy) is being considered.

The Society of Gynecologic Oncologists recommendations state that there is insufficient data to support routine use of PET-CT in asymptomatic patients.[32] It suggests that CT and/or PET should be used when recurrence is suspected at any time up to 5 years after treatment.

The UK Royal College of Radiologists guidelines used evidence that was not specific to recurrent cervical cancer.[33] However, it suggests that PET-CT can be used for restaging patients with cervix carcinoma considered for exenterative surgery, and for suspected recurrence when other imaging is equivocal.

Survival data from positron emission tomography/computerised tomography studies in cervical cancer

There are two publications[34,35] that contain useful information about survival in cervical carcinoma, using PET-CT to differentiate between different groups of patients, including those with persistent and recurrent cervical cancer. In Schwartz *et al.*,[35] 92 women who had been treated with chemoradiotherapy for carcinoma of the cervix (FIGO stages IB1 to IVA) and who had whole-body PET-CT between 8 and 16 weeks after initial therapy were followed up clinically for at least 6 months (range 6–49 months). PET-CT was used to investigate prognosis, linking findings with progression-free survival and cause-specific survival. Among the 92 patients, PET-CT showed a complete response in 65 (71%) and persistent tumour in 15 (16%) and identified new abnormalities in 12 (13%). The survival rates are shown in *Figure 1*. The 3-year cause-specific rates were 96% for women with a complete response to treatment and 43% for patients with persistent disease, and the 2-year survival rate was 14% for patients with any new sites of disease. The 3-year progression-free survival rates were 78% for patients with a complete response after therapy, 33% for patients with persistent disease and 0% for those with new sites of tumour.

Brooks *et al.*[34] investigated the usefulness of PET-CT imaging in 78 asymptomatic and 25 symptomatic patients following a complete response to initial chemoradiotherapy for cervical cancer. The post-therapy PET-CT was performed at 3 months after treatment completion and patients were followed up for a median of 13 months for asymptomatic patients and 8 months for symptomatic patients. Unfortunately, for the first 2 years only PET was used and for the remaining 4 years PET-CT was used. The number of women in each group is unclear. The survival curves are shown in *Figure 2*. The 3-year survival for patients with symptomatic recurrence was 19% compared with 59% for patients with asymptomatic recurrence ($p = 0.09$).

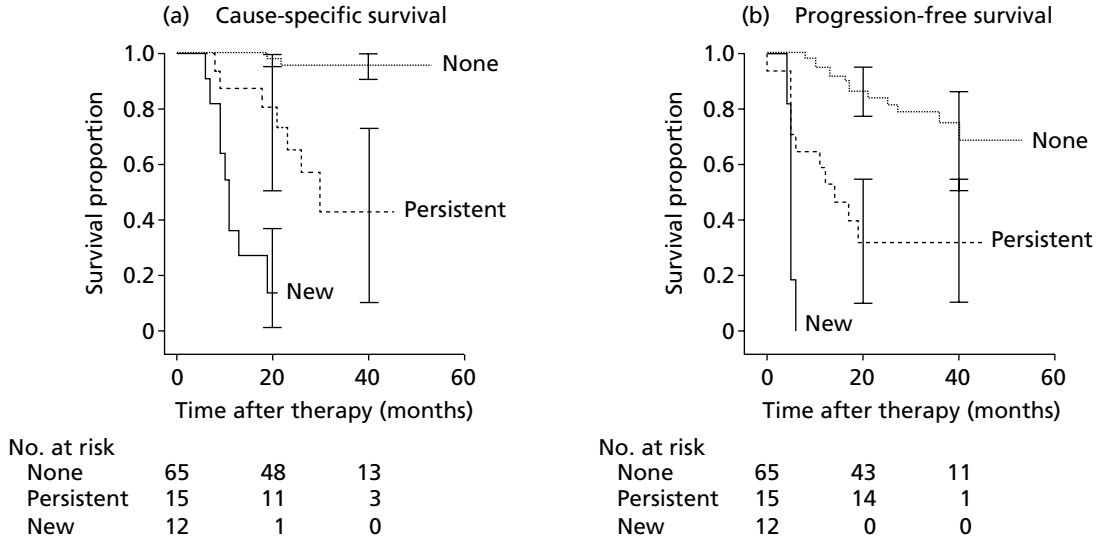

FIGURE 1 Cause-specific survival rates (a) and progression-free survival rates (b) for patients categorised by PET-CT as having no tumour, persistent tumour or new site of cervical cancer.

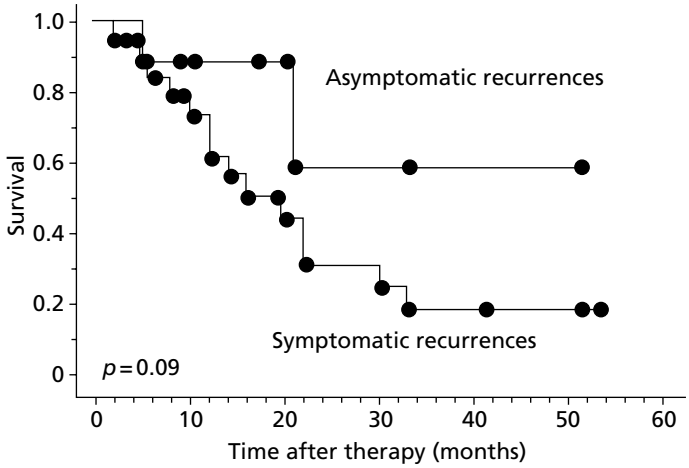

FIGURE 2 Survival in asymptomatic and symptomatic patients undergoing surveillance PET and PET-CT following one scan at 3 months.

Treatment options for recurrent cervical cancer

Treatment of recurrent cervical cancer depends on the site (central, pelvic, distant), extent of recurrence, type of previous treatment received (surgery, chemoradiotherapy, radiotherapy), time elapsed since primary treatment and patient fitness. Treatment intention is usually curative or palliative. Palliative treatment is used when there are distant metastases or multiple site recurrences and is usually chemotherapy.

Potentially curative disease is defined as:

- confirmed recurrence of the disease confined to the pelvis, provided that the patient has not received previous primary or adjuvant pelvic radiotherapy
- disease confined to the central pelvis, without pelvic side wall or extrapelvic involvement, provided that radiotherapy has been administered before recurrence
- distant recurrences at a single site (such as para-aortic lymph node) that could be completely resected or encompassed by a curative radiotherapy procedure.

In women with recurrence who had surgery for their primary tumour, radiotherapy is the treatment of choice. This may also include chemotherapy, which is often single-agent cisplatin.[3] In women who had chemoradiotherapy or radiotherapy and who have persistent cervical cancer, salvage surgery is generally considered if the patient is sufficiently fit, if the disease is localised to the pelvis only and if surgery has a high chance of completely removing the disease with clear margins.[3] Surgery can be radical hysterectomy or pelvic exenteration. Surgery for relapsed disease after radiotherapy is often associated with high morbidity as radiation fibrosis makes surgery difficult and, to enhance cure rates, surgical excision of disease often involves removal of the bladder, uterus, cervix and various amounts of the vagina (anterior exenteration) or the uterus, vagina and portions of the rectosigmoid colon and anus (posterior exenteration) or a complete pelvic clearance (exenteration). In a small number of patients, radical hysterectomy will suffice if the disease is highly localised. As exenterations are morbid surgical procedures resulting in alteration of body image and loss of bladder and/or bowel control, patients require extensive preoperative psychosocial counselling.

Objectives of this report

When this project was being defined there was some discussion around the exact focus, because the current UK imaging strategy using PET-CT is for selective use in symptomatic patients depending on symptoms and equivocal or negative findings on CT and/or MRI and to rule out the possibility of distant

metastases when salvage surgery is being considered, rather than for routine use in all symptomatic patients with suspected recurrence and as routine follow-up in asymptomatic patients. In asymptomatic patients, clinical follow-up alone may also have been a useful comparator to routine CT, MRI or PET-CT.

This research project was undertaken to evaluate the clinical effectiveness and cost-effectiveness of strategies of imaging with MRI or CT with or without PET-CT in women with asymptomatic or symptomatic recurrent cervical cancer, and for their subsequent treatment with surgery, chemotherapy and/or radiotherapy. The relationship of our clinical objectives to the range of work required is shown in *Figure 3*. The economic evaluation is in addition to these objectives and is described in *Chapter 8*.

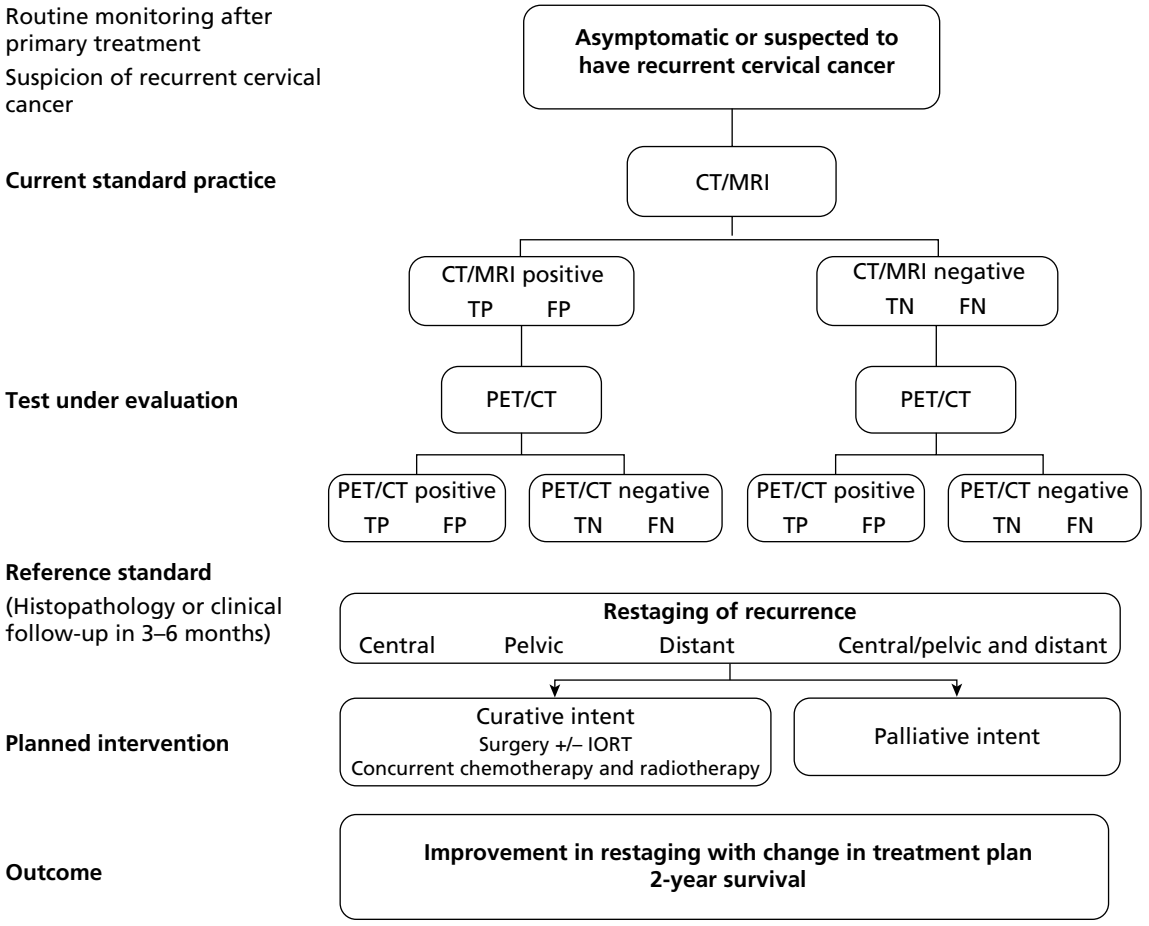

FIGURE 3 Imaging and treatment strategies in women with recurrent cervical cancer. FN, false-negative; FP, false-positive; IORT, intraoperative radiotherapy; TN, true-negative; TP, true-positive.

Chapter 3 Methods for systematic reviews and subjective elicitation

Protocol development and overview of review methods

A generic protocol was developed for undertaking the systematic reviews of test accuracy, diagnostic and therapeutic yield and effectiveness. Scoping searches for relevant systematic reviews were conducted in MEDLINE, EMBASE and The Cochrane Library (see *Appendix 2*).

Systematic reviews were carried out using established methods in line with the recommendations of the NHS Centre for Reviews and Dissemination[36] and the Cochrane Collaboration,[37] and, for diagnostic systematic reviews, using the latest methods from the Cochrane Diagnostic Test Accuracy Working Group.[38] Presentation of systematic reviews is according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[39]

Inclusion of studies, data extraction and quality assessment were carried out in duplicate with differences resolved by consensus and/or arbitration involving a third reviewer. There were no language limitations on inclusion criteria. The selection process was piloted by applying the inclusion criteria to a sample of papers first, and then a two-stage process was used, first, by screening titles and abstracts. For all references categorised as 'include' or 'uncertain' by both reviewers, the full text was retrieved whenever possible and final inclusion decisions were made on the full paper. Reference Manager 12.0 software (Thomson ResearchSoft, San Francisco, CA, USA) was used to construct a database of citations for all systematic reviews.

Clinical, methodological and statistical data extraction was carried out using data extraction sheets by at least two reviewers and discrepancies were resolved through discussion. If consensus could not be reached, disagreements were resolved by arbitration by a third reviewer. For diagnostic studies, information was extracted regarding study design and methods, characteristics of participants, PET-CT and comparison tests, and outcomes of interest (see *Appendix 3*). For the effectiveness review, separate data extraction forms were used for different study designs: comparative experimental study (part A), comparative observational study (B) and non-comparative study (C) (see *Appendix 4*). The quality assessment questions for randomised controlled trials (RCTs) were included in the data extraction sheet, but a separate form was used for case series (see *Appendix 5*). Data extraction was managed with Microsoft Office 2003 Word and Excel (Microsoft Corporation, Redmond, WA, USA). Quality was also assessed independently by two reviewers. Any disagreements were resolved through discussion or by arbitration by the third reviewer.

Methods for test accuracy and diagnostic and therapeutic impact reviews

Search strategy

A sensitive search was conducted to identify all relevant published and unpublished studies and studies in progress. All databases were searched from inception to May 2010. Search strategies were designed from a series of test searches and discussions of the results of those searches among the review team. Both medical subject heading (MeSH) terms and text words were used and included 'cervical cancer', 'PET-CT', 'CT' and 'MRI'. The strategies from MEDLINE, EMBASE and The Cochrane Library can be found in *Appendix 6*. Literature was identified from several sources including:

- general health and biomedical databases: MEDLINE (Ovid), EMBASE (Ovid), Science Citation Index, The Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)], Medion
- checking of reference lists of systematic and narrative review articles
- searching a range of relevant databases including ClinicalTrials.gov and the UK Clinical Research Network Portfolio to identify information about studies in progress, unpublished research or research reported in grey literature
- specialist search gateways (OMNI and the National Cancer Institute), general search engine (Google) and meta-search engine (Copernic) from March to May 2010
- hand-searching of *Gynecologic Oncology* from 1980 to May 2010
- authors of included studies contacted for information on relevant published or unpublished studies.

Inclusion and exclusion criteria

Population

Included:

- any women with clinical suspicion of persistent or recurrent cervical cancer after primary treatment, on the basis of one or more of clinical history, clinical examination and tests (including imaging and histology)
- any women who had had advanced-stage cervical cancer (IB2–IV) treated previously, for example with chemoradiotherapy, with a minimum gap between completion of treatment and imaging of 3 months, and who were currently asymptomatic and undergoing routine follow-up.

Excluded:

- studies in which the population contained women within 3 months of completion of treatment for primary disease were excluded because of problems associated with distinguishing treatment complications and inflammatory response from recurrence in this patient group.

Index test

Included:

- PET-CT using ^{18}F-FDG as the radioisotope tracer.

Excluded:

- PET alone without concurrent CT.

Comparator tests

- CT (local or whole body).
- MRI (local or whole body).

Reference standard

Included:

- histopathological findings or clinical follow-up for ≥6 months or both for all participants (differential reference standard was accepted because of the difficulty of biopsy when there was no indicated lesion to biopsy in test-negative patients).

Excluded:

- studies in which only some of the participants undergoing the index test also received any reference standard.

Outcome

- Studies that provided numerical data sufficient to create 2×2 tables of test results comparing index or comparator tests with the reference standard to provide information on test accuracy, giving true-positive, true-negative, false-positive and false-negative results.
- Studies that provided any information on diagnostic impact: change in diagnosis and/or staging after PET-CT compared with existing tests or reference standard.
- Studies that provided therapeutic impact: change in treatment plan after PET-CT compared with existing tests or reference standard.

Study design

Included:

- any prospective or retrospective test accuracy studies
- any diagnostic before-and-after studies investigating diagnostic and therapeutic impact with or without concurrent assessment of test accuracy
- studies with >10 participants.

Excluded:

- studies on gynaecological cancers not providing separate data for the population with cervical cancer
- studies that described only lesion-based analysis rather than person-based analysis.

Quality assessment

Test accuracy quality assessment followed the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) guidelines[40] and diagnostic and therapeutic impact quality assessment followed guidelines suggested by Meads and Davenport.[41] The items of methodological quality listed in the QUADAS guidelines[40] are a representative spectrum, selection criteria clearly described, acceptable reference standard, acceptable delay between tests, partial verification avoided, differential verification avoided, reference standard independent of the index test, index test described in sufficient detail, reference standard described in sufficient detail, index test results blinded, reference standard results blinded, relevant clinical information available, uninterpretable results reported, and withdrawals explained.

These items were tailored to assess the included studies because different aspects of quality are applicable to different topic areas. The actual quality items used for this report are listed in *Table 2*. For acceptable delay between tests, this included delay between the index test and the comparator test (within 1 month) and between the index test and PET-CT (with 1 month). There will inevitably be a delay between the index test and clinical follow-up (as this had to be >6 months). Differential verification was omitted because it was inevitable that the test positives would have a different reference standard (histology) to the test negatives (clinical follow-up).

Study quality was summarised in a table. Additional issues (e.g. study design characteristics, method of patient enrolment, technique of data collection) were also collected. Technical quality was assessed by a consultant radiologist with considerable experience in current cancer imaging techniques.

Methods of statistical analysis

RevMan version 5.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 11 (StataCorp LP, College Station, TX, USA) were used in the statistical analyses. True-positives, false-positives, true-negatives and false-negatives were taken directly from the source papers and sensitivity and specificity calculated in RevMan. Equivocal results were used in sensitivity analyses by adding the total number of equivocal results to each of the true-positives, false-positives, true negatives and false-negatives in turn to derive maximum and minimum variation in sensitivity and specificity. Summary

TABLE 2 Quality assessment items

Item	Yes	No	Unclear
1. Representative spectrum	If the stated characteristics of the spectrum of patients fulfilled the requirements of the included population	If the sample does not fit with what was pre-specified as acceptable or if groups with and without the target disorder were recruited together (e.g. sample includes both primary and recurrent cervical cancer and results not given separately)	If there is insufficient information available to make a judgement about the spectrum
2. Selection criteria clearly described	If the selection criteria described	If the selection criteria not described	If there is insufficient information available to know clearly the selection criteria
3. Acceptable reference standard	Both reference standards used meet the pre-stated inclusion criteria	One or other reference standards used do not meet the pre-stated criteria	It is unclear exactly what reference standard was used (particularly for clinical follow-up)
4. Acceptable delay between imaging tests	If the time between tests was shorter than 1 month, at least for an acceptably high proportion of patients	If the time between tests was longer than 1 month for an unacceptably high proportion of patients	If information on timing of tests is not provided
5. Partial verification avoided	If all patients, or a random selection of patients, who received the index test went on to receive verification of their disease status using a reference standard, even if the reference standard was not the same for all patients	If some of the patients who received the index test did not receive verification of their true disease state, and the selection of patients to receive the reference standard was not random	If this information is not reported by the study
6. Reference standard independent of the index test	If the index test did not form part of the reference standard	If the reference standard formally included the result of the index test	If it is unclear whether or not the results of the index test were used in the final diagnosis
7. Tests described in sufficient detail for replication	If both the index test(s) and reference standard were fully described to permit replication	If no tests described	If test descriptions unclear
8. Reference standard/index test results blinded	If test results (index or reference standard) were interpreted blind to the results of the other test, or blinding is dictated by the test order, or meets the pre-stated assumptions	If it is clear that one set of test results was interpreted with knowledge of the other	If it is unclear whether blinding took place
9. Relevant clinical information	If clinical data available on previous operations and previous imaging per patient	If clinical data not stated	If information about clinical data was unclear
10. Uninterpretable results reported	If the number of uninterpretable test results (equivocal results) is stated, or if the number of results reported agrees with the number of patients recruited (indicating no uninterpretable test results).	If it states that uninterpretable test results occurred or were excluded and does not report how many	If it is not possible to work out whether or not uninterpretable results occurred

TABLE 2 Quality assessment items (*continued*)

	Yes	No	Near
11. Withdrawals explained	If it is clear what happened to all patients who entered the study, for example if a flow diagram of study participants is reported explaining any withdrawals or exclusions, or the numbers recruited match those in the analysis	If it appears that some of the patients who entered the study did not complete the study, i.e. did not receive both the index test and reference standard, and these patients were not accounted for	If it is unclear how many patients entered and, hence, whether or not there were any withdrawals
12. Technical quality	If it is clear that the methods of imaging described in the paper are similar to those currently used	If it is clear that the methods of imaging described in the paper have since been superseded by current imaging standards	If the methods described in the paper are close to those currently in use and should not noticeably affect interpretation or results

estimates of sensitivity and specificity and summary receiver operating characteristic (SROC) curves were derived as appropriate using recognised methods for meta-analysis of test accuracy. Results were displayed graphically on forest and SROC plots.[42] Meta-analyses were undertaken when adequate results were available. A bivariate model that included a random-effects term for variation in accuracy and threshold between studies was fitted.[43] When the model failed to converge or a correlation could not be estimated properly the bivariate model was simplified to two univariate random-effects logistic regression models by assuming no correlation between sensitivity and specificity. Although no correlation between sensitivity and specificity was assumed, a confidence region is shown on the SROC plot as an indication of the uncertainty surrounding the point estimate of sensitivity and specificity.

Methods for subjective elicitation

Rationale

Subjective probabilities were elicited from clinicians representing the disciplines of radiology, oncology and gynaecology. Eliciting subjective probabilities from clinicians had three roles in the planned investigation of the clinical effectiveness of PET-CT imaging in the detection and management of recurrent cervical cancer:

1. Providing data to populate the economic model in the absence of information found in the literature.
2. Supplementing information found in the literature. Literature may be sparse, of poor quality or not transferable to the UK setting. Information gained from clinicians in the form of subjective probabilities may be used to supplement information found in the literature and to enable sensitivity analyses to be performed as part of the economic model.
3. Planning the dissemination strategy for the results of the research. If there is wide variation in accuracy estimates elicited from clinicians, or if elicited estimates of accuracy are very discrepant with those found in the literature, this may impact on the successful dissemination of the research findings to clinicians.

Probabilities elicited

Informed by the preliminary results of the systematic reviews of test accuracy (and effectiveness), the research team decided on the data priorities for elicitation as follows:

1. To determine the prevalence of recurrence in women with an initial diagnosis of stage IB–IVA cervical cancer, who are assumed to be disease free for a minimum of 3 months post completion of primary treatment:
   i. presenting with symptoms suggestive of recurrence
   ii. in the absence of symptoms

2. To determine the test accuracy of chest, abdominal and pelvic CT and/or MRI performed at the discretion of clinicians in women with an initial diagnosis of stage IB–IVA cervical cancer, who are assumed to be disease free for a minimum of 3 months post completion of primary treatment:
   i. presenting with symptoms suggestive of recurrence
   ii. in the absence of symptoms (CT and/or MRI used for surveillance)
3. To determine the test accuracy of CT and/or MRI performed at the discretion of clinicians and of PET-CT (performed regardless of the result of initial imaging) in women with an initial diagnosis of stage IB–IVA cervical cancer, who are assumed to be disease free for a minimum of 3 months post completion of primary treatment:
   i. presenting with symptoms suggestive of recurrence
   ii. in the absence of symptoms (CT and/or MRI + PET-CT used for surveillance).

Information on rate of recurrence in women post completion of primary treatment as distinct from rate of recurrence in women following imaging was absent in the literature reviewed. Elicitation of accuracy data was necessary because of a lack of disaggregation of women with and without symptoms in the literature and because of the very limited accuracy data available. Elicitation also provided the opportunity to investigate the coherence of subjective probabilities elicited with estimates in the literature.

Methods used

Subjective probabilities were elicited by two project members (CD and CM) during an educational meeting of the West Midlands Gynaecology Oncology Specialist Group on 1 July 2011 at the City Hospital, Birmingham, UK. Following the success of this initial elicitation, as judged by the face validity of the findings, the results were supplemented by purposive sampling by clinicians in the project team and by two further meetings – a gynae-oncology multidisciplinary meeting at Barts Hospital, London, UK, on 17 August 2011 and at the British Gynaecological Cancer Society Scientific Meeting at the International Convention Centre, Birmingham, UK, on 18 November 2011.

The initial elicitation exercise was preceded by a presentation outlining the aims of the project, the role of elicitation in the project, an overview of definitions of prevalence and test accuracy metrics to be elicited and a practice non-clinical elicitation exercise. Subsequent elicitations achieved by purposive sampling used a written description of the task and a printed elicitation example, except at the scientific meeting where a poster on the project was also displayed.

For the clinicians carrying out the first elicitations, the face-to-face pre-elicitation training, questions and discussion were conducted as a group to facilitate a common understanding of the problem and task and to allow participants to benefit from group discussion and interaction. Following the presentation and the non-clinical elicitation exercise (on estimated distance from London to Birmingham), participants were asked for written consent before undertaking the elicitation exercise. Participants were free to leave at any point in the exercise. Participants were instructed to undertake the elicitation exercise itself independently to ensure that variation within and across disciplines could be captured if there were sufficient numbers of respondents to allow subgroup analysis. In addition, mathematical aggregation (as opposed to behavioural aggregation) mitigates against the possibility of 'consensus' estimates being biased by the views of a minority.[44]

The elicitation exercise comprised an 11-page anonymous self-administered questionnaire (see *Appendix 7*). The questionnaire included background information on the length of time that participants had practised in their speciality, their use of current imaging techniques and their use of PET-CT. To be eligible participants did not have to have hands-on experience of using PET-CT. Use of PET-CT is not routine in this patient group and beliefs are shaped by factors other than first-hand experience, such as interaction with colleagues, published estimates of accuracy and knowledge of the technology. In addition to the probabilities elicited, participants were also asked to state the minimum important clinical difference in accuracy between imaging with CT and/or MRI and imaging with CT and/or MRI with the addition of PET-CT that they would require before choosing to use one or other imaging strategy routinely.

Accuracy data were elicited in the form of the proportion of test errors (false-positives and false-negatives) that would be expected with the use of the combinations of imaging technologies outlined above. The choice of test errors as a metric of accuracy is based on research suggesting that test accuracy metrics with test result as reference class are more intuitive[45] and that the clinical utility of a test is commonly conceptualised using test errors.[46] Test errors were used to derive positive predictive values (PPVs) and negative predictive values (NPVs). Elicited estimates of prevalence in combination with PPVs and NPVs were used to derive estimates of sensitivity and specificity for use in the economic model.

Elicitation of prevalence and test accuracy information was undertaken using the allocation of points technique whereby respondents are asked to indicate the likelihood of a value range being a true estimate by allocating a proportion of 100 points to that value range (the sum of allocated points across each value range summing to 100). In this way probability functions were obtained for each individual and were aggregated mathematically to derive an average distribution for the sample. An aggregated mean value was estimated using the average distribution and the midpoint of each value range. The variability of this aggregated mean was estimated by calculating the standard deviation (SD) across the value ranges. Microsoft Excel was used for calculations and graphical display of results.

Methods for effectiveness reviews

Search strategy

A sensitive search was conducted to identify all relevant published and unpublished trials and trials in progress. All databases were searched from inception to August 2010. Search strategies were designed from a series of test searches. Both MeSH terms and text words were used and included a variety of synonyms for recurrent cervical cancer and the interventions (chemotherapy, radiotherapy, palliative treatment, surgery). Strategies for MEDLINE, EMBASE and The Cochrane Library can be found in *Appendix 8*. Trials were identified from several sources including:

- general health and biomedical databases: MEDLINE (Ovid), EMBASE (Ovid), CENTRAL
- database searches for systematic reviews, from which primary studies could be identified, including MEDLINE (Ovid), EMBASE (Ovid) and The Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database]
- searches for studies in progress, unpublished research or research reported in the grey literature in a range of relevant databases including ClinicalTrials.gov and the UK Clinical Research Network Portfolio
- specialist search gateways (OMNI and the National Cancer Institute), general search engine (Google) and meta-search engine (Copernic) from March to May 2010
- hand-searches of *Gynecologic Oncology* from 1980 to May 2010
- reference lists of review articles and papers
- authors of the included studies, who were contacted for information on relevant published or unpublished studies.

Inclusion/exclusion criteria

Population

Included:

- Women with recurrent cervical cancer (i.e. initial treatment was apparently successful and patients now presenting after 3 months with new symptoms and signs indicating recurrence) or with persistent cervical cancer (stage IVB) at follow-up after initial treatment has been completed (i.e. patients have initial treatment that was completed and are now presenting after 3 months with symptoms and signs suggesting that the initial treatment had not been completely successful). The initial treatment could have been surgery, radiotherapy or chemotherapy or any combination of these.

Excluded:

- women with advanced cervical cancer before initial treatment together with women with recurrent or persistent cervical cancer in which the results were not presented separately
- trials with a lack of information about the primary site of cancer (e.g. studies on gynaecological cancers in which the exact site is not specified)
- trials with a lack of information on the primary treatment of participants
- patients who had undergone a variety of different initial treatments in which the results for each treatment group were not presented separately
- patients who had undergone a variety of different types of surgery in which the results were not presented separately
- patients who had undergone surgery with radiotherapy for their initial treatment.

Interventions and comparators

Any of the following treatments for recurrence were included:

- surgery with curative intent (studies must have included < 10% surgery with palliative intent)
- chemotherapy with a variety of therapeutic agents
- radiation treatment
- combination of surgery with radiotherapy
- combination of surgery with chemotherapy
- combination of radiotherapy with chemotherapy.

Excluded:

- curative and palliative intent surgery presented together in which palliative intent was ≥ 10% of participants.

Outcomes

Included:

- survival or mortality
- morbidity, symptoms
- treatment success or failure rates
- quality of life.

Excluded:

- biochemical outcomes.

Study design

Included:

- RCTs, controlled clinical trials
- case series, cohort studies or case–control studies when RCTs or controlled clinical trials were not available.

Excluded:

- studies presenting results for < 10 patients.

Quality assessment

For the two designs found (RCTs and case series), quality assessment and presentation of results have been carried out separately.

Randomised controlled trials

Quality assessment of included RCTs was performed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[37] Each study was assessed for adequate sequence generation, adequate allocation concealment, all methods of blinding used and whether or not they were effective, whether or not there was incomplete outcome data presented (attrition and exclusions from analysis), non-selective outcome reporting, and freedom from other biases. In all cases 'yes' indicated a low risk of bias and 'no' indicated a high risk of bias. 'Unclear' was used if there was insufficient detail reported. The quality of studies was summarised in tables, which were then used to create quality diagrams.

Case series

Quality assessment of case series was performed using the checklist developed by the National Institute for Health and Clinical Excellence (NICE).[47] Each study was then awarded an overall study quality grading for internal validity and an overall study quality grading for external validity:

- ++: all or most of the checklist criteria have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter.
- +: some of the checklist criteria have been fulfilled; where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.
- –: few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Methods of reporting and statistical analysis

Most results are reported in tables. Information was analysed based on the group to which the participants were allocated, regardless of whether or not they received the allocated intervention. For dichotomous data, results are presented as summary relative risks (RR) with 95% confidence intervals (CIs). Separate analyses were performed on randomised and non-randomised data. RRs were calculated from numbers of patients, using StatsDirect version 2.7.8 (StatsDirect, Altrincham, UK) or RevMan version 5.0. For adverse events, only grade 3 and grade 4 events were reported.

RevMan version 5.0 was also used for meta-analyses. Any heterogeneity of results between studies was statistically and graphically assessed and potential causes explored. To explore causes of clinical heterogeneity, a priori subgroup analyses were conducted to see whether variations in clinical factors, for example populations, interventions, outcomes or study quality, affected the estimation of effect sizes. The I^2 statistic was used to assess heterogeneity between trials. In the absence of significant heterogeneity, results were pooled using a fixed-effects model. If substantial heterogeneity was detected ($I^2 > 50\%$), possible causes were explored and subgroup analyses for the main outcomes performed. Heterogeneity that was not explained by subgroup analyses was modelled using random-effects analysis where appropriate. For outcomes for which a meta-analysis was not appropriate, the RCT and non-randomised study results were presented, where possible, on a forest plot but without summary scores, allowing a visual presentation of the effects of each included trial. For case series, a narrative summary of the findings was given.

Methods for systematic review of economic evaluations

A systematic review was conducted to find published literature and work in progress on the economic evaluation of PET-CT for use in the detection of recurrent cervical cancer. The purpose of this review was to investigate the suitability of existing cost-effectiveness models and model designs and to identify

information that could be used to populate the model subsequently developed for this project. The aim was also to identify economic studies that reported costs and consequences associated with recurrent cervical cancer detected by the use of PET-CT. Systematic reviews of the effectiveness of treatments, with meta-analysis of clinical studies, particularly RCTs, use well-established research methods but the approach for reviewing economic evaluations and costing studies is necessarily slightly different and more qualitative, primarily because of the heterogeneity that exists in economic studies, which means that formal data synthesis and meta-analyses are rarely possible. This systematic review was carried out using PRISMA guidelines with adaptations appropriate for systematic reviews of economic evaluation and costing studies.[39] In addition to the systematic review of economic evaluations, a separate literature review was conducted to find suitable generic quality-of-life values [including quality-adjusted life-years (QALYs)] for use in the economic model.

Five electronic databases were searched [EMBASE, MEDLINE, NHS Economic Evaluation Database (NHS EED), DARE and HTA database] from 1980 to October 2011. Reference lists from relevant papers were also searched. *Appendix 9* shows the detailed search strategies used. The inclusion criteria were:

- patients – those with recurrence or persistent cervical cancer who had previously completed treatment for their primary cervical cancer (primary cervical cancer alone was specifically excluded)
- intervention – PET-CT
- comparator – no PET-CT, other imaging
- outcomes – costs, cost-effectiveness, cost–utility, quality of life.

Studies were independently reviewed on the basis of their titles and abstracts by one researcher (PA). The screening process used followed established methods used to identify and categorise economic evaluation and costing studies.[29] Briefly, a three-stage process was adopted. In stage 1, each study was categorised on the basis of its title and abstract (where available) into one of four groups. The two relevant groups for this review were group A – studies suspected of being full economic evaluations on PET-CT recurrence of cervical cancer – and group B – cost studies, but not economic evaluations. Group A and group B studies would proceed to stage 2 where they would be read in full and, if confirmed in their classification, would proceed to stage 3 for quality assessment. *Appendix 9* shows the full details of the three-stage process.

Chapter 4 Diagnostic review results

Study selection

At the final update of May 2010 there were 7524 potentially relevant citations identified, of which 252 full-text articles were retrieved. Subsequently, 240 articles were excluded (see list of excluded studies in *Appendix 10*). The most common reason for exclusion was either that the study was on patients with newly diagnosed cervical cancer before primary treatment or that the study was of the incorrect design. The numbers of included and excluded citations are shown in *Figure 4*. The 12 included studies evaluated the test accuracy of PET-CT, MRI or CT imaging for persistent or recurrent cervical cancer compared with a reference standard of biopsy, clinical follow-up or both. Six studies evaluated PET-CT,[20,48–52] two evaluated MRI,[53,54] three evaluated CT[55–57] and one evaluated both MRI and CT.[58] *Table 3* shows the basic characteristics of the included studies and *Table 4* provides definitions of the reference standards used. There were no studies that directly compared PET-CT with MRI or CT separately. One of the included studies[49] compared PET-CT with standard imaging (MRI, CT or both) and gave results for both PET-CT and standard imaging in the same table.

No additional papers were found that evaluated diagnostic or therapeutic yield. One of the included studies[20] gave information on diagnostic yield and also gave 2-year disease-free survival curves for participants with positive and negative PET-CT scans.

Characteristics of included studies

Population characteristics

The characteristics of the patient populations in the included studies are shown in *Tables 5–7*. The total number of patients in the studies ranged from 20 to 75 but some of the studies included any gynaecological cancers and others reported imaging results for both recurrent and primary cervical cancer. Therefore, the tables also report the number of patients with recurrent cervical cancer only and with imaging results. Many of the studies did not report summary patient characteristics for the patients with recurrent cervical cancer and imaging results only but for the full patient group, which is not relevant here and so has not been reported. When stated, most patients had squamous cell carcinoma; fewer had adenocarcinoma. In some studies, such as that by Chung *et al.*,[20] it was stated that histologically confirmed squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the uterine cervix was a requirement for study eligibility, but for others it was unclear.

All included studies except those by Mittra *et al.*[51] and Hatano *et al.*[53] described only women who had undergone treatment for histopathologically proven cervical cancer and who had suspected recurrence based on the presence of clinical signs and/or symptoms. The Mittra *et al.* study[51] included both symptomatic and asymptomatic patients undergoing routine follow-up. The Hatano *et al.*[53] study verified whether MRI could provide accurate information to evaluate residual tumours after radiotherapy (persistent disease) and the MRI findings were compared with cytology/histopathology before and after radiotherapy.

Six studies[20,49, 50,52,56,58] described grounds on which the recurrence was suspected. Abnormal imaging and physical examination during follow-up were the main indications for performing PET-CT in the Chung *et al.*[20] study. Each patient in the Grisaru *et al.*[49] study had undergone a comprehensive evaluation of her clinical status and was scheduled for routine staging or follow-up imaging studies for suspected recurrence (but results were given only for suspected recurrence). Recurrence in Kitajima *et al.*[50] was suspected on the basis of physical examination, elevated levels of tumour markers and abnormal findings of conventional

TABLE 3 Studies included in the diagnostic review

Study	Diagnostic test(s)	Reference standard	Suspected recurrence/ asymptomatic	Number evaluable in study
Amit 2006[48]	CT then whole-body PET-CT	Histopathology	Suspected	11[a]
Chung 2007[20]	Imaging then whole-body PET-CT	Histopathology, radiology and/or clinical follow-up for 6 months	Suspected (but possibly one or more asymptomatic)	52
Grisaru 2004[49]	1. CT and/or MRI plus PET-CT (skull to mid-thigh) 2. CT and/or MRI alone	Histopathology, radiology and/or clinical follow-up	Suspected	12
Kitajima 2008[50]	Imaging then whole-body PET-CT	Histopathology, clinical follow-up for >1 year, tumour marker levels alone or with CT or PET-CT	Suspected	52
Mittra 2009[51]	Imaging then whole-body PET-CT	Histopathology or clinical follow-up	Suspected and symptomatic (disaggregation not possible)	30
Sironi 2007[52]	Imaging then whole-body PET-CT	Histopathology, clinical follow-up with radiology for >6 months	Suspected	12
Hatano 1999[53]	MRI (pelvic)	Histopathology	Unclear	35[b]
Weber 1995[54]	MRI (pelvic)	Histopathology, clinical follow-up for up to 4 years	Suspected	37[b]
Heron 1988[55]	CT (abdomen)	Histopathology, clinical follow-up	Suspected	70[b]
Park 2000[56]	CT (chest, abdomen and pelvis)	Histopathology, tumour marker, CT	Suspected	36
Walsh 1981[57]	CT (abdomen and pelvis)	Histopathology	Probably suspected	33[b]
Williams 1989[58]	CT, MRI (both pelvic)	Histopathology	Suspected	20[b]

a Gives test results for extracervical lesions only.
b Gives test results for local recurrence only, not for all recurrence.

imaging, including CT and/or MRI, or an abnormal cervical smear. In Sironi *et al.*,[52] suspicion of tumour recurrence was based on follow-up procedures (physical examination, serum tumour markers and morphological imaging studies, such as CT or MRI). In Park *et al.*,[56] recurrence was suspected also on the basis of increased levels of serum squamous cell carcinoma antigen and carcinoembryonic antigen, pain in the lower abdomen and back, oedema of the lower leg and oliguria. The suspicion of recurrence in Williams *et al.*[58] was based on the clinical features of pelvic pain, vaginal discharge, vaginal bleeding, lower limb swelling or a palpable mass on pelvic examination.

Imaging characteristics

All six PET-CT studies[20,48–52] were evaluations of PET-CT after patients had received conventional imaging (MRI and/or CT) or CT only. Of the PET-CT studies, only Amit *et al.*[48] focused on extracervical lesions, whereas the other five studies evaluated any recurrence. Only Park *et al.*[56] used CT to evaluate any recurrence and the other five MRI and CT studies evaluated local recurrence in the pelvis only.

TABLE 4 Definitions of reference standards presented in included studies

Study	Histopathological findings	Follow-up	
		Clinical	Radiological
PET-CT			
Amit 2006[48]	Histopathological examination during biopsy, random sampling of nodes	–	–
Chung 2007[20]	Histological tissue sampling during surgery or biopsy	Physical and gynaecological examination over at least 6 months	Serial imaging studies over at least 6 months
Grisaru 2004[49]	Histology during surgical exploration or guided biopsies	Clinical outcomes (all negative tissue diagnoses were followed up to confirm negative histology)	Radiological
Kitajima 2008[50]	Histopathological examination ($n = 21$)	Clinical follow-up for periods >1 year on the basis of tumour marker levels and contrast-enhanced CT findings ($n = 14$), tumour marker levels and PET-CT findings ($n = 12$) and tumour marker levels ($n = 5$)	
Mittra 2009[51]	Histological evaluation ($n = 23$)	Clinical follow-up ($n = 7$)	–
Sironi 2007[52]	Histopathological findings during surgery or imaging-guided FNA biopsy in patients who were positive on PET-CT	If negative on PET-CT: clinical outcomes with CT or MR imaging over at least 6 months	
MRI			
Hatano 1999[53]	Histopathological findings during multiple punch biopsies and cytology of tumour site only	–	–
Weber 1995[54]	Histopathology and/or surgical outcomes ($n = 34$)	Clinical follow-up for at least 4 years ($n = 3$)	–
CT			
Heron 1988[55]	Histological evaluation: at EUA ($n = 4$), by laparotomy ($n = 7$) and by CT-guided biopsy ($n = 3$)	Unequivocal progressive clinical course ($n = 25$), including post-mortem proof ($n = 2$) and supportive evidence of deterioration on follow-up ($n = 17$). For 31 patients with negative test, patients considered to be free of recurrence only if clinical condition remained stable for >2 years and/or histology	–
Park 2000[56]	Percutaneous lymph node biopsy ($n = 10$), biopsy of the pelvic mass ($n = 3$)	Tumour marker study and CT at 3- and 6-month intervals ($n = 23$)	
Walsh 1981[57]	Histological evaluation ($n = 29$): by laparotomy ($n = 10$), parametrial biopsy ($n = 6$), cervical and vaginal biopsy ($n = 6$), perineal biopsy ($n = 2$), lymph node aspiration ($n = 2$), autopsy ($n = 2$) and bone biopsy ($n = 1$)	–	–
MRI and CT			
Williams 1989[58]	Histological biopsies ($n = 10$), hysterectomy specimens ($n = 4$), open biopsy at laparotomy ($n = 2$), histological proof of distant metastatic disease ($n = 4$)	–	–

EUA, examination under anaesthetic; FNA, fine-needle aspiration.

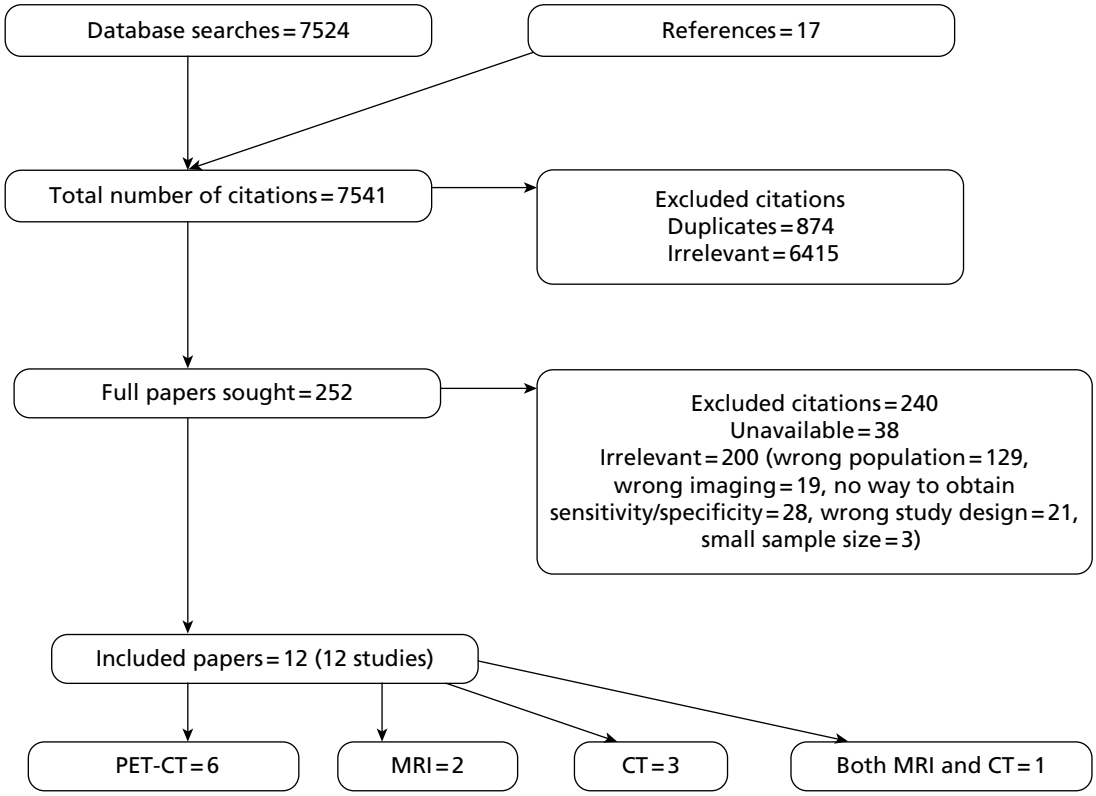

FIGURE 4 PRISMA diagram of selection process: diagnostic systematic review.

All six PET-CT studies used ^{18}F-FDG as a radioisotope tracer, with doses of 370–555 MBq,[48] 555–740 MBq,[20] 370–666 MBq,[49] 4.0 MBq/kg,[50] 400–555 MBq[51] and 370 MBq.[52] The time between injection of ^{18}F-FDG and the PET scan ranged from 30 minutes to 3 hours. The PET-CT scanning was performed mostly with a GE Discovery LS PET-CT scanner (GE Medical Systems, Milwaukee, WI, USA). In Amit *et al.*,[48] a hybrid PET-CT system combining a third-generation multislice spiral CT system [GE LightSpeed Plus (GE Medical Systems, Milwaukee, WI, USA)] with a dedicated full bismuth germanium oxide (BGO) ring PET scanner [GE Advance NXi (GE Medical Systems, Milwaukee, WI, USA)] was used. In Chung *et al.*[20] a GEMINI PET-CT system (Philips, Guildford, UK) was used, and in Kitajima *et al.*[50] all imaging and data acquisitions were performed with a Biograph Sensation 16 PET-CT scanner (Siemens Systems, Erlangen, Germany). Two studies[48,50] measured glucose levels before administration of ^{18}F-FDG.

In the three MRI studies[53,54,58] T1-weighted spin-echo and T2-weighted turbo spin-echo were used. Of the four CT studies,[55–58] two[55,58] used optional intravenous contrast medium to elucidate problems identified on initial scans. Intravenous contrast medium was used routinely in the other two studies: non-ionic contrast (150 mg)[56] and Reno-M-DIP® contrast (400 ml of 4% oral meglumine diatrizoate) (Squibb, Princeton, NJ, USA).[57]

Quality of studies

The results of the quality assessment are provided in *Table 8*. Four studies[48,49,52,53] collected patients' data prospectively (77 patients in total), seven studies[20,50,51,54,56–58] collected data retrospectively (260 patients in total) and in one of the studies[55] there was no information on the method of enrolment. Three studies[20,51,52] clearly described their inclusion criteria such as presence of symptoms indicating recurrence, new lesions on surveillance imaging, elevated serum tumour markers with or without abnormal imaging and abnormal results on physical or cytological examination on routine surveillance. Relevant clinical information such as age, FIGO stage, histology type of tumour and primary treatment were described in all studies except for those by Amit *et al.*,[48] Grisaru *et al.*[49] and Park *et al.*[56]

TABLE 5 Population characteristics of studies evaluating PET-CT

Characteristics	Amit 2006[48]	Chung 2007[20]	Grisaru 2004[49]	Kitajima 2008[50]	Mittra 2009[51]	Sironi 2007[52]
Total *n* in study	75	52	53	52	30	25
n with recurrent cervical cancer and imaging results	11	52	12	52	30	12
Age (years), mean (range)	NR	53 (32–77)	NR	58 (37–78) (median)	50 (28–87)	49.6
FIGO initial stage	NR	IA1 ($n = 4$); IA2 ($n = 3$); IB1 ($n = 19$); IIA ($n = 11$); IIB ($n = 10$); IIIB ($n = 1$); IVA ($n = 4$)	NR	I ($n = 12$); II ($n = 15$); III ($n = 21$); IV ($n = 4$)	IB2 ($n = 2$); IIA ($n = 4$); IIB ($n = 10$); IIIA ($n = 1$); IIIB ($n = 11$); IVA ($n = 2$)	IIB ($n = 6$); IIIA ($n = 5$); IIIB ($n = 1$)
Type of tumour pathology	NR	SCC ($n = 45$); ADC ($n = 5$); NEC ($n = 2$)	NR	SCC ($n = 42$); ADC ($n = 8$); ASC ($n = 2$)	SCC ($n = 22$); ADC ($n = 5$); other ($n = 3$)	NR
Previous treatment	NR	SR ($n = 43$); RT ($n = 5$); CHRT ($n = 4$)	NR	SR + CHRT ($n = 20$); SR + CH ($n = 12$); CHRT ($n = 12$); SR ($n = 8$)	NR	SR + CH ($n = 6$); SR + RT ($n = 1$); SR + CH + RT ($n = 5$)
Inclusion criteria	Patients with proven recurrent cervical cancer	Had symptoms suspecting recurrence; had new lesions on surveillance imaging studies; had elevated serum tumour markers with or without abnormal imaging studies; had abnormal results on physical or cytological examination on routine surveillance; wanted surveillance PET-CT scan for fear of recurrence without evidence of disease[a]	Patients with proven gynaecological malignancy	Patients who had undergone treatment for histopathologically proven uterine cervical cancer and who had suspected recurrence	Patients with histologically confirmed carcinoma of the uterine cervix who were subjected to primary treatment with curative intention and who reached complete remission after initial treatment	Patients who had undergone primary surgical treatment and postoperative adjuvant therapy for uterine cancer
Exclusion criteria	NR	Had previously been diagnosed with malignant disease other than non-melanoma skin malignancy; had been diagnosed as unsuited for treatment with curative intent at the time of disease recurrence; had skin or pulmonary lesions or impaired renal functions or other hepatic or colonic pathology	NR	NR	Other malignancies, had an initial diagnosis of advanced carcinoma of the cervix not suitable for treatment with curative intent, did not achieve complete remission	Negative (normal) findings at routine follow-up examinations, serum glucose level >200 mg/dl

ADC, adenocarcinoma; ASC, adenosquamous carcinoma; CH, chemotherapy; CHRT, chemoradiotherapy; NEC, neuroendocrine carcinoma; NR, not reported; RT, radiotherapy; SCC, squamous cell carcinoma; SR, surgery.

a No patients were in the asymptomatic category of the inclusion criteria.

TABLE 6 Population characteristics of studies evaluating MRI and MRI+CT

Characteristics	Hatano 1999[53]	Weber 1995[54]	Williams 1989[58]
Imaging	MRI	MRI	MRI and CT
Total *n* in study	42	37	20
n with recurrent cervical cancer and imaging results	35	37	20
Age (years), mean (range)	62.3	48 (19–83)	NR
FIGO initial stage	NR	IB ($n = 16$); IIA ($n = 2$); IIB ($n = 16$); IIIB ($n = 3$)	IB ($n = 7$); IIA ($n = 2$); IIB ($n = 5$); IIIA ($n = 3$); IIIB ($n = 3$)
Type of tumour pathology	NR	SCC ($n = 33$); ADC ($n = 4$)	SCC ($n = 18$); AC ($n = 1$); ADC ($n = 1$)
Previous treatment	NR	RT ($n = 37$)	Abdominal/Wertheim's hysterectomy ($n = 6$); subtotal hysterectomy ($n = 2$); anterior exenteration ($n = 2$); external-beam irradiation ($n = 10$)
Inclusion criteria	NR	Patients with histopathological diagnosis of cervical carcinoma, who underwent primary RT and then MRI after the initiation of RT	Patients with a diagnosis of suspected recurrent carcinoma of the cervix in whom pathological verification of the imaging results was available
Exclusion criteria	NR	NR	NR

AC, anaplastic carcinoma; ADC, adenocarcinoma; NR, not reported; RT, radiotherapy; SCC, squamous cell carcinoma.

TABLE 7 Population characteristics of studies evaluating CT

Characteristics	Heron 1988[55]	Park 2000[56]	Walsh 1981[57]
Total *n* in study	70	36	36
n with recurrent cervical cancer and imaging results	64	36	31
Age (years), mean (range)	45 (28–80)	53	(23–68)
FIGO initial stage	NR	NR	NR
Type of tumour pathology	NR	NR	NR
Previous treatment	NR	SR ($n = 13$); RT ($n = 14$); SR + RT ($n = 9$)	NR
Inclusion criteria	Patients with suspected recurrent carcinoma of the cervix	Patients with uterine cervical cancer	Patients with previously treated cervical carcinoma
Exclusion criteria	NR	NR	NR

NR, not reported; RT, radiotherapy; SR, surgery.

TABLE 8 Quality of all diagnostic studies

Study	Test	1	2	3	4	5	6	7	8	9	10	11	12	Comments
Amit 2006[48]	PET-CT	Y	N	Y	U	Y	Y	N	U	N	N	N	Y	Extrapelvic recurrence only
Chung 2007[20]	PET-CT	Y	Y	Y	U	Y	U	N	U	Y	N	NA	Y	
Grisaru 2004[49]	PET-CT (CT and/or MRI)	U	N	Y	U	Y	Y	N	Y	N	N	NA	Y	
Kitajima 2008[50]	PET-CT	Y	Y	Y	U	Y	Y	N	Y	Y	N	NA	Y	
Mittra 2009[51]	PET-CT	Y	Y	Y	U	Y	U	N	U	Y	N	NA	Y	
Sironi 2007[52]	PET-CT	Y	Y	Y	Y	Y	Y	N	Y	Y	N	NA	Y	
Hatano 1999[53]	MRI	Y	U	Y	U	Y	Y	N	U	Y	N	N	N	Tumour site only
Weber 1995[54]	MRI	U	U	Y	U	Y	Y	N	U	N	N	NA	N	Pelvic recurrence only
Heron 1988[55]	CT	Y	U	N	U	N	Y	N	U	Y	N	NA	N	Local recurrence only
Park 2000[56]	CT	U	U	N	U	Y	N	N	U	U	N	NA	N	
Walsh 1981[57]	CT	Y	Y	Y	Y	Y	Y	N	U	N	Y	Y	N	Pelvic recurrence only
Williams 1989[58]	MRI/CT	Y	U	Y	U	Y	Y	N	Y	N	N	NA	N	Local (central) recurrence only

N, no; NA, not applicable; U, unclear; Y, yes.

1 – representative spectrum; 2 – selection criteria clearly described; 3 – acceptable reference standard; 4 – acceptable delay between imaging tests; 5 – partial verification avoided; 6 – reference standard independent of the index test; 7 – tests described in sufficient detail for replication; 8 – reference standard/index test blinded; 9 – relevant clinical information; 10 – uninterpretable results reported; 11 – withdrawals explained; 12- technical quality.

In all of the included studies the reference standard for diagnosis of cervical cancer was histopathology with or without clinical/radiological follow-up. Four of the studies[48,53,57,58] used only histopathology as the reference standard, whereas in the other studies diagnosis was supported by clinical follow-up. Selection bias (using the imaging study being investigated as part of the inclusion criteria into the study) was present in at least four studies.[20,50–52]

Information to judge the presence of incorporation bias (in which the index test forms part of the reference standard) was unclear in almost all of the studies, but in Kitajima *et al.*[50] the index test (PET-CT) was clearly part of the reference standard when the final diagnosis of 12 patients was based on the results of tumour marker level and PET-CT findings. Two studies reported the mean time between index test and reference standard, which was 2.3 weeks[52] and 1 week.[57] Readers of PET-CT, MRI and CT studies were reported to be blind to patients' clinical details and final diagnosis in only four studies.[49,50,54,58]

With regard to technical quality, the methods used in the more modern studies were similar to currently used imaging methods, whereas the methods used in the older studies were not. In the PET-CT studies there was slight variation found in whether or not and how much oral hydration was used as well as slight differences in acquisition times and injected doses. Chung *et al.*[20] used oral contrast for CT, but this should not affect the PET interpretation or results. Heron *et al.*[55] incorporated lymphangiography, which is now no longer used.

Test accuracy

The numerical results for all included studies are shown in *Table 9*.

TABLE 9 Numerical results of imaging studies

Study name, date	Diagnostic test(s)	TP	FP	FN	TN	Equivocal
Amit 2006[48]	PET-CT	6	0	1	4	–
Chung 2007[20]	PET-CT	28	4	3	17	–
Grisaru 2004[49]	PET-CT	10	0	0	2	–
	CT and/or MRI	2	1	6	1	1[a]
Kitajima 2008[50]	PET-CT	23	2	2	25	–
Mittra 2009[51]	PET-CT	22	2	1	5	–
Sironi 2007[52]	PET-CT	5	0	1	6	–
Hatano 1999[53]	MRI	1	0	0	34	–
Weber 1995[54]	MRI	18	1	3	15	–
Heron 1988[55]	CT	24	2	2	36	6
Park 2000[56]	CT	14	3	4	15	–
Walsh 1981[57]	CT	27	2	2	0	2
Williams 1989[58]	CT	10	2	1	7	–
	MRI	9	2	2	7	–

FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.
a Plus one patient who could not be imaged as allergic to contrast medium.

Positron emission tomography/computerised tomography

Six PET-CT test accuracy studies were found.[20,48–52] Five studies[20,49–52] evaluated local recurrence and distance metastasis and one study[48] evaluated extrapelvic recurrence only. The sensitivities and specificities and their 95% CIs are shown in *Figure 5* and a SROC space plot is shown in *Figure 6*. The sensitivities and specificities of local and distant recurrence were 83–100% and 71–100%, respectively, and the sensitivity and specificity of distant recurrence only were 86% and 100%. The summary estimates of the sensitivity and specificity of PET-CT for the detection of cervical cancer recurrence were 92.2% (95% CI 85.1% to 96.0%) and 88.1% (95% CI 77.9% to 93.9%), respectively. Sensitivity analysis, omitting one study[48] that reported accuracy for distant recurrence only, did not affect accuracy estimates to any significant degree [sensitivity 92.6% (95% CI 85.3% to 96.4%); specificity 87.3% (95% CI 76.6% to 93.5%)]. The results tables of the univariate random-effects regression model for the meta-analysis and sensitivity analysis are in *Appendix 11*.

Magnetic resonance imaging

Three MRI test accuracy studies were found and all evaluated the pelvis only.[53,54,58] Weber *et al.*[54] and Williams *et al.*[58] included women with clinical suspicion of recurrence and Hatano *et al.*[53] included women with residual, advanced-stage cervical cancer (stage IB2–IV). Previous treatment was radiotherapy in Hatano *et al.*[53] and Weber *et al.*[54] and 50% surgery and 50% radiotherapy in Williams *et al.*[58] All three studies investigated local recurrence in the pelvis only. Distant recurrence was noted in Williams *et al.*[58] (4/20), but these women were not included in the numerical results for sensitivity and specificity. Distant metastases are also mentioned in Hatano *et al.*[53] Because of clinical heterogeneity between these studies, no meta-analysis was conducted. The sensitivities and specificities and their 95% CIs are shown in *Figure 7* and a SROC space plot in *Figure 8*. The sensitivities and specificities of MRI in pelvic recurrence varied between 82% and 100% and 78% and 100% respectively.

FIGURE 5 Sensitivity and specificity of the PET-CT studies. FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

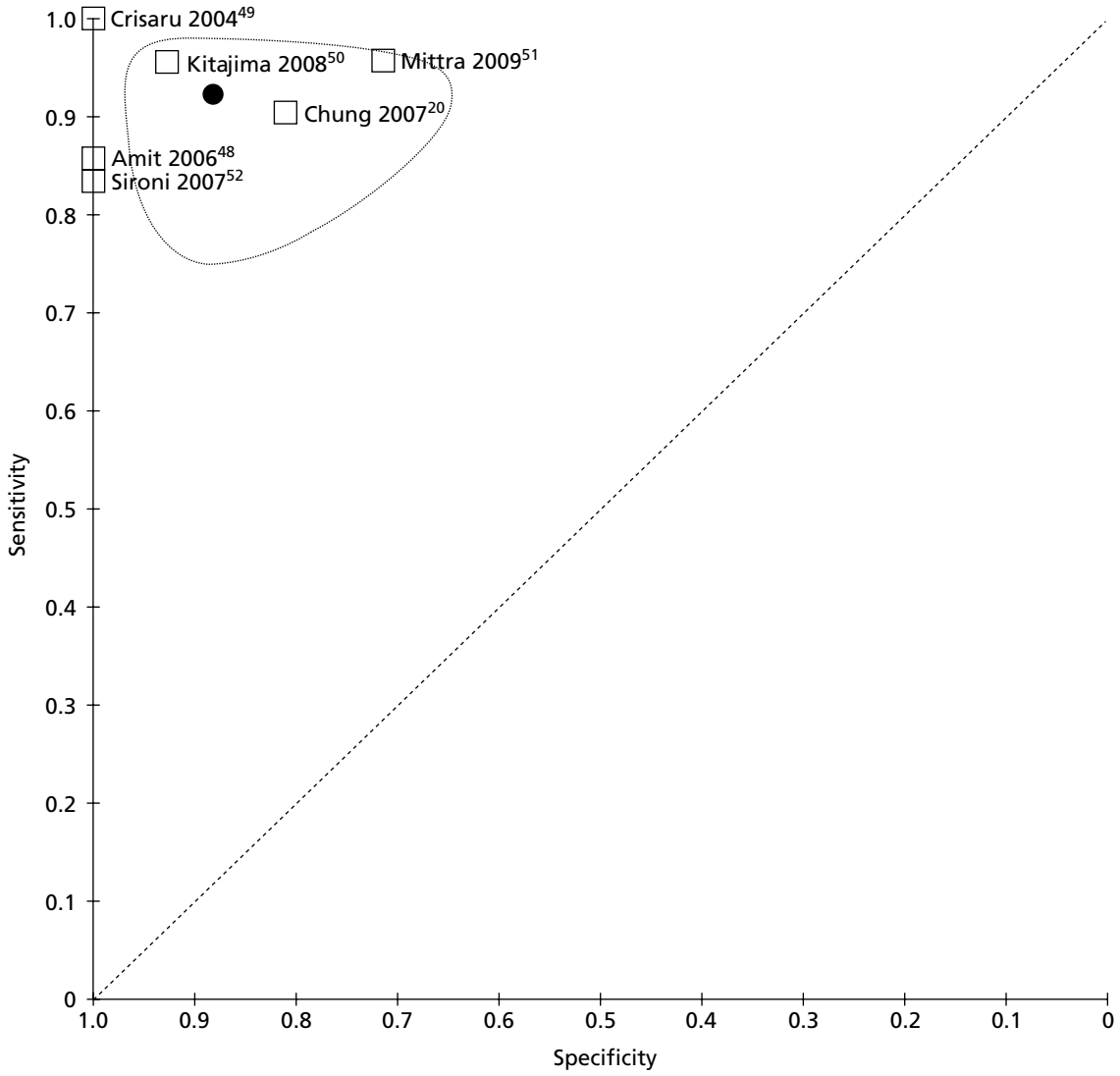

FIGURE 6 Summary receiver operating characteristic space plot for the PET-CT studies.

Computerised tomography

Four CT test accuracy studies were found.[55–58] Heron *et al.*,[55] Walsh *et al.*[57] and Williams *et al.*[58] investigated local recurrence only, whereas Park *et al.*[56] investigated local and distant recurrence. [As mentioned in the MRI section, Williams *et al.*[58] also mentioned 4 (of 20) women with distant recurrence, who were not included in the sensitivity and specificity statistics.] There is little information available on the patients included in Heron *et al.*[55] and Walsh *et al.*[57] Also, both Heron *et al.*[55] and Walsh *et al.*[57] have equivocal results. For six patients in the Heron *et al.*[55] study, the CT findings were classified as equivocal; all of these patients had undergone radiotherapy, making differentiation between radiation fibrosis and recurrence difficult. For two patients in Walsh *et al.*,[57] CT images could not differentiate radiation sequelae from tumour. The sensitivities and specificities and their 95% CIs are shown in *Figure 9* and a SROC space plot is shown in *Figure 10*. Because of clinical heterogeneity and lack of information about patients, no meta-analysis was conducted. The sensitivities and specificities of CT in pelvic recurrence (excluding the equivocal results) varied between 78% and 93% and 0% and 95% respectively. Sensitivity analysis around the equivocal results for Heron *et al.*[55] varied the sensitivity from 75% to 94% and the specificity from 82% to 95%. Sensitivity analysis around the equivocal results for Walsh *et al.*[57] varied the sensitivity from 87% to 94% and the specificity from 0% to 50%.

FIGURE 7 Sensitivity and specificity of the MRI studies. FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

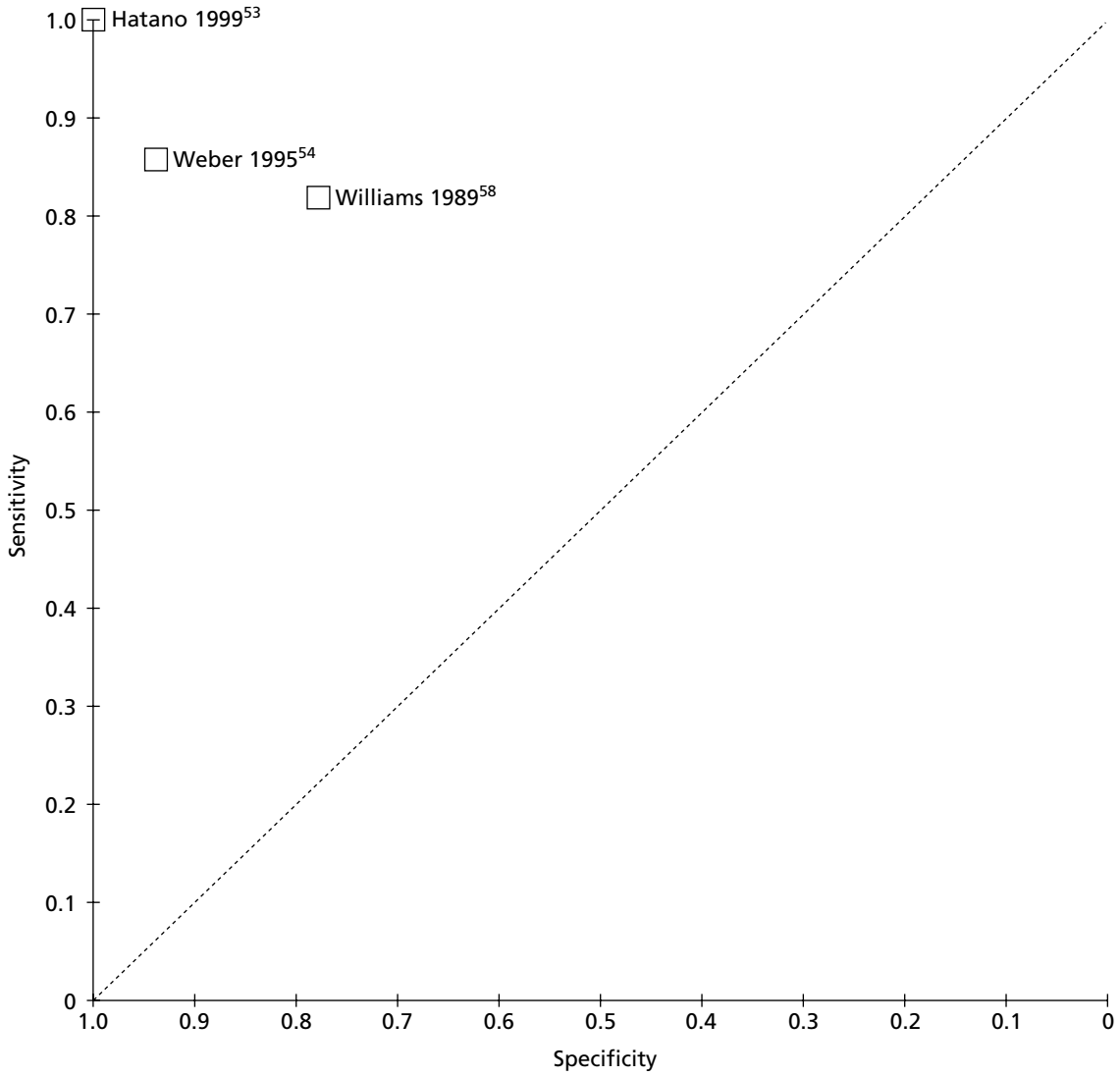

FIGURE 8 Summary receiver operating characteristic space plot for the MRI studies.

Comparison of standard imaging followed by positron emission tomography/computerised tomography with standard imaging only

One study[49] gave results in one table for both standard imaging alone and standard imaging with whole-body PET-CT with the same reference standard of histology or clinical evidence of disease, allowing comparisons to be made. Unfortunately, the part of the body imaged with standard imaging was not provided in the paper. The results are provided in *Table 10*. This shows that the PET-CT results are closer to the reference standard results than the standard imaging results.

Diagnostic and therapeutic impact

One included PET-CT study[20] reported information on the diagnostic and therapeutic impact of the imaging. None of the included MRI or CT studies provided any details on whether or how the management of patients was altered by imaging.

In Chung *et al.*,[20] the mean age of patients was 53 years (range 32–77 years) and they had primarily stage I (50%) and stage II (40%) cancer. The results of PET-CT imaging were found to have an impact on the management of 12 patients (23%) by initiating previously unplanned treatment (four patients), changing the previously planned therapeutic approach (five patients) or eliminating a previously planned

FIGURE 9 Sensitivity and specificity of the CT studies. FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

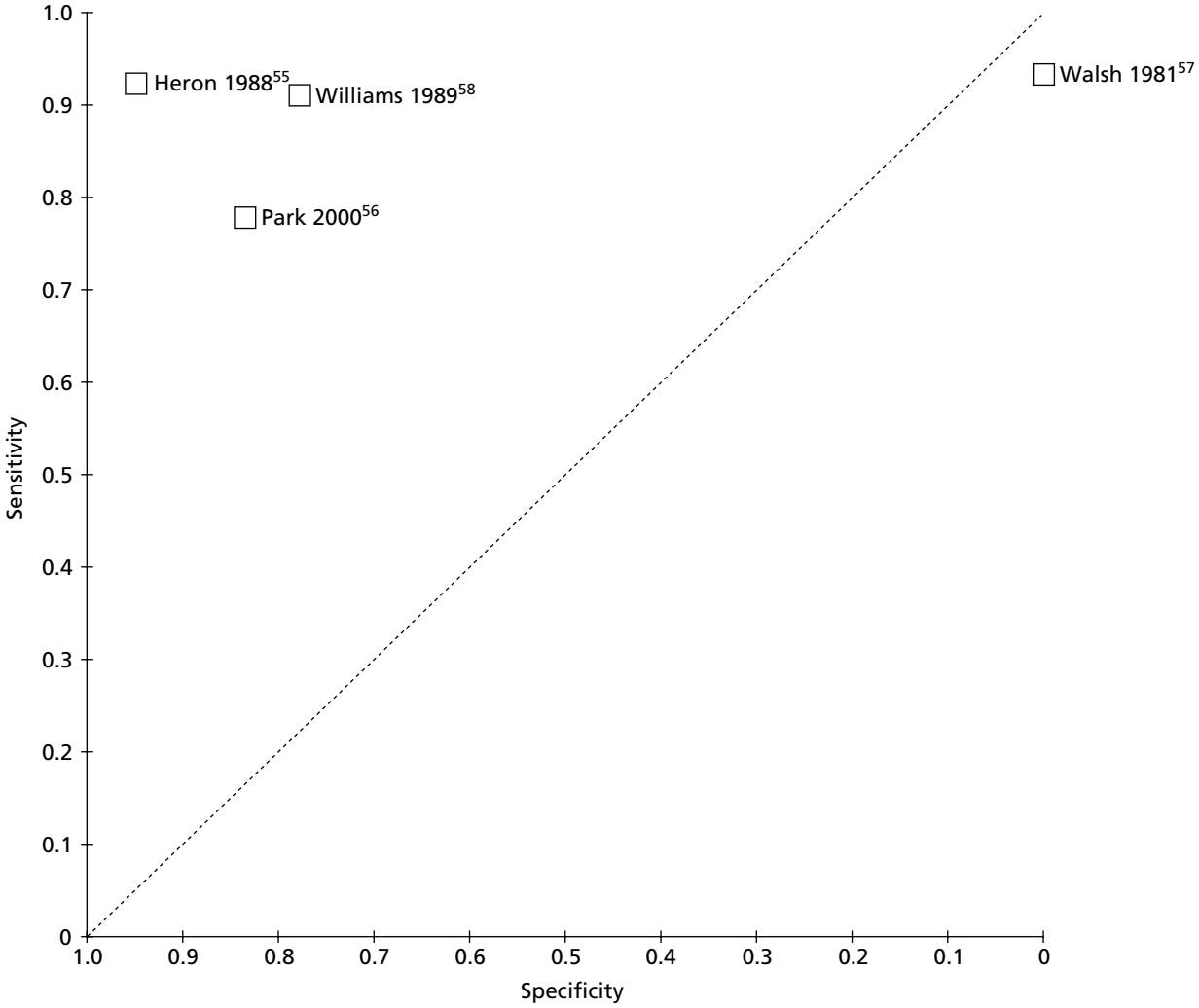

FIGURE 10 Summary receiver operating characteristic space plot for the CT studies.

diagnostic procedure (three patients). The PET-CT led to additional invasive diagnostic procedures in nine patients: mediastinoscopic biopsy in three patients, PET-CT-guided pelvic lymph node biopsy in three patients, supraclavicular lymph node biopsy in two patients and bone biopsy in one patient. The PET-CT assisted in the planning of the therapeutic strategy in nine patients.

Chung *et al.*[20] also reported the prognostic outcomes of patients undergoing PET-CT giving 2-year disease-free survival rates and survival curves for women with positive and negative PET-CT results. The 2-year disease-free survival rates for women with a positive and a negative PET-CT result for recurrence were 10.9% and 85.0% respectively ($p = 0002$). The survival curves are reproduced in *Figure 11*.

TABLE 10 Comparison of standard imaging with PET-CT

Patient	Standard imaging	Standard imaging followed by PET-CT	Histology/clinical follow-up
1	–	+	+
2	–	+	+
3	+	–	–
4	–	+	+
5	+/–	+	+
6	–	–	–
7	–	+	+
8	+	+	+
9	Not possible	+	+
10	–	+	+
11	–	+	+
12	+	+	+

+, presence of tumour; –, absence of tumour.

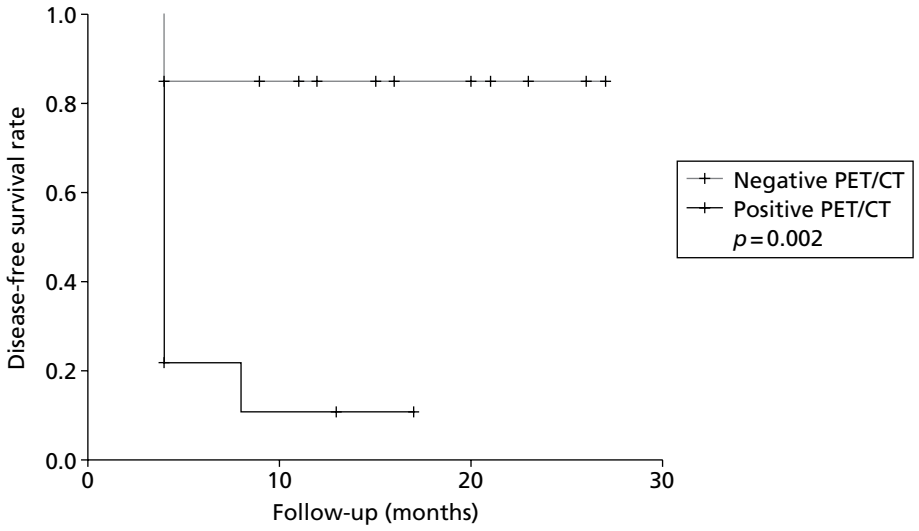

FIGURE 11 Two-year disease-free survival of patients with positive and negative PET-CT scans (from Chung *et al.*[20]).

Chapter 5 Results of the elicitation of subjective probabilities

The first face-to-face elicitation exercise resulted in responses from nine experts and subsequent sampling resulted in a further 12 completed elicited probabilities questionnaires. Prevalence of recurrence information was elicited from all respondents (21) and accuracy from 17–18 respondents. The self-reported characteristics of respondents and their reported use of imaging technologies are outlined in *Table 11* and *Figure 12*.

Prevalence of recurrence

Individual respondents' prevalence of recurrence results are in *Table 82* (symptomatic) and *Table 83* (asymptomatic) in *Appendix 12*. The mean elicited prevalence of recurrence in women presenting with symptoms a minimum of 3 months after completion of primary treatment was 47.8% (SD 20.8) and that for asymptomatic women was 16.7% (SD 13.1).

Accuracy

Individual respondents' accuracy results (PPVs, NPVs) for MRI and/or CT and for MRI and/or CT with PET-CT for symptomatic and for asymptomatic women are given in *Tables 85–92* in *Appendix 12*. Note that PPVs are the proportion of women who test positive on either CT or MRI at the discretion of a clinician (and PET-CT if used and performed regardless of the result of initial imaging) who are confirmed as having recurrence of cervical cancer on the basis of histology, and NPVs are the proportion of women who test negative on either CT or MRI at the discretion of a clinician (and PET-CT if used and performed regardless of the result of initial imaging) who are confirmed as not having recurrence on the basis of clinical follow-up. Summary results are shown in *Table 12*. These are shown graphically in *Figures 13* and *14* for symptomatic and asymptomatic women respectively.

Minimum important clinical difference in accuracy between imaging with computerised tomography and/or magnetic resonance imaging and imaging with computerised tomography and/or magnetic resonance imaging plus positron emission tomography/computerised tomography

The average minimum important increase in accuracy from the addition of PET-CT to CT and/or MRI that was considered necessary to warrant introduction of PET-CT as a routine investigation in this sample of clinical experts was similar for asymptomatic and symptomatic patients: a 7.7% reduction in false-positives and a 6.4% reduction in false-negatives for symptomatic women and an 8.7% reduction in false-positives and a 6.3% reduction in false-negatives for asymptomatic women. Mean elicited estimates of the differences in test accuracy between CT and/or MRI and CT and/or MRI plus PET-CT were 2.6 and 3.6 for PPV and NPV, respectively, for symptomatic women and 4.6 and 3.4 for PPV and NPV, respectively, for asymptomatic women.

The results suggest that, in our sample of experts, the elicited increase in accuracy as a result of the addition of PET-CT to MRI and/or CT is smaller than the elicited minimum important difference in accuracy required to justify the routine addition of PET-CT for the investigation of women post completion of primary treatment for cervical cancer, that is, all of the differences in false-positives and false-negatives in *Table 12* are smaller than the minimum important clinical differences listed in the paragraph above.

Comparison with systematic review results

Comparison of elicited estimates of accuracy with those reported in the literature are complicated because of the age of the CT and MRI studies, the lack of disaggregation between symptomatic and asymptomatic

TABLE 11 Characteristics of respondents to the elicitation exercise

Speciality and years of experience[a,b]	Use of imaging technologies (% of symptomatic consultations for recurrence)			
	MRI	CT	MRI and CT	Experience with PET-CT
Gynaecological oncology (8 years)	20	20	60	No
Gynaecological oncology (15 years)[c]	70	90	60	No
Radiology (10 years)	NA	NA	NA	NA
Radiology (20 years	NA	NA	NA	NA
Obstetrics and gynaecology (SPR) (5 years)	30	60	10	1 year – 'To decide on treatment planning: Need surgery?'
Gynaecological oncology (5 years)	10	80	10	4 years – 'To decide on treatment planning: Prior to exenteration'
Gynaecological oncology (21 years)	NS	NS	NS	No
Not reported (7 years)	'depends on symptoms . . . MRI 100% if pelvic symptoms'			3 years – 'To exclude distant recurrence in patients with proven local recurrence'
Gynaecological oncology (10 years as a consultant)[c]	50	30	30	5 years – 'Patients undergoing primary chemoradiation to determine extent of any lymphadenopathy. Patients with local recurrence after surgery prior to chemoradiation to determine extent of lymphadenopathy. Prior to consideration of exenteration'
Gynaecological oncology (15 years)	70	30	0	3 years – 'Isolated central pelvic recurrence to confirm no metastatic disease prior to exenteration'
Gynaecological oncology (3 years as a consultant)	10	90	0	3 years – 'To clarify nature of lesions seen on CT or MRI and to rule out other sites of disease if further surgery contemplated'
Gynaecological oncology (15 years)	25	50	25	2 years – 'Suspected recurrence. Consideration for exenterative surgery'
Gynaecological oncology (10 years)	10	80	10	3 years – 'If recurrence suspected on the basis of clinical examination/CT/MRI'

patients and a paucity of estimates of the combined accuracy of CT and MRI. *Table 13* illustrates that elicited estimates of the accuracy of CT/MRI and CT/MRI plus PET-CT in symptomatic women are similar to estimates in the literature. For asymptomatic women the elicited specificities of CT/MRI and CT/MRI plus PET-CT are comparable to literature-based estimates but elicited estimates of sensitivity are lower. This is most likely to be a function of the spectrum of patients in included studies; inclusion of symptomatic patients in studies in the literature would be expected to result in higher sensitivity.

TABLE 11 Characteristics of respondents to the elicitation exercise (*continued*)

Speciality and years of experience[a,b]	Use of imaging technologies (% of symptomatic consultations for recurrence)			
	MRI	CT	MRI and CT	Experience with PET-CT
Gynaecological oncology (28 years)	100	0	0	'Assessment of multiple site recurrence'
Gynaecological oncology (5 years)	20	30	50	2 years – 'Pre-exenteration or if biopsy difficult/inconclusive'
Gynaecological oncology (3 years as a consultant)	60	10	30	3 years – 'After initial imaging to determine suitability for radical salvage treatment to help exclude occult distant mets'
Oncology (NS)	20	60	20	3 years – '? local recurrence where MRI cannot differentiate between recurrence and effects of radiotherapy. Proven local recurrence for staging prior to exenteration'
Gynaecological oncology (34 years)	0	90	10	8 years – 'Those with advanced disease or recurrent disease. Those requiring surgery following radiotherapy or chemoradiation'
Gynaecological oncology (3 years)	20	20	60	1 year – 'If CT/MRI positive for central recurrence and considering exenteration as a management option'
Gynaecological oncology (30 years)	30	50	20	3 years – 'If further treatment is being considered – especially exenteration'
Gynaecological oncology (30 years)	30	40	30	3 years – 'Exenteration candidates. Equivocal CT/MRI'

NA, not applicable; NS, not stated; SPR, specialist registrar.

a Years of experience were variably reported as years practising in a discipline or years practising as a consultant. When respondents clarified this it is indicated in the table.

b All respondents were consultants in their discipline with the exception of one SPR.

c When numbers from a clinician did not sum to 100, they were adjusted to 100%.

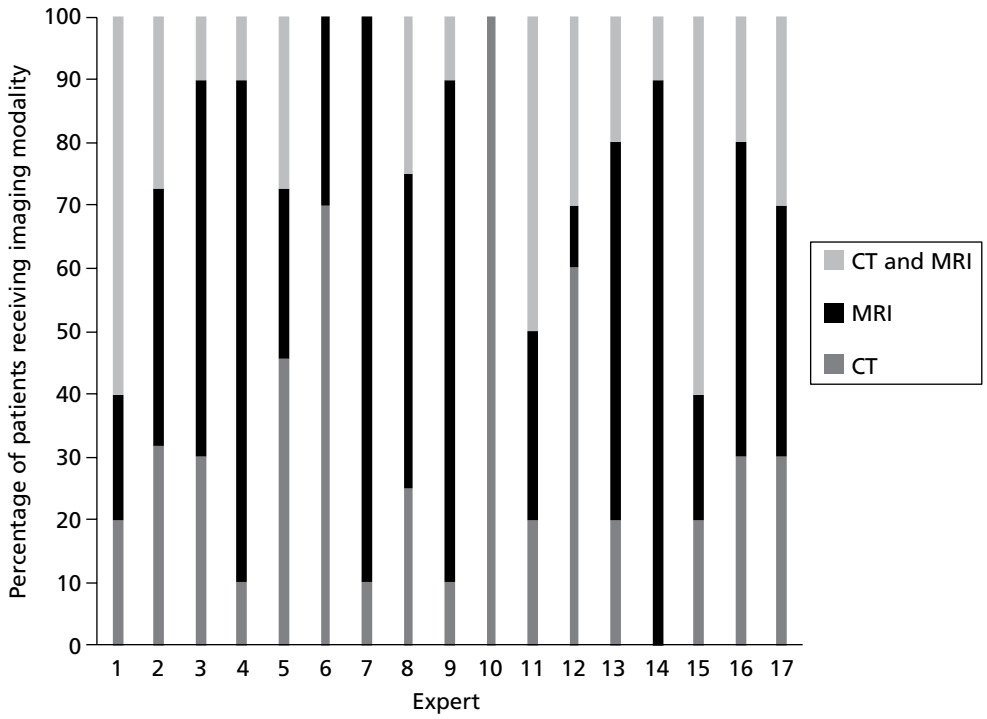

FIGURE 12 Use of imaging (MRI and/or CT) in patients presenting with suspected cervical cancer recurrence.

TABLE 12 Subjective elicitation summary accuracy results

		MRI and/or CT	MRI and/or CT and PET-CT	Difference in false-positives and false-negatives
Symptomatic	PPV (%)	88.4 (SD 9.2)	91.0 (SD 8.2)	2.6
	NPV (%)	86.8 (SD 8.7)	90.7 (SD 7.2)	3.6
Asymptomatic	PPV (%)	85.6 (SD 9.8)	90.2 (SD 7.7)	4.6
	NPV (%)	90.0 (SD 7.7)	93.4 (SD 5.5)	3.4

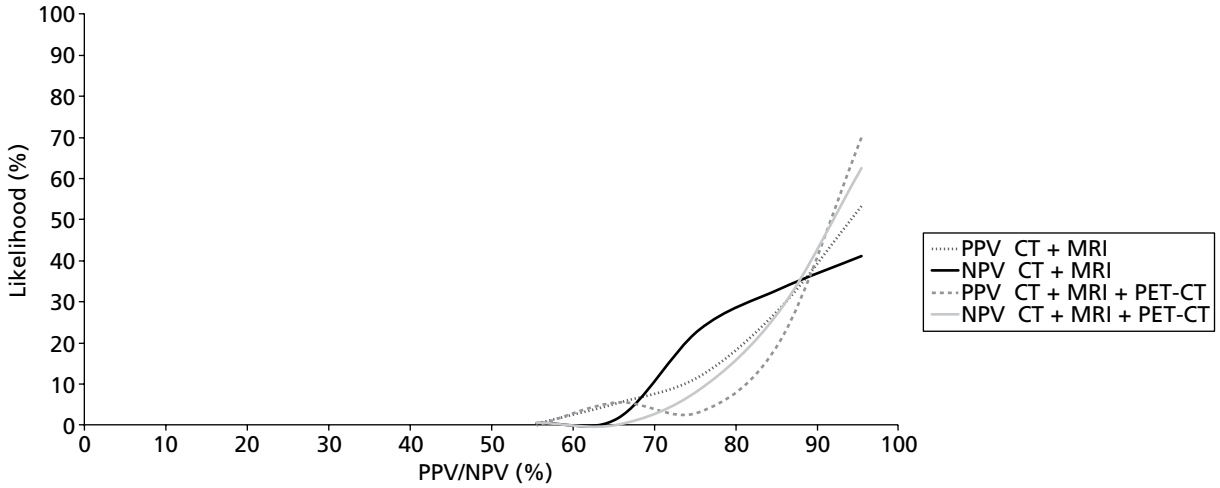

FIGURE 13 Elicited estimates of the accuracy of CT and/or MRI and CT and/or MRI with PET-CT in symptomatic women a minimum of 3 months after completion of primary treatment for cervical cancer.

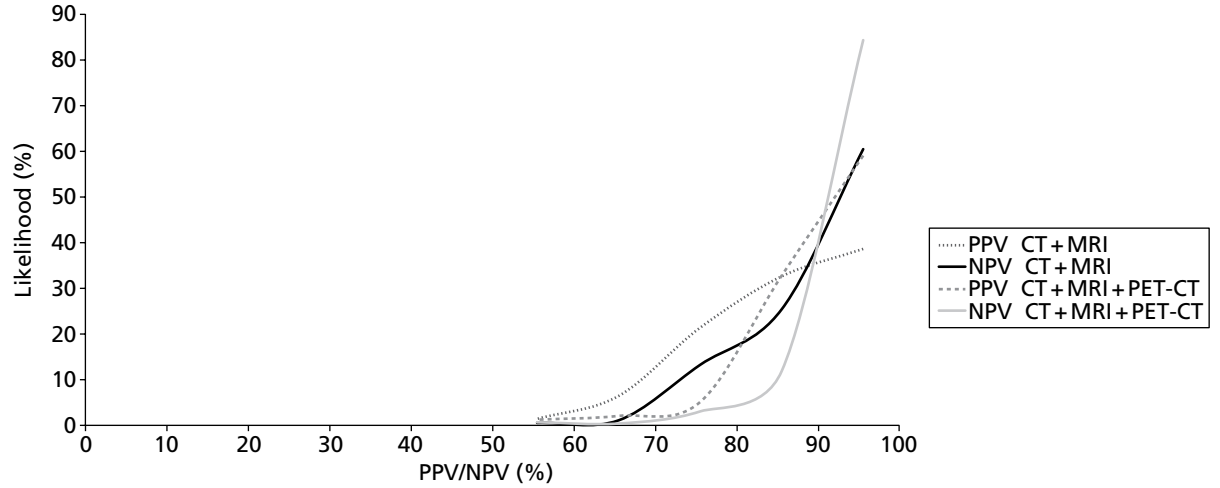

FIGURE 14 Elicited estimates of the accuracy of CT and/or MRI and CT and/or MRI with PET-CT in asymptomatic women a minimum of 3 months after completion of primary treatment for cervical cancer.

TABLE 13 Comparison of systematic review and elicitation accuracy results

	Asymptomatic women				Symptomatic women			
	Literature		Elicited[a]		Literature		Elicited[a]	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Clinical follow-up and MRI ± CT	–	–	45.43	98.47	–	–	85.09	89.78
CT	–	–	–	–	78–93[b]	78–95[b]	–	–
MRI	–	–	–	–	82–100[b]	78–100[b]	–	–
Clinical follow-up, MRI ± CT and PET-CT	–	–	65.25	98.58	83–100[b]	71–100[b]	89.71	91.88

a Elicited estimates of sensitivity and specificity based on prevalence of recurrence in asymptomatic and symptomatic women of 16.7% and 47.8% respectively.

b Estimates of sensitivity and specificity for CT, MRI and PET-CT based mainly on symptomatic women but frequently not distinguished according to presentation (asymptomatic or symptomatic women) in the literature.

Chapter 6 Effectiveness review

The database searches for primary studies identified 24,972 citations, 24,943 citations from the database searches and 29 citations from other sources such as reference lists. Of these, 4618 were duplicates, leaving 20,354 unique citations. Sifting of titles and abstracts excluded 19,994 citations, leaving 360 full-text articles to be assessed for eligibility. Of these, 42 papers were unavailable and 250 papers were excluded as irrelevant: 118 on the wrong population (many with primary and recurrent cervical cancer presented together), 24 on the wrong intervention, 33 with irrelevant outcomes and 75 with inadequate study designs. For a list of excluded papers, see *Appendix 13*. One existing systematic review[59] and a relevant guideline[3] were found. The systematic review included 15 RCTs on chemotherapy in recurrent, metastatic or persistent cervical cancer. The searches for this systematic review were to 2006. Additional searches found four RCTs on chemotherapy. For surgery and radiotherapy, no systematic reviews or RCTs were found and all included studies were case series. In total, 68 papers were included: 19 RCTs of chemotherapy (25 papers), 27 case series in surgery and 16 case series in radiotherapy and chemoradiotherapy (*Table 14* and *Figure 15*).

Chemotherapy agents

Nineteen RCTs (25 publications) compared one or more chemotherapeutic agents in women with recurrent or persistent or advanced (stage IVB) cervical cancer. There were eight RCTs with single-agent cisplatin regimens, four with cisplatin-based chemotherapy regimens, three with carboplatin (CBDCA)-based chemotherapy regimens and four with non-platinum-containing agents (*Table 15*). There were no RCTs investigating the effectiveness of cisplatin compared with placebo or no treatment in which both arms were given another chemotherapeutic agent. Baseline characteristics are shown in *Appendix 14*. The results for each category are given in the following sections.

Effectiveness of single cisplatin agents

Characteristics of included studies

Eight RCTs gave information about the effectiveness of single cisplatin agents as palliative treatment for recurrent, persistent or advanced cervical cancer (see *Table 15*). Baseline characteristics, including previous treatment, stage and site of disease, presented in *Table 16*, were well balanced between groups.

TABLE 14 Summary of identified studies: effectiveness review

Characterisitics	Chemotherapy	Chemoradiotherapy	Surgery
Population	Population with multiple site and distant recurrence	Population with recurrence after previous surgical treatment only	Population with recurrence after previous chemoradiotherapy or radiotherapy only
Intervention	Chemotherapy agents	Radiotherapy, chemoradiotherapy	Surgery: pelvic exenteration, radical hysterectomy
Number of studies	Single-agent cisplatin: 8; cisplatin-based chemotherapy: 4; other platinum agents: 3; non-platinum-containing agents: 4	Radiotherapy: 9; chemoradiotherapy: 7	Pelvic exenteration: 20; radical hysterectomy: 7
Type of evidence	RCTs	Non-comparative case series	Non-comparative case series

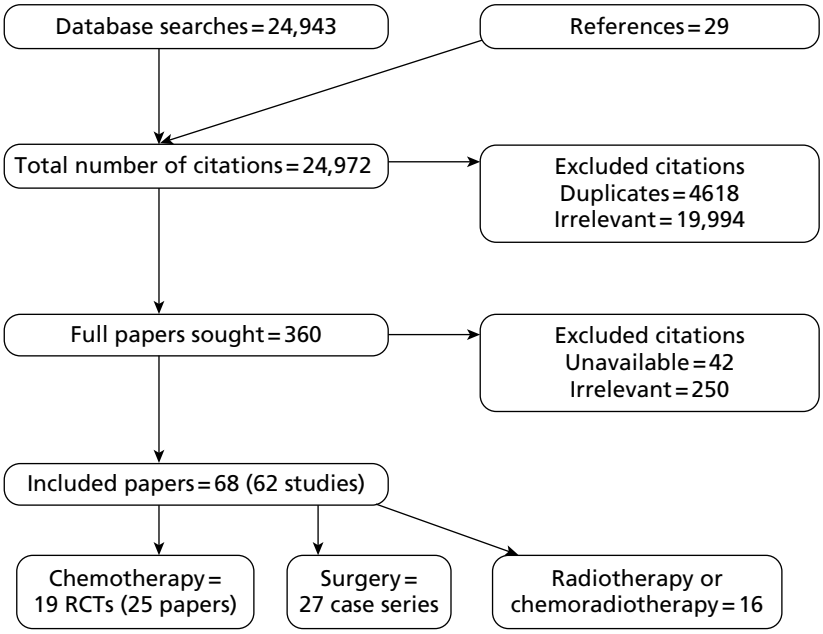

FIGURE 15 PRISMA diagram for effectiveness studies.

TABLE 15 Chemotherapy RCT treatment comparisons and outcomes measured

Study	Population	Intervention(s)	Comparator(s)	Outcomes measured
Alberts 1987[60]	Advanced and recurrent squamous cell	Mitomycin C, vincristine, bleomycin and cisplatin Mitomycin C and cisplatin	Cisplatin	Response rates, AEs
Barlow 1973[61]	Recurrent or prior	Bleomycin Adriamycin and bleomycin	Adriamycin	Response rates, OS, duration of response
Bezwoda 1986[62]	Recurrent or metastatic	*Cis*-diamminedichloroplatinum plus methotrexate	Hydroxyurea	OS, response rate, AEs
Bloss 2002[63]	Advanced (stage IVB), recurrent or persistent squamous cell	Cisplatin, ifosfamide and bleomycin	Cisplatin and ifosfamide	OS, PFS, response rates, AEs
Bonomi 1985[64]	Advanced squamous cell	Cisplatin 100 mg	Cisplatin 20 mg Cisplatin 50 mg	OS, PFS, duration of response, response rates, AEs
Cadron 2005[65]	Recurrent or with distant metastases	Cisplatin, ifosfamide and 5-fluorouracil	Cisplatin	OS, response rates
[a]Garin 2001[66]	Advanced (stage IVB)	Irinotecan and cisplatin Irinotecan and cisplatin as first-line palliative treatment	Irinotecan	Response rates, AEs
[b]Greenberg 1977[67]	Recurrent and advanced (stage IVB)	Bleomycin Adriamycin and bleomycin	Adriamycin	OS, response rates
Lira-Puerto 1991[68]	Recurrent	CBDCA	Iproplatin	OS, PFS, response rates, AEs

TABLE 15 Chemotherapy RCT treatment comparisons and outcomes measured (*continued*)

Study	Population	Intervention(s)	Comparator(s)	Outcomes measured
Long 2005[69–73]	Advanced, recurrent or persistent	Methotrexate, vinblastine, doxorubicin and cisplatin Cisplatin and topotecan	Cisplatin	OS, PFS, response rates, QoL, AEs
McGuire 1989[74]	Recurrent	CBDCA	Iproplatin	OS, PFS, response rates, AEs
Monk 2010[75]	Recurrent, advanced (stage IVB) and persistent	Pazopanib and lapatinib	Lapatinib Pazopanib	OS, PFS, response rates, AEs
Monk 2009[76]	Advanced (stage IVB), recurrent or persistent	Vinorelbine and cisplatin Gemcitabine and cisplatin Topotecan and cisplatin	Paclitaxel and cisplatin	OS, PFS, response rates, QoL, AEs
Moore 2004[77,78]	Recurrent or persistent, advanced (stage IVB) squamous cell	Cisplatin and paclitaxel	Cisplatin	OS, PFS, response rates, QoL, AEs
Mountzios 2009[79]	Primary metastatic or recurrent	Cisplatin, ifosfamide and paclitaxel	Cisplatin and ifosfamide	OS, PFS, response rates, AEs
Omura 1997[80]	Recurrent or persistent, advanced (stage IVB) squamous cell	Cisplatin and mitolacol Cisplatin and ifosfamide	Cisplatin	OS, PFS, duration of response, response rates, AEs
Thomsen 1998[81]	Advanced or recurrent	CBDCA	Teniposide	OS, PFS, response rates, AEs
Vermorken 2001[82]	Recurrent, advanced (stage IVB) squamous cell	Bleomycin, vindesine, mitomycin, cisplatin	Cisplatin	OS, PFS, duration of response, response rates, AEs
[b]Wallace 1978[83]	Recurrent and advanced (stage IVB)	Adriamycin and vincristine Adriamycin and cyclophosphamide	Adriamycin	OS, PFS, response rates, AEs

AE, adverse event; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

a Abstract only.

b Data from Hirte *et al.*'s systematic review.[59]

Quality of studies

All studies were RCTs with no blinding, but the description of randomisation was provided in only three trials.[71,78,80] In Long *et al.*,[71] patients were randomly assigned to the treatment regimens with equal probability using a fixed-block design; patients were stratified by treating institution only. In Moore *et al.*,[78] randomisation (with equal probability to each of the treatment arms) was carried out using a block design that balanced the sequence of assigned arms within parent institutions. In Omura *et al.*,[80] patients were prospectively stratified according to whether or not they had received previous radiation-sensitizer treatment (hydroxyurea, cisplatin or fluorouracil) and by Karnofsky performance score, and were then centrally randomised with equal probability to three groups.

Description of allocation concealment was not reported in any of the included studies. Several studies had methodological ambiguities. In Alberts *et al.*,[60] one of the treatment arms, cisplatin, was dropped early because of poor accrual; the number of patients in the cisplatin group was much lower than in the other two groups (9 vs 54 and 51). In Cadron *et al.*,[65] the intention had been to include 200 patients in the trial but because of poor accrual the trial was stopped prematurely and only 24 patients were included. In Long *et al.*,[71] the methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) arm was closed by the

TABLE 16 Characteristics of the populations in the included RCTs: single-agent cisplatin

	Alberts 1987[60]			Bonomi 1985[64]			Cadron 2005[65]	
Parameter	MVBC	MC	C	50 mg C	100 mg C	20 mg C	C	PIF
Number of patients (randomised)	54	51	9	167	185	145	13	11
Age (years), median (range)	47.5 (20–77)	51 (23–78)	51 (29–63)	49 (21–78)	53 (22–85)	49 (22–79)	53 (40–80)	56 (45–66)
Previous treatment								
Chemotherapy	NR	NR	NR	NR	NR	NR	NR	NR
Radiotherapy	NR	NR	NR	156	170	134	5	5
Surgery	NR	NR	NR	NR	NR	NR	NR	NR
Chemotherapy and radiotherapy	NR	NR	NR	NR	NR	NR	NR	NR
Surgery and radiotherapy	NR	NR	NR	NR	NR	NR	5	5
Stage								
IVB	100%	100%	100%	NR	NR	NR	NR	NR
Persistent	NR	NR	NR	NR	NR	NR	NR	NR
Recurrent	100%	100%	100%	NR	NR	NR	100%	100%
Site of disease								
Pelvic	NR	NR	NR	96	103	78	64%[a]	60%[a]
Distant	Pulmonary 31%; lymph nodes 31%	Pulmonary 14%; lymph nodes 25%	Pulmonary 44%; lymph nodes 22%	71	82	67	36%[a]	40%[a]
Both	35%	37%	22%	NR	NR	NR	NR	NR

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; IC, irinotecan, cisplatin; ICFL, irinotecan, cisplatin in first line; IR, irinotecan; MC, mitomycin C, cisplatin; MVBC, mitomycin C, vincristine, bleomycin, cisplatin; NR, not reported; P, pazopanib; PIF, cisplatin, ifosfamide, 5-fluorouracil.

a If the tumour recurred both inside and outside an earlier irradiated area, the site of recurrence was recorded as inside.

b In both groups there was one patient with no site of disease recorded.

Garin 2001[66]			Long 2005[71]			Moore 2004[78]		Omura 1997[80]			Vermorken 2001[82]	
I	IC	C	C	CT	MVAC	C	CP	C	CM	CIFX	BEMP	P
39	27	31	146	147	63	134	130	140	147	151	143	144
48	48	48	48 (27–76)	46 (22–84)	–	46 (22–84)	48.5 (21–77)	47.3 (24–85)	48.8 (22–84)	46.3 (23–83)	53 (25–72)	52 (28–76)
0	0	0	82	85	–	40	31	36	45	38	3	0
NR	NR	NR	NR	NR	–	123	118	123	127	128	101	110
NR	NR	NR	NR	NR	–	NR	NR	NR	NR	NR	60	68
NR	NR	NR	NR	NR	–	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	–	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	17	18	–	68	78	140	147	151	17	13
NR	NR	NR	11	17	–	66	52	NR	NR	NR	NR	NR
NR	NR	NR	118	112	–			NR	NR	NR	NR	NR
NR	NR	NR	60[b]	68[b]	–	66	52	68	60	74	NR	NR
NR	NR	NR	63[b]	58[b]	–	49	61	63	70	62	69	68
NR	NR	NR	22[b]	20[b]	–	19	17	9	17	15	69	71

Data Safety Monitoring Board after four treatment-related deaths occurred among 63 patients, and results for the MVAC arm were not reported. In Vermorken *et al.*,[82] 45 patients from the cisplatin group received bleomycin, vindesine, mitomycin and cisplatin (BEMP) as second-line treatment. The quality assessment results are shown in *Figures 16* and *17*.

Effectiveness results

Overall survival, progression-free survival and overall response duration

In Alberts *et al.*,[60] median survival durations associated with receiving cisplatin, mitomycin C and cisplatin and mitomycin C, vincristine, bleomycin and cisplatin (MVBC) treatment were 17.0, 7.0 and 6.9 months respectively. However, because of the small number of patients in the cisplatin arm, meaningful comparison with other treatments cannot be made. Bonomi *et al.*[64] found no appreciable differences in median survival duration and time to tumour progression for any of the cisplatin regimens. In Cadron *et al.*,[65] median survival in the cisplatin group amounted to 13 months and in the group treated with cisplatin, ifosfamide and 5-fluorouracil regimen to 12.3 months; data for progression-free survival were not provided. In Long *et al.*,[71] median survival was 6.5 months in the cisplatin-treated group and 9.4 months in the group receiving the cisplatin/topotecan combination. The unadjusted and adjusted RR estimates for survival were 0.76 (95% CI 0.59 to 0.98) and 0.77 (95% CI 0.60 to 0.99), respectively, favouring the combination. Statistically significant differences were also observed in progression-free survival, favouring the combination [unadjusted RR 0.76 (95% CI 0.60 to 0.97); adjusted for covariates 0.74 (95% CI 0.58 to 0.94)]. In Moore *et al.*,[78] the median progression-free survival for patients receiving cisplatin alone and cisplatin and paclitaxel was 2.8 and 4.8 months respectively ($p = 0.001$). There was no difference in median survival between patients receiving cisplatin alone and patients receiving cisplatin and paclitaxel (8.8 months and 9.7 months respectively). In Omura *et al.*,[80] progression-free survival was statistically significantly longer for cisplatin and ifosfamide than for cisplatin alone (median, 4.6 vs 3.2 months, $p = 0.003$); however, there was no difference between cisplatin and mitolactol and cisplatin alone. There was no significant difference in survival between cisplatin and either of the combination regimens. In Vermorken *et al.*[82] there was neither a significant difference in progression-free survival nor a significant difference in overall survival between BEMP and cisplatin although, according to the authors, for the former, a trend in favour of BEMP existed.

The results for median overall survival, progression-free survival and duration of response are given in *Tables 17–19* respectively.

Response rates

Response rates, complete response rates and partial response rates for the RCTs are shown in *Table 20*. This shows that combinations are mostly more effective than single-agent cisplatin, but there is not always consistency in effect direction between the three response rates. For several RCTs[65,66,80,82] the complete response rates were not statistically significant, whereas the response rates and/or partial response rates were significant.

Quality of life

Two RCTs had separate publications with quality-of-life data – quality-of-life data from the study by Long *et al.*[71] were reported in Monk *et al.*[72] and quality-of-life data from the study by Moore *et al.*[78] were reported in McQuellon *et al.*[77] For Long *et al.*,[71] patients completed quality-of-life assessments using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire, the neurotoxicity (NTX) subscale, the Brief Pain Inventory (BPI), the Cx subscale and the UNISCALE at four time points during the study. However, there were no statistically significant differences in quality of life up to 9 months after randomisation between cisplatin plus topotecan and cisplatin. It should be noted that in the combination arm increased toxicity was observed.

In the study by Moore *et al.*,[78] patients were assessed at baseline and at three time points thereafter (prior to chemotherapy cycles 2, 3 and 4) on the FACT-G and subscales. Despite increased toxicity (grades 3–4

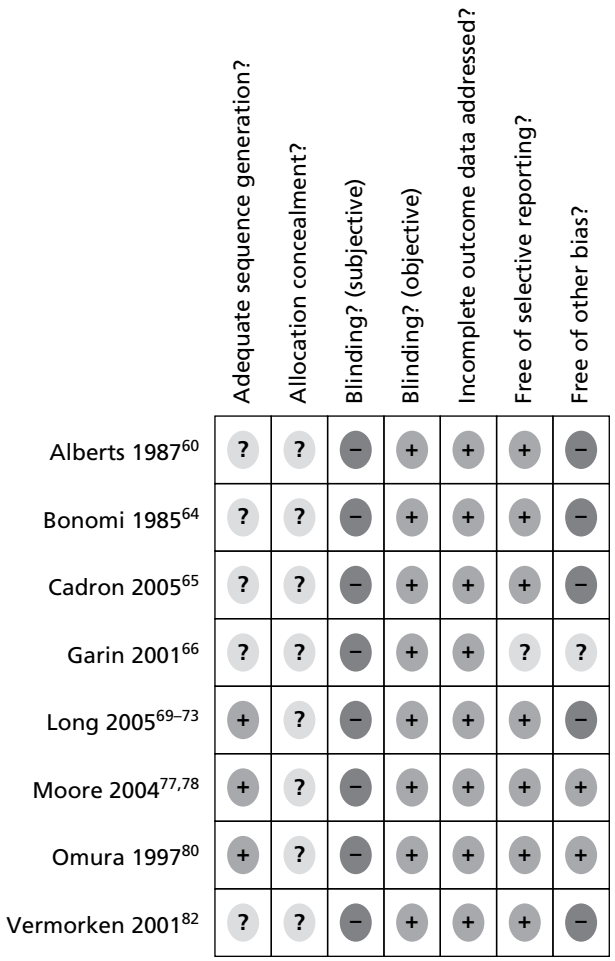

FIGURE 16 Methodological quality on individual items for the eight included RCTs: single-agent cisplatin.

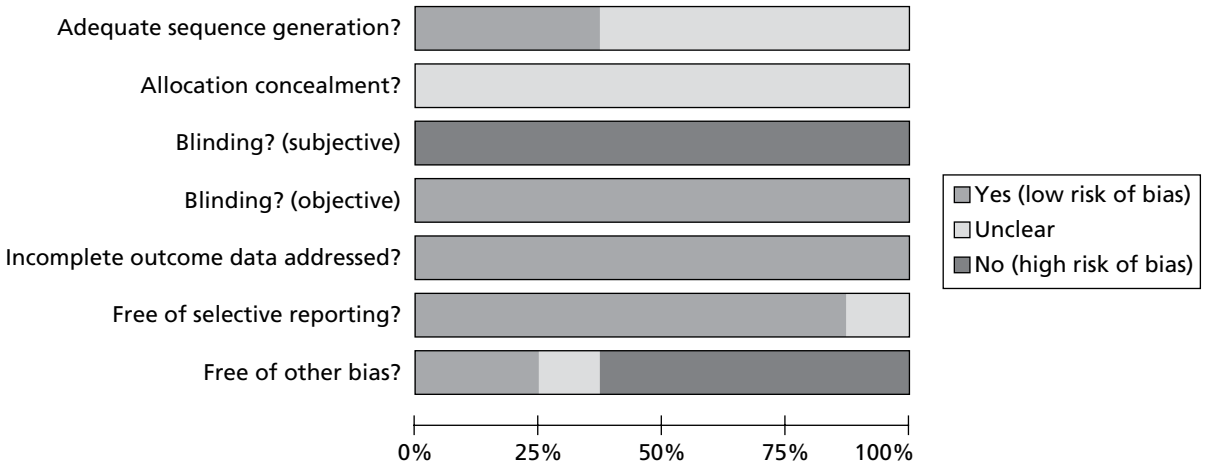

FIGURE 17 Summary of the quality and reporting assessment of the eight included RCTs: single-agent cisplatin.

TABLE 17 Overall survival: single-agent cisplatin

Study	Comparison	Median OS, months (range)	Hazard ratio (95% CI)
Alberts 1987[60]	MVBC	6.9	NR
	MC	7	
	C	17	
Bonomi 1985[64]	50 mg C	7.1	NR
	100 mg C	7	
	20 mg C	3.9	
Cadron 2005[65]	PIF	12.3 (2–19)	NR
	C	13 (2–84)	
Long 2005[71]	CT	9.4	0.76[a] (0.59 to 0.98, $p = 0.017$)
	C	6.5	
Moore 2004[78]	CP	9.7	NR
	C	8.8	
Omura 1997[80]	CIFX	8.3	NR ($p = 0.835$)
	CM	7.3	
	C	8	
Vermorken 2001[82]	BEMP	10.1 (8.3–12.5)[b]	NR
	C	9.3 (8.1–11.2)[b]	

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; MC, mitomycin C, cisplatin; NR, not reported; OS, overall survival; PIF, cisplatin, ifosfamide, 5-fluorouracil.

a RR.

b 95% CI.

TABLE 18 Progression free-survival: single-agent cisplatin

Study	Comparison	Median PFS, months (range)	Hazard ratio
Bonomi 1985[64]	50 mg C	3.7	NR
	100 mg C	4.6	
	20 mg C	3.9	
Long 2005[71]	CT	4.6	0.76[a] (0.60 to 0.97, $p = 0.014$)
	C	2.9	
Moore 2004[78]	CP	4.8	NR
	C	2.8	
Omura 1997[80]	CIFX	4.6	NR ($p = 0.003$)
	CM	3.3	
	C	3.2	
Vermorken 2001[82]	BEMP	5.3 (4.0–7.0)[b]	NR
	PC	4.5 (4.0–5.0)[b]	

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; NR, not reported; PC, paclitaxel, cisplatin; PFS, progression-free survival.

a RR.

b 95% CI.

TABLE 19 Overall duration of response: single-agent cisplatin

Study	Comparison	Median duration of response, months (range)	Hazard ratio
Alberts 1987[60]	MVBC	5.4	NR
	MC	7.2	
	C	7.3	
Bonomi 1985[64]	50 mg C	4.9	NR
	100 mg C	4.1	
	20 mg C	4.8	
Omura 1997[80]	CIFX	10	NR
	CM	7.7	
	C	5.5	
Vermorken 2001[82]	BEMP	9.2	NR
	C	7.1	

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; MC, mitomycin C, cisplatin; NR, not reported.

TABLE 20 Response rates (RRs): single-cisplatin agent

Study	Comparison	Response rate (95% CI)	Complete response rate (95% CI)	Partial response rate (95% CI)
Alberts 1987[60]	MC vs C	0.76 (0.32 to 2.29)	0.35 (0.05 to 2.63)	0.97 (0.32 to 3.69)
	MVBC vs MC	1.15 (0.58 to 2.26)	0.53 (0.12 to 2.37)	1.46 (0.65 to 3.28)
Bonomi 1985[64]	50 mg C vs 100 mg C	0.66 (0.45 to 0.97)	0.79 (0.42 to 1.48)	0.57 (0.33 to 1.00)
	20 mg C vs 50 mg C	1.21 (0.79 to 1.86)	0.86 (0.41 to 1.77)	1.54 (0.85 to 2.80)
	20 mg C vs 100 mg C	0.62 (0.43 to 0.88)	0.68 (0.34 to 1.33)	0.88 (0.53 to 1.44)
Cadron 2005[65]	PIF vs C	4.40 (0.81 to 27.05)	0.36 (0.00 to 3.91)	9.82 (1.38 to infinity)
Garin 2001[66]	IC vs C	1.91 (0.80 to 4.57)	3.34 (0.15 to 80.83)	1.72 (0.70 to 4.21)
	IC vs I	2.89 (1.11 to 7.51)	4.29 (0.18 to 101.42)	2.60 (0.98 to 6.91)
Long 2005[71]	CT vs C	1.99 (1.20 to 3.33)	3.48 (1.24 to 9.88)	1.56 (0.84 to 2.91)
Moore 2004[78]	CP vs C	1.86 (1.24 to 2.83)	2.58 (1.21 to 5.57)	1.55 (0.90 to 2.66)
Omura 1997[80]	CM vs C	1.18 (0.74 to 1.90)	1.48 (0.66 to 3.31)	1.01 (0.54 to 1.92)
	CIFX vs C	1.74 (1.14 to 2.67)	1.96 (0.92 to 4.18)	1.62 (0.92 to 2.86)
Vermorken 2001[82]	BEMP vs C	1.76 (1.08 to 2.90)	1.51 (0.57 to 3.99)	1.87 (1.03 to 3.42)

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; I, ifosfamide; IC, irinotecan, cisplatin; MC, mitomycin C, cisplatin; PIF, cisplatin, ifosfamide, 5-fluorouracil.

anaemia and grades 3–4 neutropenia) in the combination arm (cisplatin and paclitaxel) there were no statistically significant differences in scores between the groups at any assessment point.

Adverse events

Haematological toxicity (neutropenia, febrile neutropenia, thrombocytopenia, leucopenia and anaemia) was generally more frequently associated with cisplatin in combination with other agents than with cisplatin monotherapy (*Tables 21–24*). Infections were more common with combination therapy than with single-agent cisplatin (cisplatin + topotecan arm: 26/147, cisplatin-only arm: 12/146;[71] BEMP arm: 7/143, cisplatin-only arm: 3/144[82]). There was little difference in neuropathy between combination therapy and single-agent cisplatin (cisplatin + paclitaxel arm: 4/129, cisplatin-only arm: 6/130;[78] BEMP arm: 7/143, cisplatin-only arm: 3/144[82]). Alopecia was also more common with combination therapy than with single-agent cisplatin (MVBC arm: 12/54, mitomycin C and cisplatin arm: 2/51, cisplatin-only arm: 0/9;[60] BEMP arm: 81/143, cisplatin-only arm: 31/144[82]). The results for nausea and/or vomiting are shown in

TABLE 21 Neutropenia and febrile neutropenia: single-agent cisplatin

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Garin 2001[66]	IC vs C	22/27	3/31	8.42 (2.83 to 25.05)
	IC vs I	22/27	13/39	2.44 (1.51 to 3.95)
[a]Long 2005[71]	CT vs C	103/147	2/146	51.15 (14.37 to 186.73)
[b]Long 2005[71]	CT vs C	27/147	12/146	2.23 (1.20 to 4.22)
Moore 2004[78]	CP vs C	86/129	4/130	21.63 (8.65 to 118.25)
[b]Moore 2004[78]	CP vs C	86/129	4/130	21.63 (8.65 to 118.25)
Omura 1997[80]	CM vs C	19/145	1/137	17.95 (2.44 to 132.29)
	CIFX vs C	55/146	1/137	51.61 (7.24 to 367.83)

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; I, ifosfamide; IC, irinotecan, cisplatin.

a Grades 3 and 4 neutropenia only.

b Febrile neutropenia.

TABLE 22 Thrombocytopenia: single-agent cisplatin

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Alberts 1987[60]	MC vs C	9/51	0/9	3.65 (0.54 to infinity)
	MVBC vs MC	13/54	9/51	1.36 (0.64 to 2.91)
Bonomi 1985[64]	50 mg C vs 100 mg C	2/162	2/180	1.11 (0.20 to 6.24)
	20 mg C vs 50 mg C	4/143	2/162	2.27 (0.49 to 10.47)
	20 mg C vs 100 mg C	4/143	2/180	2.24 (0.49 to 10.34)
Long 2005[71]	CT vs C	46/147	4/146	11.42 (4.45 to 29.99)
Moore 2004[78]	CP vs C	5/129	3/130	1.68 (0.45 to 6.26)
Omura 1997[80]	CM vs C	23/145	1/137	21.73 (2.98 to 158.73)
	CIFX vs C	28/146	1/137	26.27 (3.62 to 190.48)

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; MC, mitomycin C, cisplatin.

Table 25. There were no significant differences between the combination therapy and the single-agent cisplatin arms.

Effectiveness of cisplatin combinations

Characteristics of included studies

Four RCTs contained relevant information about the effectiveness of cisplatin combinations as palliative treatment for recurrent, metastatic or persistent cervical cancer.[62,63,76,79] Baseline characteristics (including previous treatment and stage or site of disease) presented in *Table 26* were well balanced between the groups. However, not all relevant clinical information was presented in all publications.

TABLE 23 Leucopenia: single-agent cisplatin

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Alberts 1987[60]	MC vs C	9/51	0/9	3.65 (0.54 to infinity)
	MVBC vs MC	10/54	9/51	1.05 (0.46 to 2.37)
Bonomi 1985[64]	50 mg C vs 100 mg C	1/162	12/180	0.09 (0.01 to 0.70)
	20 mg C vs 50 mg C	6/143	1/162	22.60 (3.66 to 140.53)
	20 mg C vs 100 mg C	6/143	12/180	2.09 (0.84 to 5.00)
Long 2005[71]	CT vs C	93/147	1/146	92.37 (16.69 to 524.25)
Moore 2004[78]	CP vs C	69/129	4/130	17.38 (6.90 to 44.98)

C, cisplatin; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; MC, mitomycin C, cisplatin.

TABLE 24 Anaemia: single-agent cisplatin

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Long 2005[71]	CT vs C	56/147	34/146	1.64 (1.15 to 2.35)
Moore 2004[78]	CP vs C	39/129	17/130	2.31 (1.33 to 2.56)

C, cisplatin; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan.

TABLE 25 Nausea and/or vomiting: single-agent cisplatin

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Alberts 1987[60]	MC vs C	10/51	2/9	0.88 (0.29 to 3.38)
	MVBC vs MC	8/54	10/51	0.76 (0.32 to 1.76)
Garin 2001[66]	IC vs C	1/27	0/31	3.43 (0.15 to 80.83)
	IC vs I	1/27	2/39	0.72 (0.07 to 7.57)
Long 2005[71]	CT vs C	21/147	13/146	1.60 (0.85 to 3.06)
Moore 2004[78]	CP vs C	13/129	16/130	0.82 (0.42 to 1.61)
Omura 1997[80]	CM vs C	10/145	12/137	0.79 (0.36 to 1.76)
	CIFX vs C	17/146	12/137	1.33 (0.66 to 2.68)

C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; CP, cisplatin, paclitaxel; CT, cisplatin, topotecan; I, ifosfamide; IC, irinotecan, cisplatin; MC, mitomycin C, cisplatin.

TABLE 26 Characteristics of the populations in the included RCTs: cisplatin combinations

	Monk 2009[76]				Mountzios 2009[79]		Bloss 2002[63]		Bezwoda 1986[62]	
Parameter	VC	GC	TC	PC	IP	ITP	CIB	IP	Hydroxyurea	C + MTX
Number of patients (randomised)	117	119	118	118	74	79	141	146	13	37 (12)[a]
Age (months), median (range)	49 (24–76)	45 (20–89)	48 (25–75)	50 (29–81)	55 (28–75)	50 (25–78)	46 (21–80)	45 (25–77)	43 (10.1)[b]	39 (8.3)[b]
Previous treatment										
Chemotherapy	NR	NR	NR	NR	10 (14%)	16 (20%)	33 (23.4%)[c]	30 (20.5%)[c]	NR	NR
Radiotherapy	NR	NR	NR	NR	19 (26%)	17 (22%)	123 (87.2%)	132 (90.4%)	Radical, 9; palliative, 3	Radical, 20 (5%); palliative, 9 (3%)
Surgery	NR	NR	NR	NR	5 (7%)	3 (4%)	NR	NR	0	2 (1%)
Chemotherapy and radiotherapy	70	79	72	81	9 (12%)	14 (18%)	NR	NR	NR	NR
Surgery and radiotherapy	NR	NR	NR	NR	30 (41%)	25 (32%)	NR	NR	0	3
Stage										
IVB	17	20	20	17	NR	NR	NR	NR	NR	NR
Persistent	14	12	14	12	NR	NR	NR	NR	NR	NR
Recurrent	77	80	77	74	NR	NR	NR	NR	NR	NR
Site of disease										
Pelvic	NR	NR	NR	NR	NR	NR	56 (39.7%)	54 (37%)	6	28 (7%)
Distant	NR	NR	NR	NR	NR	NR	85 (60.3%)	92 (63%)	Bone, 3; nodes, 6; lung, 4; other, 2	Bone, 9; nodes, 19; lung, 13; other, 6
Both	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

C, cisplatin; CIB, cisplatin, ifosfamide, bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; MTX, methotrexate; NR, not reported; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

a Initial 12 patients randomly allocated to receive DDP + MTX.

b Mean (SD).

c Previous cisplatin treatment (as a radiation sensitiser).

Quality of studies

Only two studies[63,76] specified the method of randomisation in their reports. Description of allocation concealment was not reported in any of the included RCTs. Until January 2004, the Monk *et al.*[76] study consisted of only two arms comparing cisplatin plus paclitaxel with cisplatin plus vinorelbine. Primary analyses excluded those 41 patients. In Bezwoda *et al.*,[62] after a preliminary analysis of the results, the hydroxyurea arm of the study was discontinued and a further 25 patients received the *cis*-diamminedichl oroplatinum(II) (DDP) plus methotrexate regimen. *Figures 18* and *19* show the results of the quality assessment.

Effectiveness results

Overall and progression-free survival

Overall and progression-free survival results are presented in *Tables 27* and *28* respectively. All four trials reported median overall survival, and values were highest for the cisplatin, ifosfamide and paclitaxel arm in Mountzios *et al.*,[79] reaching 15.4 months (95% CI 8.6 to 22.3 months). The hazard ratio was given by Monk *et al.*[76] and Mountzios *et al.*[79] These results indicate that there were no statistically significant differences between chemotherapeutic schemes in any of the included studies.

The progression-free survival results were available in three RCTs[63,76,79] and hazard ratios were provided by two.[76,79] Multivariate Cox analysis for progression-free survival was performed in Mountzios *et al.*[79] and indicated a statistically significantly longer progression-free survival for the cisplatin, ifosfamide and paclitaxel arm [hazard ratio 0.70 (95% CI 0.49 to 0.99), $p = 0.046$].

Response rate

All of the RCTs reported response rates but complete and partial response rate was available only in three trials;[62,76,79] Bloss *et al.*[63] did not report complete and partial response rates. Response rates and risk ratios are presented in *Table 29*.

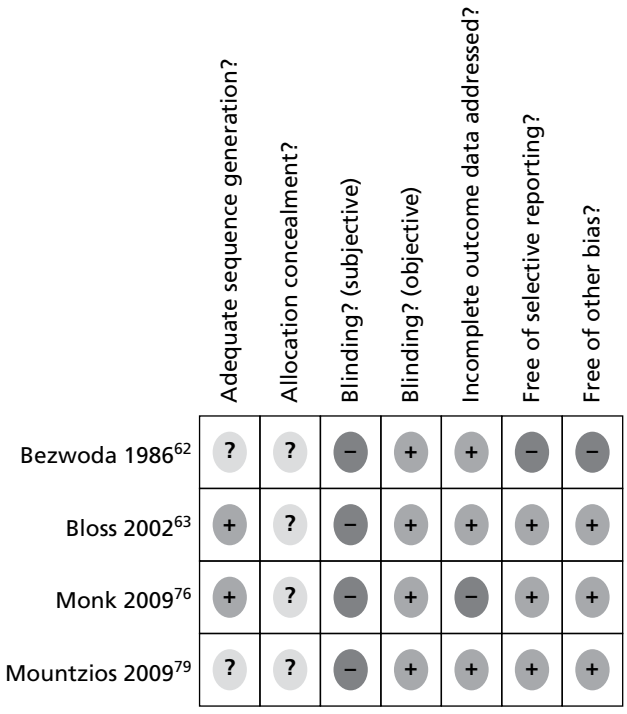

FIGURE 18 Methodological quality on individual items for the four included RCTs: [62,63,76,79] cisplatin combinations.

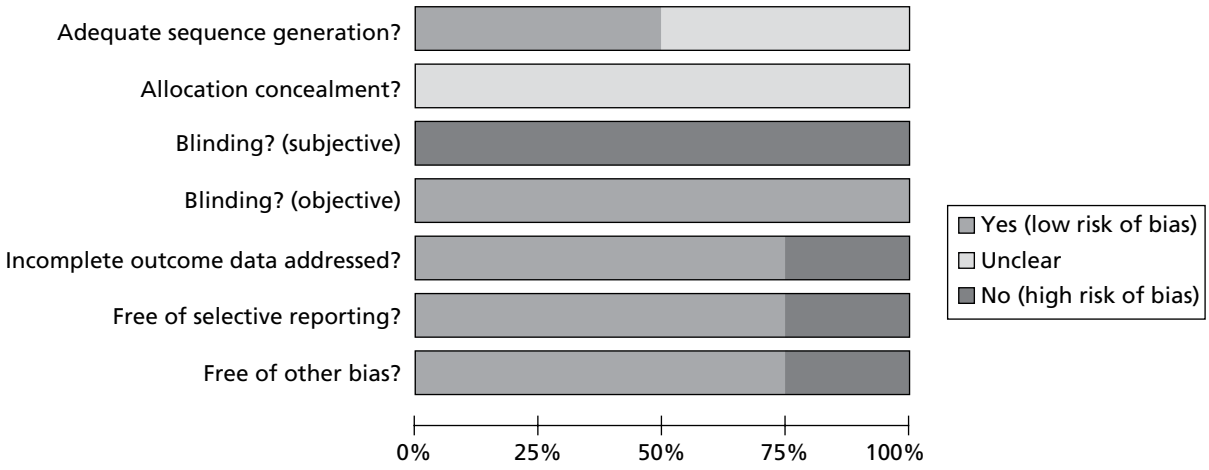

FIGURE 19 Summary of the quality and reporting assessment of the four included RCTs:[52,63,76,79] cisplatin combinations.

TABLE 27 Overall survival: cisplatin combinations

Study	Comparison	Median OS, months (range)	Hazard ratio (95% CI)
Bezwoda 1986[62]	Hydroxyurea	4	NR
	C + MTX[a]	9	
	C + MTX	11	
Bloss 2002[63]	IP	8.5	NR
	CIB	8.4	
Monk 2009[76]	VC	9.99 (8.25–12.25)	1.15 (0.79 to 1.67)[b]
	GC	10.28 (7.62–11.60)	1.32 (0.91 to 1.92)[b]
	TC	10.25 (8.61–11.66)	1.26 (0.86 to 1.82)[b]
	PC	12.87 (10.02–16.76)	
Mountzios 2009[79]	IP	13.2 (10.9–15.5)[c]	0.75 (0.53 to 1.08)
	ITP	15.4 (8.6–22.3)[c]	

C, cisplatin; CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; MTX, methotrexate; NR, not reported; OS, overall survival; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

a Initial 12 patients randomly allocated to receive DDP + MTX.

b Compared with PC reference arm.

c 95% CI.

Quality of life

Monk *et al.*[76] reported quality of life measured with the Functional Assessment of Cancer Therapy – Cervix Trial Outcome Index (FACT-Cx TOI), the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity four-item scale (FACT/GOG-NTX) and the BPI but detailed data were not presented in the publication. After adjustment for baseline score, age and performance status at randomisation, there were no statistical differences between any of the experimental arms and the control arm.

TABLE 28 Progression-free survival: cisplatin combinations

Study	Comparison	Median PFS, months (range)	Hazard ratio (95% CI)
Bloss 2002[63]	IP	4.6	NR
	CIB	5.1	
Monk 2009[76]	VC	3.98 (3.19–5.16)	1.36 (0.97 to 1.90)[a]
	GC	4.70 (3.58–5.59)	1.39 (0.99 to 1.96)[a]
	TC	4.57 (3.71–5.75)	1.27 (0.90 to 1.78)[a]
	PC	5.82 (4.53–7.59)	
Mountzios 2009[79]	IP	6.3 (4.3–8.2)[b]	0.70 (0.49 to 0.99)
	ITP	7.9 (6.1–9.8)[b]	

CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; NR, not reported; PC, paclitaxel, cisplatin; PFS, progression-free survival; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

a Compared with PC reference arm.

b 95% CI.

TABLE 29 Response rates (RRs): cisplatin combinations

Study	Comparison	Response rate (95% CI)	Complete response rate (95% CI)	Partial response rate (95% CI)
Bezwoda 1986[62]	Hydroxyurea vs C + MTX	0.06 (0.00 to 0.97)	0.25 (0.01 to 4.18)	0.08 (0.01 to 1.28)
Bloss 2002[63]	CIB vs IP	0.97 (0.69 to 1.36)	NR	NR
Monk 2009[76]	VC vs PC	0.89 (0.57 to 1.38)	2.54 (0.69 to 9.32)	0.71 (0.42 to 1.18)
	GC vs PC	0.77 (0.48 to 1.21)	0.31 (0.03 to 2.90)	0.82 (0.51 to 1.32)
	TC vs PC	0.80 (0.51 to 1.26)	0.62 (0.11 to 3.63)	0.82 (0.51 to 1.33)
Mountzios 2009[79]	IP vs ITP	0.56 (0.38 to 0.81)	0.44 (0.20 to 0.94)	0.64 (0.38 to 1.09)

C, cisplatin; CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; MTX, methotrexate; NR, not reported; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

Adverse events

Haematological adverse events were high in all RCTs (*Tables 30–33*). Bezwoda *et al.*[62] did not specify the grade of reported adverse events. The authors mentioned that therapy was generally well tolerated but that all patients receiving high-dose hydroxyurea developed leucopenia with a nadir 10–14 days after the initial loading dose; however, all patients recovered rapidly. Haematological toxicity was rare in the cisplatin plus methotrexate-treated patients (two patients) and stomatitis occurred in only one patient. In Bloss *et al.*[63] toxicity was graded according to standard Gynecologic Oncology Group (GOG) criteria, in Monk *et al.*[76] the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0, was used for characterising adverse events and dose modifications and in Mountzios *et al.*[79] The World Health Organization criteria were used in the assessment of toxicity. It was not appropriate to combine toxicity results because of differences in chemotherapy regimens in the RCTs.

Bezwoda *et al.*[62] mentioned that three patients developed hypokalaemia and three developed symptomatic hypocalcaemia, two of whom also had hypomagnesaemia. Monk *et al.*[76] reported a significantly smaller proportion of patients with adverse events such as vomiting and nausea in the topotecan/cisplatin and

TABLE 30 Neutropenia and febrile neutropenia: cisplatin combinations

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Bloss 2002[63]	CIB vs IP	117/137	117/144	1.05 (0.95 to 1.17)
Monk 2009[76]	VC vs PC	83/106	79/101	1.00 (0.87 to 1.16)
	GC vs PC	46/109	79/101	0.54 (0.42 to 0.69)
	TC vs PC	90/109	79/101	1.06 (0.92 to 1.21)
[a]Monk 2009[76]	VC vs PC	15/106	13/101	1.10 (0.55 to 2.19)
	GC vs PC	7/109	13/101	0.50 (0.21 to 1.20)
	TC vs PC	11/109	13/101	0.78 (0.37 to 1.67)
Mountzios 2009[79]	IP vs ITP	22/72	20/77	1.18 (0.70 to 1.97)
[a]Mountzios 2009[79]	IP vs ITP	2/72	7/77	0.31 (0.07 to 1.42)

CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

a Febrile neutropenia.

TABLE 31 Thrombocytopenia: cisplatin combinations

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Bloss 2002[63]	CIB vs IP	28/137	23/144	1.28 (0.78 to 2.11)
Monk 2009[76]	VC vs PC	8/106	7/101	1.09 (0.41 to 2.89)
	GC vs PC	31/109	7/101	4.10 (1.89 to 8.90)
	TC vs PC	38/109	7/101	5.03 (2.35 to 10.75)
Mountzios 2009[79]	IP vs ITP	8/72	8/77	1.07 (0.42 to 2.70)

CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

TABLE 32 Leucopenia: cisplatin combinations

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Bloss 2002[63]	CIB vs IP	118/137	121/144	1.03 (0.93 to 1.13)
Monk 2009[76]	VC vs PC	72/106	64/101	1.07 (0.88 to 1.31)
	GC vs PC	47/109	64/101	0.68 (0.52 to 0.88)
	TC vs PC	77/109	64/101	1.11 (0.92 to 1.35)
Mountzios 2009[79]	IP vs ITP	1/72	2/77	0.53 (0.05 to 5.77)

CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

TABLE 33 Anaemia: cisplatin combinations

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
Bloss 2002[63]	CIB vs IP	29/137	32/144	0.95 (0.61 to 1.49)
Monk 2009[76]	VC vs PC	31/106	17/101	1.74 (1.03 to 2.94)
	GC vs PC	37/109	17/101	2.02 (1.22 to 3.35)
	TC vs PC	38/109	17/101	2.07 (1.25 to 3.43)
Mountzios 2009[79]	IP vs ITP	6/72	8/72	0.75 (0.27 to 2.05)

CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

TABLE 34 Nausea and/or vomiting: cisplatin combinations

Study	Comparison	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)
[a]Bloss 2002[63]	CIB vs IP	33/137	31/144	1.12 (0.73 to 1.72)
[b]Monk 2009[76]	VC vs PC	14/106	20/101	0.67 (0.36 to 1.25)
	GC vs PC	11/109	20/101	0.51 (0.26 to 1.01)
	TC vs PC	9/109	20/101	0.42 (0.20 to 0.87)
[c]Monk 2009[76]	VC vs PC	14/106	20/101	0.67 (0.36 to 1.25)
	GC vs PC	11/109	20/101	0.51 (0.26 to 1.01)
	TC vs PC	9/109	20/101	0.42 (0.20 to 0.87)
[a]Mountzios 2009[79]	IP vs ITP	11/72	5/77	2.35 (0.86 to 6.44)

CIB, cisplatin, ifosfamide and bleomycin; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; PC, paclitaxel, cisplatin; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin.

a Nausea and vomiting.

b Nausea.

c Vomiting.

gemcitabine/cisplatin arms compared with the paclitaxel/cisplatin arm (*Table 34*). No significant differences in frequency of non-haematological adverse drug reactions between the chemotherapeutic arms was observed in the other RCTs. In Mountzios *et al.*[79] alopecia occurred in 48 out of 72 patients in the cisplatin and ifosfamide arm, and 52 out of 77 patients in the cisplatin, ifosfamide and paclitaxel arm.

Effectiveness of other platinum agents

Characteristics of included studies

Three RCTs evaluated the effectiveness of other platinum agents as palliative treatment for recurrent, persistent or advanced cervical cancer.[68,74,81] Baseline characteristics including previous treatment and stage and site of disease are presented in *Table 35* showing that the groups were comparable in each of the included studies. Chemotherapy as previous treatment was given in the study by Lira-Puerto *et al*.[68] and radiotherapy and surgery were given in all trials.

Quality of studies

The description of randomisation was provided only in McGuire *et al.*[74] None of the trials gave any details of the method of allocation concealment. In the study by Lira-Puerto *et al*.,[68] accrual was suspended in two institutions because of termination of support. The results of the quality assessment are provided in *Figures 20* and *21*.

TABLE 35 Characteristics of the populations in the included RCTs: other platinum-agents

	McGuire 1989[74]		Lira-Puerto 1991[68]		Thomsen 1998[81]	
Parameter	CBDCA	CHIP	CBDCA	CHIP	CBDCA	T
Number of patients (randomised)	175	177	48	41	13	15
Age (years), median (range)	47 (23–74)	49 (25–94)	48 (26–67)	44 (30–59)	52 (33–62)	52 (31–71)
Previous treatment						
Chemotherapy	NR	NR	5	2	NR	NR
Radiotherapy	159 (91%)	164 (93%)	47	41	83%	86%
Surgery	108 (62%)	101 (57%)	2	4	25%	29%
Chemotherapy and radiotherapy	NR	NR	4	2	NR	NR
Surgery and radiotherapy	NR	NR	NR	NR	NR	NR
Stage						
IVB	NR	NR	0	1	NR	NR
Persistent	NR	NR	NR	NR	NR	NR
Recurrent	NR	NR	NR	NR	100%	93%
Site of disease						
Pelvic	NR	NR	23	30	NR	NR
Distant	NR	NR	Lung, 1; bone, 2; inguinal nodes, 6; para-aortic nodes, 1; distant nodes, 4; other, 3; fibrosis only, 1	Lung, 7; bone, 2; inguinal nodes, 8; para-aortic nodes, 3; distant nodes, 9; other, 4; fibrosis only, 1	NR	NR
Both	NR	NR	14	9	NR	NR

CHIP, iproplatin; NR, not reported; T, teniposide.

Effectiveness results

Overall and progression-free survival

All RCTs reported overall survival and two reported progression-free survival (*Tables 36* and *37*). There was little difference in overall survival or progression-free survival between arms in each RCT. Hazard ratio results were not supplied for any of the included studies.

Response rate

Two of the RCTs[68,74] gave response rates, complete response rates and partial response rates for the same treatment comparisons and so meta-analysis was possible (*Figures 22–24*). There were no statistically significant differences in terms of frequency of response rate (overall, partial, complete) between these cisplatin agents. However, it should be noted that there were differences between studies in the frequency of response rate in the CBDCA arms (ranging from 15% to 33%) as well as in the iproplatin (CHIP) arms

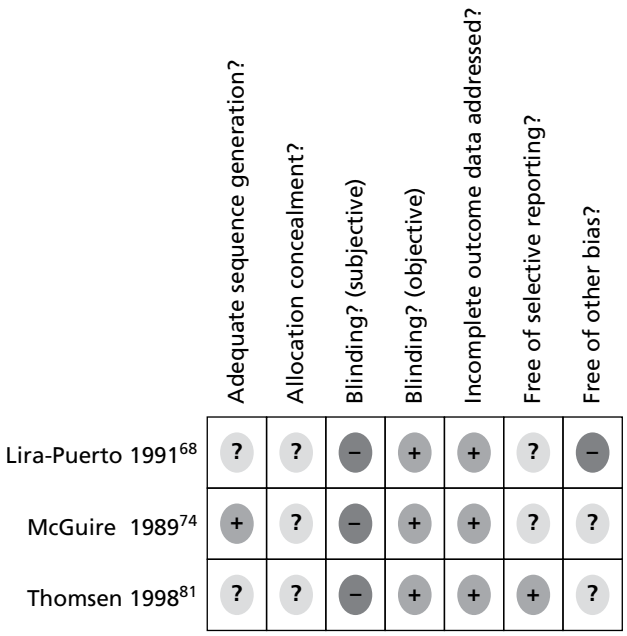

FIGURE 20 Methodological quality on individual items for the three included RCTs: [68,74,81] other platinum agents.

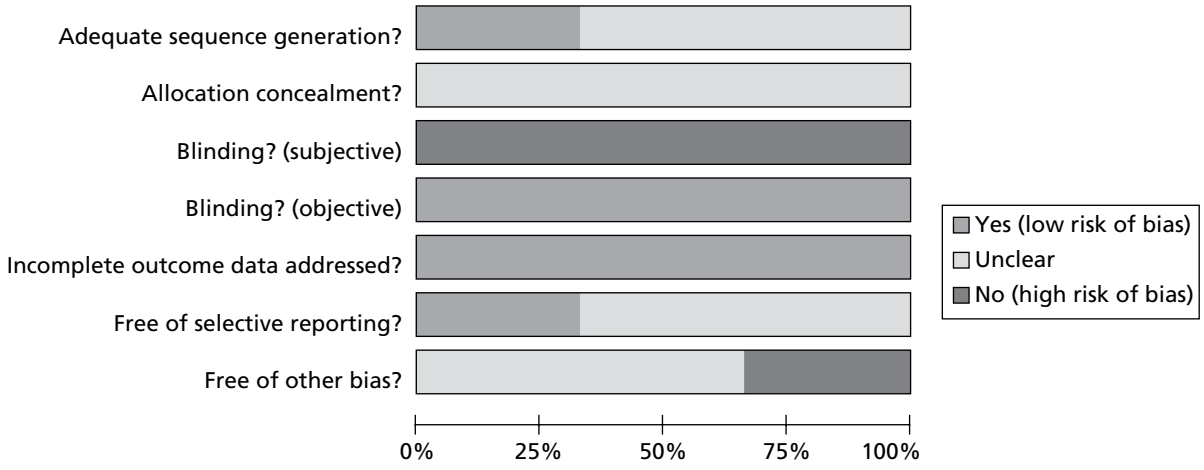

FIGURE 21 Summary of the quality and reporting assessment of the three included studies:[68,74,81] other platinum agents.

(11–30%), and in the frequency of partial response rate in the CBDCA arms (10–33%) and the CHIP arms (7–25%).

Quality of life

None of the studies assessed quality of life.

Adverse events

Data on haematological toxicity was supplied for all trials. Lira-Puerto *et al.*[68] reported drug reactions of Eastern Cooperative Oncology Group (ECOG) grade 2 or more. Meta-analysis of thrombocytopenia rates comparing CBDCA with CHIP indicated no statistical differences between chemotherapeutic agents (*Figure 25*). There were no differences in leucopenia rates in two RCTs (CBDCA arm 17/176 vs CHIP arm 8/180;[74] CBDCA arm 0/12 vs teniposide arm 1/14[81]). Neurological adverse events (grades 2, 3 or 4) were

TABLE 36 Overall survival: other platinum agents

Study	Comparison	Median OS, months (range)	Hazard ratio (95% CI)
McGuire 1989[74]	CBDCA	6.2	NR
	CHIP	5.5	
Lira-Puerto 1991[68]	CBDCA	7.5	NR
	CHIP	7.6	
Thomsen 1998[81]	CBDCA	40 (20–49)[a]	NR
	T	41 (34–56)[a]	

CHIP, iproplatin; NR, not reported; OS, overall survival; T, teniposide.
a Weeks.

TABLE 37 Progression-free survival: other platinum agents

Study	Comparison	Median PFS, months (range)	Hazard ratio (95% CI)
McGuire 1989[74]	CBDCA	2.7	NR
	CHIP	3	
Thomsen 1998[81]	CBDCA	20 (11–31)[a]	NR
	T	17 (12–32)[a]	

CHIP, iproplatin; NR, not reported; PFS, progression-free survival; T, teniposide.
a Weeks.

seen in 1 out of 47 patients treated with CBDCA and 6 out of 41 patients treated with CHIP in the study by Lira-Puerto *et al.*[68] and in 6 out of 176 and 6 out of 180 patients, respectively, in the study by McGuire *et al.*[74] Gastrointestinal adverse events such as nausea and vomiting were experienced less often in patients receiving CBDCA (57/176) than in patients receiving CHIP (95/180) [RR 0.61 (95% CI 0.48 to 0.79)] in the study by McGuire *et al.*,[74] but there was no difference in gastrointestinal adverse events between CBDCA (2/12) and teniposide (2/14) in the study by Thomsen and Pfeiffer.[81]

Effectiveness of non-platinum agents

Characteristic of included studies

Four studies gave evidence on the effectiveness of non-platinum agents for the treatment of recurrent, persistent or advanced cervical cancer.[61,67,75,83] Because two studies[67,83] were, unfortunately, impossible to obtain, analysis was conducted on the basis of the systematic review by Hirte *et al.*[59] Baseline characteristics including previous treatment and stage and site of disease are presented in *Table 38*; however, not all relevant clinical information was presented in all publications.

Quality of studies

As full texts were impossible to obtain for Greenberg *et al.*[67] and Wallace *et al.*,[83] the quality assessment was based on the systematic review by Hirte *et al.*[59] A description of the allocation concealment procedure was not reported in any of the RCTs and blinding was not used in any of the RCTs. In Barlow *et al.*,[61] two patients with squamous cell tumours were mistakenly randomised as non-squamous cell tumours and received adriamycin (ADM) alone (group of 21 + 2 patients). In Monk *et al.*,[75] patients were initially randomly assigned to combination and monotherapy arms. The protocol was later amended after receiving

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.1.1 carboplatin vs teniposide						
Thomsen 1998[81]	4	12	4	14	100.0%	1.17 (0.37 to 3.69)
Subtotal (95% CI)		**12**		**14**	**100.0%**	**1.17 (0.37 to 3.69)**
Total events	4		4			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.26$ ($p = 0.79$)						
1.1.2 carboplatin vs iproplatin						
Lira-Puerto 1991[68]	12	46	12	40	41.8%	0.87 (0.44 to 1.71)
McGuire 1989[74]	27	175	19	177	58.2%	1.44 (0.83 to 2.49)
Subtotal (95% CI)		**221**		**217**	**100.0%**	**1.16 (0.71 to 1.90)**
Total events	39		31			
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 1.29$, df = 1 ($p = 0.26$); $I^2 = 22\%$						
Test for overall effect: $z = 0.61$ ($p = 0.54$)						

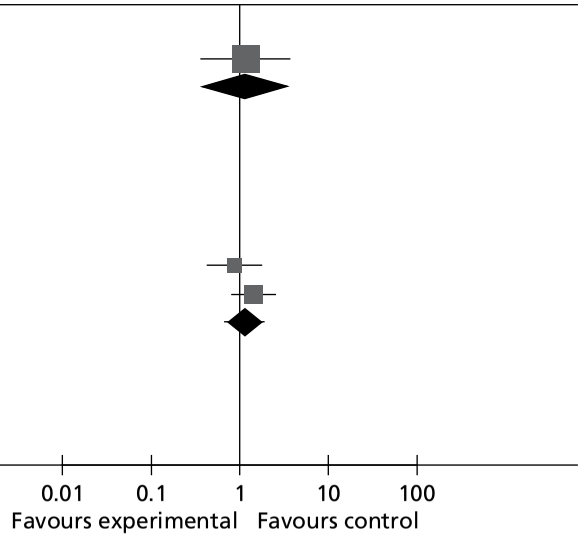

FIGURE 22 Response rate: other platinum agents.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.2.1 carboplatin vs teniposide						
Thomsen 1998[81]	0	12	1	14	100.0%	0.38 (0.02 to 8.65)
Subtotal (95% CI)		**12**		**14**	**100.0%**	**0.38 (0.02 to 8.65)**
Total events	0		1			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.60$ ($p = 0.55$)						
1.2.2 carboplatin vs iproplatin						
Lira-Puerto 1991[68]	2	46	2	40	19.5%	0.87 (0.13 to 5.89)
McGuire 1989[74]	10	175	7	177	80.5%	1.44 (0.56 to 3.71)
Subtotal (95% CI)		**221**		**217**	**100.0%**	**1.31 (0.56 to 3.05)**
Total events	12		9			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.22$, df = 1 ($p = 0.64$); $I^2 = 0\%$						
Test for overall effect: $z = 0.62$ ($p = 0.53$)						

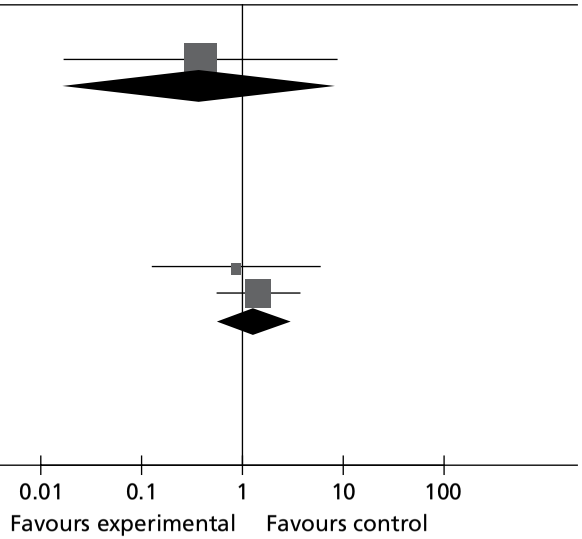

FIGURE 23 Complete response: other platinum agents.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.2.1 carboplatin vs teniposide						
Thomsen 1998[81]	0	12	1	14	100.0%	0.38 (0.02 to 8.65)
Subtotal (95% CI)		**12**		**14**	**100.0%**	**0.38 (0.02 to 8.65)**
Total events	0		1			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.60$ ($p = 0.55$)						
1.2.2 carboplatin vs iproplatin						
Lira-Puerto 1991[68]	2	46	2	40	19.5%	0.87 (0.13 to 5.89)
McGuire 1989[74]	10	175	7	177	80.5%	1.44 (0.56 to 3.71)
Subtotal (95% CI)		**221**		**217**	**100.0%**	**1.31 (0.56 to 3.05)**
Total events	12		9			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.22$, df = 1 ($p = 0.64$); $I^2 = 0\%$						
Test for overall effect: $z = 0.62$ ($p = 0.53$)						

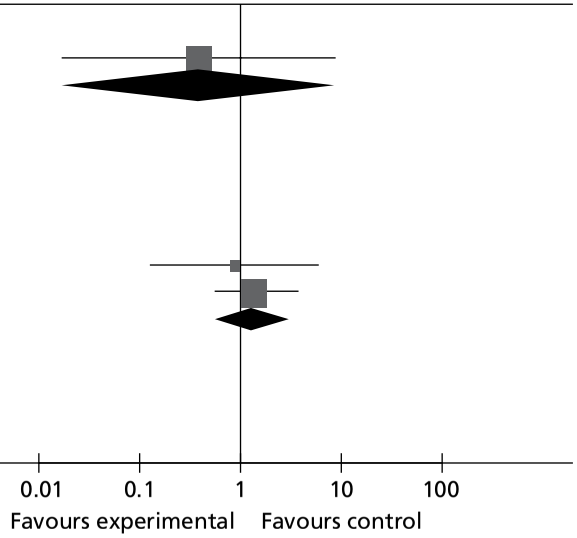

FIGURE 24 Partial response: other platinum agents.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
2.1.1 carboplatin vs teniposide						
Thomsen 1998[81]	1	12	0	14	100.0%	3.46 (0.15 to 77.86)
Subtotal (95% CI)		**12**		**14**	**100.0%**	**3.46 (0.15 to 77.86)**
Total events	1		0			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.78$ ($p = 0.43$)						
2.1.2 carboplatin vs iproplatin						
Lira-Puerto 1991[68]	6	47	13	41	29.9%	0.40 (0.17 to 0.96)
McGuire 1989[74]	29	176	33	180	70.1%	0.90 (0.57 to 1.41)
Subtotal (95% CI)		**223**		**221**	**100.0%**	**0.75 (0.50 to 1.12)**
Total events	35		46			
Heterogeneity: $\chi^2 = 2.57$, df = 1 ($p = 0.11$); $I^2 = 61\%$						
Test for overall effect: $z = 1.42$ ($p = 0.16$)						

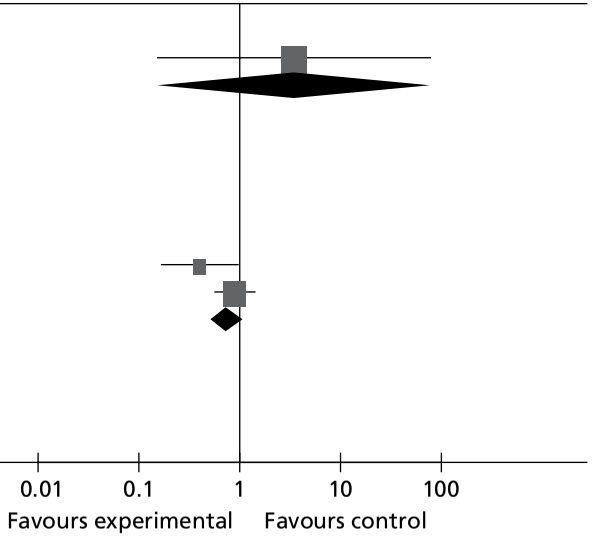

FIGURE 25 Thrombocytopenia: other platinum agents.

TABLE 38 Characteristics of the populations in the included RCTs: non-platinum agents

	Barlow 1973[61]			Greenberg 1977[67]		Monk 2010[75]			Wallace 1978[83]		
Parameter	ADM	BLEO	ADM + BLEO	ADM	ADM + BLEO	P	P + L	L	ADM	ADM + V	ADM + Cyclo
Number of patients (randomised)	21 (+ two patients mistakenly randomised)	10	23	9	11	74	76	78	61	61	52
Age (years), median (range)	54.5 (13–83)			NR	NR	49.5 (29–73)	48.5 (28–82)	49 (23–81)	NR	NR	NR
Previous treatment											
Chemotherapy	NR[a]	NR[a]	NR[a]	11%	18%	5	3	5	NR	NR	NR
Radiotherapy	NR[a]	NR[a]	NR[a]	100%	100%	24	24	18	NR	NR	NR
Surgery	NR	NR	NR	NR	NR	1	0	1	NR	NR	NR
Chemotherapy and radiotherapy	NR	NR	NR	NR	NR	26	30	30	NR	NR	NR
Surgery and radiotherapy	NR	NR	NR	NR	NR	0	2	2	NR	NR	NR
Stage											
IVB	NR[b]	NR[b]	NR[b]	100%	100%	6	6	3	100%	100%	100%
Persistent	NR[b]	NR[b]	NR[b]	100%	100%	NR	NR	NR	100%	100%	100%
Recurrent	100%	100%	100%	100%	100%	95%	95%	92%	100%	100%	100%
Site of disease											
Pelvic	NR	NR	NR	0%	45%	NR	NR	NR	NR	NR	NR
Distant	NR	NR	NR	22%	0%	NR	NR	NR	NR	NR	NR
Both	NR	NR	NR	77%	55%	NR	NR	NR	NR	NR	NR

BLEO, bleomycin; Cyclo, cyclophosphamide; L, lapatinib; NR, not reported; P, pazopanib; V, vincristine.

a 45 patients underwent previous radiotherapy and/or chemotherapy.

b Patients with disease no longer amenable to therapy with surgery or irradiation, or who represented failures of chemotherapy with agents considered effective for their disease.

results of a formal interim analysis and combination therapy was discontinued. In the same study, the unconfirmed response rate (not verified on a second scan) was 19% for pazopanib-treated patients and 9% for lapatinib-treated patients. The results of the quality assessment are shown in *Figures 26* and *27*.

Effectiveness results

Overall and progression-free survival

Barlow *et al.*[61] did not report overall survival or progression-free survival and Greenberg *et al.*[67] did not report progression-free survival. Monk *et al.*[75] demonstrated better overall survival and progression-free survival with pazopanib than with lapatinib. Hazard ratios were not supplied for any of the other RCTs.[61,67,83] The overall survival results are shown in *Table 39* and the progression-free survival results are shown in *Table 40*.

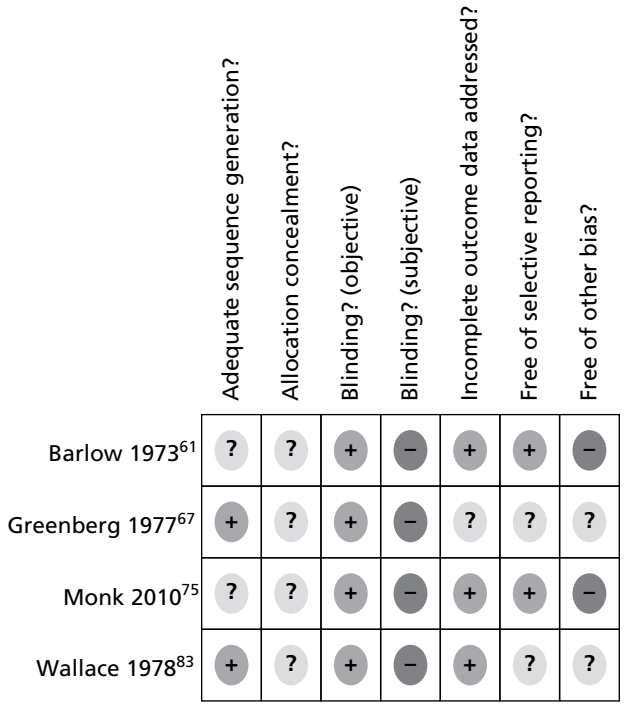

FIGURE 26 Methodological quality on individual items for the four included RCTs: [61,67,75,83] non-platinum agents.

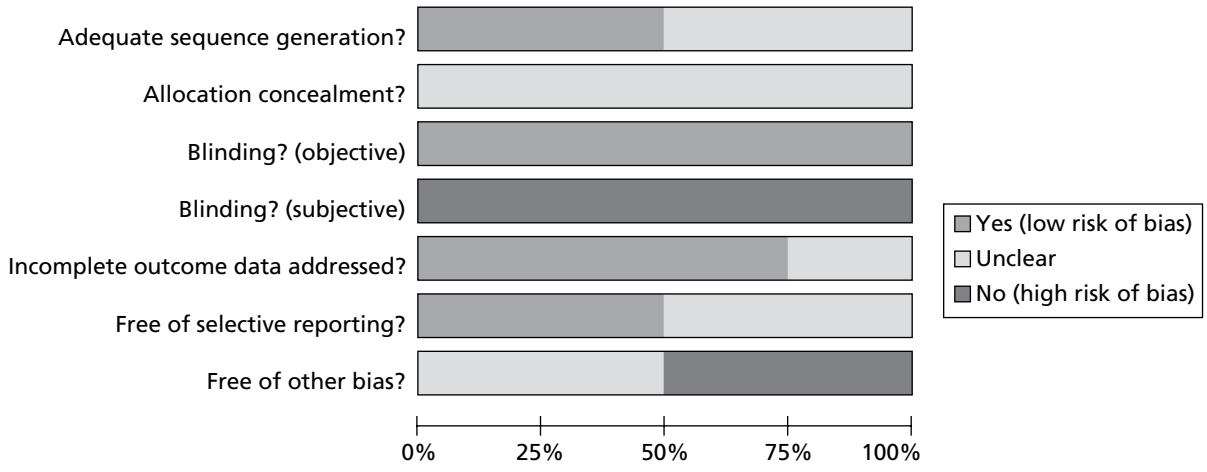

FIGURE 27 Summary of the quality assessment of the four included RCTs: [61,67,75,83] non-platinum agents.

TABLE 39 Overall survival: non-platinum agents

Study	Comparison	Median OS, months (range)	Hazard ratio (95% CI)
Greenberg 1977[67]	ADM	4	NR
	ADM + BLEO	4.3	
Monk 2010[75]	P	50.7[a]	0.67 (0.56 to 0.99)
	P + L	NR	
	L	39.1[a]	
Wallace 1978[83]	ADM	5.9	NR
	ADM + V	5.5	
	ADM + Cyclo	7.3	

BLEO, bleomycin; Cyclo, cyclophosphamide; L, lapatinib; NR, not reported; OS, overall survival; P, pazopanib; V, vincristine.
a Weeks.

TABLE 40 Progression-free survival: non-platinum agents

Study	Comparison	Median PFS, months (range)	Hazard ratio (95% CI)
Monk 2010[75]	P	18.1[a]	0.66 (0.48 to 0.91)
	P + L	NR	
	L	17.1[a]	
Wallace 1978[83]	ADM	3.3	NR
	ADM + V	3.4	
	ADM + Cyclo	3.9	

Cyclo, cyclophosphamide; L, lapatinib; NR, not reported; P, pazopanib; PFS, progression-free survival; V, vincristine.
a Weeks.

Response rate

There were no statistically significant differences between any of the non-platinum agents in the frequency of overall, complete and partial response rates (*Table 41*). In Monk *et al.*,[75] 9% of the pazopanib arm and four patients (5%) in the lapatinib arm achieved a confirmed tumour response. It should be noted that the unconfirmed response rate was 19% for pazopanib-treated patients and 9% for lapatinib-treated patients.

Quality of life

None of the RCTs reported quality of life.

Adverse events

Haematological grade 3 or 4 adverse events were presented in Monk *et al.*[75] and Wallace *et al.*[83] No statistically significant differences were observed between the treatment arms for neutropenia (pazopanib arm 2/74 vs lapatinib arm 0/76[75]), thrombocytopenia (ADM + vincristine arm 2/61 vs ADM arm 4/61 vs ADM + cyclophosphamide arm 1/52[83]), leucopenia (ADM + vincristine arm 15/61 vs ADM arm 15/61 vs ADM + cyclophosphamide arm 12/52[83]) and anaemia (pazopanib arm 2/74 vs lapatinib arm 4/76[75]). The frequency of non-haematological adverse events (grade 3 or above) was low in patients receiving non-platinum agents. The most common adverse event was diarrhoea (pazopanib arm 8/74 vs lapatinib arm 10/76[75]). In Monk *et al.*,[75] the results for nausea were 2 out of 74 patients in the pazopanib arm compared with 1 out of 76 patients in the lapatinib arm; for anorexia there were 2 out of 74 patients in

TABLE 41 Response rates (RRs): non-platinum agents

Study	Comparison	Response rate (95% CI)	Complete response rate (95% CI)	Partial response rate (95% CI)
Barlow 1973[61]	ADM vs BLEO	3.89 (0.22 to 68.67)	2.33 (0.11 to 48.99)	2.33 (0.11 to 48.99)
	ADM + BLEO vs ADM	0.53 (0.09 to 3.11)	0.53 (0.04 to 7.44)	0.53 (0.04 to 7.44)
	ADM + BLEO vs BLEO	2.19 (0.12 to 39.90)	1.31 (0.06 to 28.41)	1.31 (0.06 to 28.41)
Greenberg 1977[67]	ADM + BLEO vs ADM	NR	Not estimable	0.08 (0.00 to 1.21)
Monk 2010[75]	P vs L	1.84 (0.56 to 6.04)	1.05 (0.07 to 16.55)	2.11 (0.55 to 8.12)
Wallace 1978[83]	ADM + V vs ADM	0.75 (0.34 to 1.65)	0.14 (0.02 to 1.13)	1.60 (0.55 to 4.62)
	ADM + Cyclo vs ADM	0.68 (0.29 to 1.61)	0.50 (0.14 to 1.85)	0.94 (0.27 to 3.31)

BLEO, bleomycin; Cyclo, cyclophosphamide; L, lapatinib; NR, not reported; P, pazopanib; V, vincristine.

the pazapanib arm compared with 1 out of 76 patients in the lapatinib arm; and for vomiting there was 1 out of 74 patients in the pazapanib arm compared with none (out of 76 patients) in the lapatinib arm.

Radiotherapy or chemoradiotherapy

Study selection

Included in this section are studies in which participants have recurrent or persistent cervical cancer that was initially treated with surgery and who now have evidence of recurrence. The interventions are radiotherapy or radiotherapy with chemotherapy (chemoradiotherapy). The search for relevant studies did not identify any RCTs but 16 case series met the inclusion criteria: nine evaluated radiotherapy[84–92] and seven evaluated chemoradiotherapy.[93–99] The results of the quality assessment for the radiotherapy and chemoradiotherapy studies are presented in *Appendix 15*.

Radiotherapy

Population characteristics

The characteristics of the populations in the radiotherapy studies are presented in *Table 42*. Most of the nine case series[84–92] included a small number of patients (median 82 cases, range 18–130 cases). Study locations included the UK, the USA, Japan, the Netherlands and Germany. The majority of women presented with early-stage cervical cancer, but in three studies[86,87,91] there was no information about FIGO stage. The proportion of patients with recurrent or persistent disease in the pelvis as the only site of cancer (central recurrence) was lower than the proportion developing distant metastases. Patients with central recurrence, defined as confined to the vagina or paravaginal tissues not extending to the pelvis, constituted 44% of the total population in the included studies. Squamous cell carcinoma was the most common histological type of cancer, being present in 79% of patients; adenocarcinoma was present in 10.33%. The histological type was not available in four studies.

Description of the intervention

Descriptions of the salvage radiotherapy in curative intent and previous surgery are provided in *Table 43*. Radical hysterectomy was the most common previous surgery type and was performed in 61.8% of patients.

TABLE 42 Characteristics of patients: radiotherapy

Study	Study location	Population	Total *N*/*n* analysed	Age (years)	FIGO stage	Histological cell type	Site of disease
Ciatto 1980[84]	NR	Inclusion criteria: recurrence in the pelvis of carcinoma of the cervix uteri treated primarily by operation alone Exclusion criteria: previous radiotherapy, distant metastases, poor general condition, too extensive local disease, unsuitable even for palliative measures	115/110	NR	NR	NR	Central, 29; peripheral limited, 41; peripheral massive, 45
Deutsch 1974[85]	University Health Center of Pittsburgh, PA, USA	Inclusion criteria: recurrence following surgery of the primary tumour Exclusion criteria: advanced local recurrence invading adjacent bones, concomitant distant metastases, patients who received high dose of supervoltage pelvic irradiation as a prophylactic measure following surgery	38/34	NR	Benign, 4; carcinoma of stump, 3; carcinoma in situ, 1; stage I, 16; stage IIA, 3; stage IIB, 7; stage IIIA, 1; stage IIIB, 1; unknown, 2	NR	Limited to vagina, 3; vagina and parametrial mass, 6; vagina and pelvic wall mass, 4; pelvic wall mass, 12; parametrial mass, 2; bladder and rectum, 1
Hille 2003[86]	University Hospital, Göttingen, Germany	Inclusion criteria: patients treated primarily with radical surgery, developed recurrence, histologically confirmed recurrence Exclusion criteria: NR	26/26	Median 52	Stage IA/B, 18; stage IIA/B, 8; stage III or IV, 0	SCC, 22; ADC, 2; ASC, 1; AA, 1	NR
Ito 1997[87]	Department of Radiology, Keio University Hospital, Japan	Inclusion criteria: centrally recurrent tumours of the vaginal stump following hysterectomy for cervical cancer Exclusion criteria: NR	90/90	NR	NR	SCC, 90	Centrally recurrent tumours of the vaginal stump, 90
Jain 2007[88]	NR	Inclusion criteria: women who were diagnosed with locoregional recurrence after primary surgery alone, no adjuvant radiotherapy Exclusion criteria: palliative radiotherapy	147/130	Median 47, range 23–84	Stage 0, 1; stage I, 71; stage II, 7; missing, 51	SCC, 82; ADC, 25; ASC, 8; other, 6; unknown, 9	NR

continued

TABLE 42 Characteristics of patients: radiotherapy (*continued*)

Study	Study location	Population	Total *N*/*n* analysed	Age (years)	FIGO stage	Histological cell type	Site of disease
Jobsen 1989[89]	Department of Clinical Oncology, University Hospital of Leiden, the Netherlands	Inclusion criteria: locoregional recurrence following surgery of the primary tumour Exclusion criteria: concomitant distant metastases	18/18	NR	Stage IB, 17; stage IIA, 1	AC 2; UC 2; SCC 14	Limited to the vagina, 4; vaginal pelvic wall mass, 10; pelvic wall mass, 4
Lucraft 1981[90]	Christie Hospital and Holt Radium Institute, Manchester, UK	Inclusion criteria: postoperative residual or recurrent carcinoma of the uterine cervix Exclusion criteria: cervical stump carcinoma	82/82	Mean 51.9	Incidental findings, 35; carcinoma in situ, 27; stage IA, 6; stage IB, 12; stage III, 2	SCC 76; ADC 6	NR
Potter 1990[91]	University of Alabama at Birmingham, AL, USA	Inclusion criteria: patients with cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy, recurrence confined to the pelvis Exclusion criteria: NR	35/35	NR	NR	NR	Central pelvic, 23; lateral pelvic, 12
Tan 1991[92]	NR	Inclusion criteria: patients treated primarily with radical surgery, developed recurrence Exclusion criteria: NR	110/100	Mean 53	Stage IB, 43; stage IIA, 27; stage IIB, 3; stages IIIA and IIIB, 2; original staging not known, 25	NR	Central recurrence, 48; peripheral limited, 43; peripheral massive, 9

AA, adenoacanthoma; AC, anaplastic carcinoma; ADC, adenocarcinoma; ASC, adenosquamous carcinoma; NR, not reported; SCC, squamous cell carcinoma; UC, undifferentiated carcinoma/unknown carcinoma.

TABLE 43 Description of the intervention: radiotherapy

Study	Total *N*/*n* analysed	Previous therapy	Type of treatment	Interval between previous therapy and recurrence
Ciatto 1980[84]	115/110	Total hysterectomy without PLND, 89; radical hysterectomy with PLND, 26	External irradiation of the entire pelvis with supervoltage beams; the intended mid-pelvic absorbed dose ranged from 4000 to 5000 rad in 4.5–5.0 weeks. In case of central recurrence, booster dose was given with a vaginal mould delivering 3000 rad at the mucosal surface. In case of peripheral recurrence women were given the booster dose with external irradiation to a max. of 5500–6000 rad through reduced fields	Mean 18 months
Deutsch 1974[85]	38/34	Total hysterectomy or excision of a cervical stump without PLND, 17; radical hysterectomy with PLND, 21	Pelvic external supervoltage radiotherapy (6 MV, HVL 15 mm Pb) via four portals: anterior–posterior portals usually measured 15 × 15 cm on the skin and lateral portals 10 × 15 cm or 8 × 15 cm depending on the anterior–posterior diameter of the patient. The intended mid-pelvic absorbed dose usually ranged from 4500 to 5747 rad in 4.5–5.5 weeks (nominal standard dose = 1480–1729 ret) Additional intravaginal therapy: vaginal ovoid with radium calculated to deliver 5000 rad at the tissue surface in 35 hours (three patients)	Mean 1.8 years, range 3.5 months–6.4 years
Hille 2003[86]	26/26	Wertheim–Meigs surgery, 21; subtotal hysterectomy, 5	External irradiation without afterloading therapy: 39.6/50.4 Gy or 56 Gy was given to the whole pelvis with a four-field box technique; each field was treated daily. A boost to the site of recurrence of 10 Gy/9 Gy/10.8 Gy was given. If para-aortic lymph node metastases existed, they were treated with 46/50.4 Gy. In total, a dose of 50–64 Gy was delivered to the site of recurrence – patients with recurrence at the pelvic/rectal wall or in case of a high tumour burden intravaginally Combination of external irradiation and vaginal brachytherapy: 45/50.4 Gy was given to the whole pelvis by external beam radiotherapy using a four-field box technique. A boost of 9 Gy was given in case of tumours at the pelvic wall, sometimes with midline blocking respecting the afterloading applicator, sometimes without midline blocking. Each single field was treated daily. High-dose-rate brachytherapy using a single linear source arrangement was given with either 2 × 5 Gy or 3 × 5 Gy. If para-aortic lymph node metastases existed, they were treated with 46/50.4 Gy. In total, a dose of 55–65 Gy was delivered to the site of recurrence – patients with recurrence of the vaginal stump with low tumour burden	Median 26 months

continued

TABLE 43 Description of the intervention: radiotherapy (*continued*)

Study	Total *N*/*n* analysed	Previous therapy	Type of treatment	Interval between previous therapy and recurrence
Ito 1997[87]	90/90	Hysterectomy	Intracavitary radiotherapy or a combination of external and intracavitary External irradiation, using a 6-MV photon beam, was given to 10/43 patients with small tumours, 18/33 with medium tumours and 8/14 with large tumours. Whole-pelvis irradiation (50 Gy) was delivered using conventional anterior–posterior parallel opposed fields. Following 30 Gy, a central shield (4-cm width) was inserted to cover the brachytherapy target area in the patients with small or medium tumours, to avoid overdosage to the bladder and rectum. Patients with large tumours received 50 Gy whole-pelvis irradiation without a central shield. All patients in this series received high dose rate intracavitary brachytherapy using a caesium-137 source (7.4×1010 Bq) for each colpostat. Patients with small or medium tumours received 5 Gy intracavitary irradiation twice a week to a total dose of 30 Gy in six fractions. As an alternative fractionation schedule, some patients received 6 Gy irradiation once a week to a total dose of 24 Gy. Patients with large tumours received 15 Gy in three fractions or 12 Gy in two fractions	Median time to recurrence 28 months, range 3 months–36 years
Jain 2007[88]	147/130	Wertheim's hysterectomy, 79; simple hysterectomy, 44; subtotal hysterectomy, 2; another surgical procedure, 5	If disease in pelvic nodes only (55/130) external beam radiotherapy only was delivered using megavoltage photons, giving a homogeneous dose distribution with a four-field arrangement, in which the anterior and posterior fields are either rectangular (box) or hexagonal in shape Women with vault recurrence alone or with nodes (75/130) were treated with external beam and intracavitary radiotherapy to the vaginal vault – delivered using either low-dose rate, pre- and after-loaded caesium or high-dose-rate iridium sources, to give a dose equivalent of 48 hours of radium according to the Manchester system. The two most frequently used regimens were 45 Gy given in 20 fractions over 28 days (29/130) and 40 Gy given in 20 fractions over 28 days (28/130)	Median 1.3 years, range 24 days–14.9 years
Jobsen 1989[89]	18/18	Radical hysterectomy and pelvic lymphadenectomy, 13; total hysterectomy abdominal, 3; vaginal hysterectomy, 2	Whole-pelvis external supervoltage irradiation – cobalt or linear accelerator, using three or four portals; anterior–posterior portals measured 14.0×14.0 cm (median) and the lateral or oblique portals measured 12.0×14.0 cm (15 patients). Part of the pelvis was irradiated (two patients); vaginal applicator only (one patient) Total dose: 40.0–60.0 Gy, given in four to five fractions per week of 2.0–2.5 Gy (14 patients); 5080–6240 rad – patients treated with cobalt, three-weekly fractions given to a total dose (three patients); 60.0 Gy at a depth of 0.5 cm, patient treated with a vaginal application only (one patient)	Median 17 months, range 4–95 months

Study	Total *N*/*n* analysed	Previous therapy	Type of treatment	Interval between previous therapy and recurrence
Lucraft 1981[90]	82/82	Abdominal hysterectomy ± oophorectomy; vaginal hysterectomy; Wertheim's hysterectomy; radium treatment	Radical teletherapy to whole pelvis: anterior–posterior beams each 14×10 cm and two lateral beams of 10×10 cm giving a mid-pelvic dose of 4250 cGy in 3 weeks, using an 8-MeV linear accelerator. In patients who had not had previous surgery this dose could safely have been increased to 4750 cGy Radical teletherapy to whole pelvis plus brachytherapy to vaginal vault pelvis: technique was as described for radical teletherapy to whole pelvis followed by radium insertion to the vaginal vault (single 48-hour insertion of two Manchester ovoids giving a approximate dose at point A of 900 cGy) Radical brachytherapy to vaginal vault: single 96-hour insertion of two Manchester ovoids to vaginal vault giving an approximate dose at point A of 1800 cGy Palliative teletherapy to whole pelvis: technique used in most cases was similar to that described above for radical teletherapy to whole pelvis but the dose was reduced to 3250 cGy in eight fractions in 10–11 days Radical teletherapy to a volume less than the whole pelvis: patients with disease at the vaginal vault (four patients): three were treated by a MV symmetrical three-field technique and one by a MV 360° rotation. The volumes encompassed ranged from 7×7×7 cm to 8×8×8 cm and the doses from 5000 to 5250 cGy in 3 weeks Remaining patients: MV treatment by a parallel opposed pair of beams to disease in the left parametrium giving 4250 cGy in 16 fractions in 3 weeks	NR
Potter 1990[91]	35/35	Radical hysterectomy and pelvic lymphadenectomy, 35	31 patients were treated primarily and received 5000- to 6600-rad whole-pelvis therapy, with only three receiving < 5900 rad; four were retreated for recurrence after having received adjuvant pelvic radiotherapy after radical hysterectomy. Three patients received < 5000-rad whole-pelvis therapy because of failure to respond or the progression of disease. One patient was treated by interstitial implant to the vaginal lesion. Another received 3000-rad whole-pelvis irradiation followed by vaginal ovoids, receiving an additional 6000-rad surface dose	NR
Tan 1991[92]	110/100	Radical hysterectomy and PLND, 65; total hysterectomy, 15; unknown, 20	(1) (January 1980–December 1985) Mid-pelvic dose for central recurrence via anterior–posterior portals – 45 Gy followed by a local boost to the vaginal stump with 30 Gy delivered by a perineal teletherapy method. For the peripheral limited group, the anteroposterior mid-pelvic dose was 50 Gy followed by a boost of up to 10 Gy in the parametrium delivered via reduced portals. In the vaginal stump, a local boost of 15–20 Gy was delivered by the perineal teletherapy method (2) (1985–) Mid-pelvic anteroposterior dose – 36 Gy followed by a brachytherapy dose of 30 Gy at 0.5 cm beneath the vaginal mucosa and then teletherapy from anteroposterior portals with midline block up to a dose in the parametrium of 14–20 Gy. For the peripheral massive group, a palliative dose of 45–50 Gy was given to the midpelvis	Mean 20.4 months; 65% occurred within 2 years

HVL, half-value layer; max., maximum, NR, not reported; PLND, pelvic lymph node dissection.

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Results

Overall survival and progression-free survival The reported 2-year survival rates ranged from 12% to 85% and 5-year survival rates ranged from 2% to 82%. Patients with pelvic side wall recurrences were found to have poorer prognoses than patients with central recurrences only (range 2–15% and 42–82%, respectively, for 5-year survival). Data for 10-year overall survival were provided in Ito *et al.*,[87] with a 52% rate for patients with centrally recurrent tumours of the vaginal stump following hysterectomy for cervical cancer. Additionally, they showed that survival was greatly influenced by the tumour size of the vaginal stump so that the 10-year survival rate of patients with small-sized tumours was 72%, whereas the corresponding survival rate of patients with medium-sized tumours was 48% (*Table 44*).

Complications Five studies gave complication rates.[86–88,90,92] In Hille *et al.*,[86] grade 3 late toxicity was observed in 8% of patients, including intestinal bleeding after 7 months and fistulae between the rectosigmoid colon and the vagina, removed subsequently by surgery. In Ito *et al.*,[87] late complications of radiotherapy, including intestinal and urinary complications of grade 2 and grade 3, occurred in 32% of patients. In Jain *et al.*,[88] one patient suffered from morbidity in the sigmoid colon requiring surgical resection and in Lucraft[90] seven cases of complications were observed, including transient proctitis, intermittent haematuria and severe acute bowel reactions. In Tan *et al.*,[92] major complications included fistulae, proctitis and cystitis (see *Table 44*).

Chemoradiotherapy

Population characteristics

Seven studies[93–99] were identified and their baseline patient characteristics are provided in *Table 45*. Most included a small number of patients (median 30 cases, range 13–49 cases). Study location included the USA, the UK, Canada, Japan, Italy and the Netherlands. The majority of women presented with early-stage cervical cancer. In three studies[93,94,97] there were no data on FIGO stage. In each of the studies the proportion of patients with disease recurrent or persistence in the pelvis as the only site of cancer (central recurrence) was lower than the proportion developing distant metastases. Patients with central recurrence constituted 37% of the total population in the included studies. Squamous cell carcinoma was the most common histological type of cancer, being present in 77% of patients. The histological type was not available in Haasbeek *et al.*[94]

Description of the intervention

Descriptions of the salvage chemotherapy and radiotherapy given are provided in *Table 46*. Radical hysterectomy was the most common previous surgery type and was performed in 81% of patients.

Results

Overall survival and progression-free survival Overall survival and progression-free survival results are presented in *Table 47*. Results for 2-year survival ranged between 44% and 93%. Patients with central recurrences had a 63–69% 5-year survival rate; the rate for studies with mixed recurrence was between 41% and 47%; and the rate for patients with recurrence extending to the pelvic wall was between 18% and 28%. Data for 10-year overall survival were provided in Grigsby *et al.*[93] and Haasbeek *et al.*,[94] with a range of 33–35% with central recurrence or recurrence extending to pelvic wall. Survival rates were also available for subpopulations of patients with central recurrence (55%) and recurrence extending to the pelvic wall (15%). In Grigsby *et al.*,[93] 15-year overall survival for patients with central or with pelvic wall involvement was 35%. Central recurrences had a higher 5-year progression-free survival probability than those from all other patients (24–48% vs 1–27%).

Complications Grade 3/4 adverse events were observed in 27% of patients in Grigsby *et al.*,[93] 17% in Haasbeek *et al.*[94] and 31% in Maneo *et al.*[96] Tsuda *et al.*[98] presented results for particular adverse events: grade 3/4 leucocytopenia/neutrocytopenia – 66.7%; grade 4 haematological toxicity – 20%; grade 3

TABLE 44 Effectiveness results: radiotherapy

Study	Total *N*/*n* analysed	Overall survival	Disease-free status	Recurrence	Mortality/morbidity	Complications
Ciatto 1980[84]	115/110	2-year overall survival: central recurrence, 85%; peripheral limited recurrence, 47%; peripheral massive recurrence, 12% 5-year overall survival: central recurrence, 82%; peripheral limited recurrence, 31%; peripheral massive recurrence, 2%	Disease-free status: central recurrence, 24%; peripheral limited recurrence, 14%; peripheral massive recurrence, 1%	Recurrence: central, 4%; peripheral limited, 25%; peripheral massive, 44%	NR	NR
Deutsch 1974[85]	38/34	NR	Disease-free status: 15.7%	NR	Mortality: during therapy, 3; first year, 14; second year, 6; >2.5 years 10	NR
Hille 2003[86]	26/26	5-year overall survival: all 26 patients, 28%; central, without infiltration of the pelvic wall, 42%; central, with infiltration of the pelvic wall, 10%	5-year relapse-free survival: all 26 patients, 24%; central, without infiltration of the pelvic wall, 48%; central, with infiltration of the pelvic wall, 27%	Overall tumour relapse: all 26 patients, 14 (54%); only in the pelvis, 6; distant metastases, 3; both local and distant, 5 Median time to relapse: overall, 11 months; pelvis only, 6 months; distant metastases only, 16 months; pelvis and distant metastases, 11 months	NR	Late toxicity, 2 (8%)
Ito 1997[87]	90/90	5-year overall survival: 63% 10-year overall survival: 52%		Small size group: local failure, 10%; distant metastases, 11% Medium size group: local failure, 49%; distant metastases, 37% Large size group: local failure, 63%; distant metastases, 100%,	NR	Late complications of radiotherapy: grades 2 and 3 intestinal and urinary complications, 32%

continued

TABLE 44 Effectiveness results: radiotherapy (*continued*)

Study	Total *N*/*n* analysed	Overall survival	Disease-free status	Recurrence	Mortality/morbidity	Complications
Jain 2007[88]	147/130	2-year overall survival: all 130 patients, 40.2%; vault recurrence, 55.4%; nodal recurrence, 12.5%; vault and nodal recurrence, 24.5%	NR	Recurrence: pelvic only, 21 (16.2%); distant only, 20 (15.4%); pelvic and distant, 28 (21.5%); unknown, 14 (10.8%) Time to disease progression: median 21 months	Morbidity: 1/88 (1.1%)	Sigmoid colon, 1
Jobsen 1989[89]	18/18	Overall 5-year survival: 8 (44%)	5-year disease-free survival: 7 (39%)	Recurrence: 5 (28%); limited to the vagina, 0, vaginal–pelvic wall mass, 4, pelvic wall mass, 1	NR	NR
Lucraft 1981[90]	82/82	NR	NR	NR	Mortality: suspected residual disease, 7/44 (15.91%); definite residual disease, 9/10 (90%); recurrent disease, 15/28 (53.57%)	Transient proctitis, 3; intermittent haematuria, 2; severe acute bowel reaction, 2
Potter 1990[91]	35/35	NR	5-year disease-free survival: central pelvic recurrence, 6/20 (30%) (three patients excluded as <3 months' follow-up); lateral pelvic recurrence, 4/12 (33%)	NR	NR	NR
Tan 1991[92]	110/100	5-year survival rate: all 100 patients, 28%; central recurrence, 42%; group with peripheral limited recurrence, 15%	NR	Objective response: overall, 15 (15%); bone metastasis, 7 (7%); neck metastasis, 4 (4%); lung metastasis, 4 (4%); liver metastasis, 1 (1%)	NR	Proctitis, 5%; cystitis, 2%; vesicovaginal fistula, 2%; rectovaginal fistula, 2%.

NR, not reported.

TABLE 45 Characteristics of patients: chemoradiotherapy

Study	Study location	Population	Total *N*/*n* analysed	Age (years)	FIGO stage	Histological cell type	Site of disease
Grigsby 2004[93]	Mallinckrodt Institute of Radiology, St Louis, MO, USA	Inclusion criteria: diagnosis of recurrent cervical cancer after a radical hysterectomy and lymph node dissection; signed a study-specific informed consent approved by the Washington University Human Studies Committee; histologically confirmed recurrent cervical cancer Exclusion criteria: NR	22/22	Mean 40.8, range 30.5–64.3	NR	SCC, 17; ASC, 3; ADC, 1; GCC, 1	Vaginal apex, 8; lateral pelvic side wall disease, 9; vaginal apex and pelvic side wall, 5
Haasbeek 2008[94]	Academic Medical Center, Amsterdam, the Netherlands	Inclusion criteria: pelvic recurrence after hysterectomy Exclusion criteria: distant disease at time of recurrence, patients treated by surgery, patients who had previously received adjuvant postoperative radiotherapy, patients treated with palliative radiation schedules	35/35	Median 46, range 24–80	NR	NR	Pelvic wall, 20; central recurrence, 15
Ijaz 1998[95]	Department of Radiation Oncology and Department of Gynecologic Oncology, University of Texas, TX, USA	Inclusion criteria: recurrent cervical carcinoma after radical hysterectomy Exclusion criteria: concomitant distant metastasis, postoperative adjuvant radiotherapy	50/49	Median 35, range 20–76	Stage IB, 49; stage IIA, 1	SCC, 34; AC, 16	Vaginal limited, 5; paravaginal extension without pelvic wall involvement, 11; central, with pelvic wall extension, 13; isolated pelvic wall, 21; para-aortic lymph node samplings, 18

continued

TABLE 45 Characteristics of patients: chemoradiotherapy (*continued*)

Study	Study location	Population	Total *N*/*n* analysed	Age (years)	FIGO stage	Histological cell type	Site of disease
Maneo 1999[96]	Clinica Ostetrica Cinecologica, University of Milan, Italy	Inclusion criteria: biopsy-proven recurrent carcinoma of the uterine cervix after initial radical surgery, confined pelvis and/or para-aortic lymph nodes, no previous radiotherapy, WHO performance status not >2, adequate haematological function and hepatic function and a life expectancy of at least 3 months Exclusion criteria: clinical or radiological evidence of disease outside the pelvis or para-aortic nodes	35/30	Mean 49, range 27–74	Stage IB–IA, 26; stage IIB–III, 9	SCC, 32; ADC, 3	Central pelvis, 28; para-aortic metastases, 7
Thomas 1987[97]	Princess Margaret Hospital, Toronto, ON, Canada; the Wellesley Hospital, Toronto, ON, Canada	Inclusion criteria: patients previously treated with radical hysterectomy and pelvic lymph adenectomy who developed recurrence Exclusion criteria: clinical or radiological evidence of disease outside of the pelvis or para-aortic nodes	17/17	NR	NR	SCC, 13; AC, 1	Central pelvic disease, 2; central and pelvic side wall, 8; central plus side wall and para-aortic nodes, 1; side wall only, 2; side wall and para-aortic nodes, 4
Tsuda 2003[98]	Clinical Oncology and Radiation Oncology, Osaka City General Hospital, Japan	Inclusion criteria: local recurrence of cervical cancer without extrapelvic recurrence, age <75 years, an ECOG performance status of 0–2, no distant metastases Exclusion criteria: extrapelvic recurrence, distant metastases	15/13	Median 51, range 32–68	Stage I, 9; stage II, 5; stage III, 1	SCC, 9; ADC, 6	Central, 1; pelvic, 14
Virostek 1996[99]	University of Alabama at Birmingham, AL, USA	Inclusion criteria: patients treated primarily with radical surgery and who developed recurrence	30/30	<30 years, 7; 30–40 years, 9; 40–50 years, 12; >50 years, 2	Stage 0, 3; stage I, 2; stage IB, 24; unknown, 1	SCC, 23; ADC, 2; ASC, 4; other, 1	Central recurrence, 20; pelvic wall recurrence, 10

AC, anaplastic carcinoma; ADC, adenocarcinoma; ASC, adenosquamous carcinoma; GCC, glassy cell carcinoma; NR, not reported; SCC, squamous cell carcinoma; WHO, World Health Organization.

TABLE 46 Description of the intervention: chemoradiotherapy

Study	Total *N*/*n* analysed	Previous therapy	Type of treatment	Interval between previous therapy and recurrence
Grigsby 2004[93]	22/22	Radical hysterectomy, 22	External irradiation: s.d. 1.8 Gy midplane tumour, five fractions per week to the whole pelvis; dose to the whole pelvis was 50.4 Gy (22 patients) External irradiation without brachytherapy: t.t.d. ranged from 50.4 Gy to 70.2 Gy; t.t.d. for the four patients who received boost irradiation with interstitial brachytherapy ranged from 69.6 Gy to 86.6 Gy (18 patients) Four patients received additional interstitial brachytherapy, with low-dose rate after loading iridium-192 needles. The minimum tumour dose rate was about 0.40 Gy/hour Chemotherapy and irradiation were initiated and given concurrently Cisplatin 75 mg/m^2 on days 1, 22 and 43 with irradiation 5-fluorouracil i.v. at a dose of 1000 mg/m^2 for 4 consecutive days on days 1, 2, 3 and 4; days 22, 23, 24 and 25; and days 43, 44, 45 and 46 of irradiation	NR
Haasbeek 2008[94]	35/35	Radical hysterectomy, 7; abdominal hysterectomy, 6; vaginal hysterectomy, 3; Wertheim–Okabayash, 12; Wertheim, 4; other, 8	Radiotherapy: external beam radiotherapy to the whole pelvis, usually with a box technique, followed by a boost to the tumour by external beam radiotherapy, low-dose-rate brachytherapy or both, aiming at a total dose to the boost planning target volume of at least 60 Gy, but preferably higher. Brachytherapy was applied using a vaginal cylinder, ring or individually customised applicator to boost central tumour mass in the vaginal vault, when applicable (35 patients) Radiotherapy and hyperthermia: locoregional hyperthermia treatment using a four-waveguide applicator system. Thermometry catheters were placed in the rectum, bladder and vagina for temperature monitoring. The objective was to reach a temperature of 41 °C for at least 60 minutes for the vaginal measurement as surrogate for tumour temperature (six patients) Radiochemotherapy: chemotherapy – weekly courses of concurrent cisplatin (40 mg/m^2) (three patients)	Median 1.6 years, range 0.13–34 years
Ijaz 1998[95]	50/49	Radical hysterectomy and PLND, 50	External beam irradiation was delivered using anteroposterior opposing fields or anteroposterior plus lateral fields with 18- to 25-MV photon beams. Most patients who were treated with curative intent received 40–50 Gy to the whole pelvis at 1.8–2.0 Gy per fraction, followed by reduced fields of external beam irradiation or brachytherapy Chemotherapy with cisplatin and bleomycin with mitomycin C and/or fluorodeoxyuridine before radiotherapy – seven patients; three patients received neoadjuvant or concurrent intravenous chemotherapy	Median 10.5 months

continued

TABLE 46 Description of the intervention: chemoradiotherapy (*continued*)

Study	Total *N*/*n* analysed	Previous therapy	Type of treatment	Interval between previous therapy and recurrence
Maneo 1999[96]	35/30	Radical hysterectomy with systematic bilateral PLND, 29; radical hysterectomy with systematic bilateral PLND and chemotherapy, 6	External photon beam radiotherapy: 6- or 15-MV machine; four-field technique; whole-pelvic radiation dose was 50.4 Gy in 5 weeks at a rate of 1.8 Gy per day, five fractions per week. The initial dose was followed by an external boost of radiation to a smaller volume in patients with partial response and residual central pelvic disease, to a max. dose of 70 Gy. After a 2-week rest, patients with vaginal involvement received one or two intravaginal caesium applications (20 Gy at a depth of 0.5 cm from the vaginal mucosa). Patients with documented para-aortic nodal metastases received 45 Gy in 25 fractions with a shaped field for the para-aortic area Chemotherapy: CBDCA (75 mg/m^2 i.v.) administered in bolus on days 1–4; 5-fluorouracil (1000 mg/m^2/24 hours) administered by a 96-hour continuous infusion. Three cycles of chemotherapy were planned with a 4-week interval. The first two cycles of chemotherapy were administered during external radiotherapy; the third cycle was delivered in the ninth week of treatment	NR
Thomas 1987[97]	17/17	Radical hysterectomy and PLND, 17	Radiotherapy: with a 2.5-week interruption to allow the delivery of chemotherapy concurrently with each part of the radiotherapy. The radiation dose was 46 Gy in 24 fractions Chemotherapy: mitomycin C was given at a dose of 6 mg/m^2 by i.v. push on the first day of each part of the radiotherapy in eight patients. 5-fluorouracil was delivered by continuous intravenous infusion in 5% dextrose and water or in isotonic dextrose and saline, at a dose of 1 g/m^2 daily for the first 3 or 4 days of radiotherapy in each part of the split course. Eleven received 4-day infusions and seven received 3-day infusions	Median 6 months, range 1–165 months

Study	Total *N*/*n* analysed	Previous therapy	Type of treatment	Interval between previous therapy and recurrence
Tsuda 2003[98]	15/13	Radical hysterectomy, 10; total hysterectomy, 5	Chemotherapy: CBDCA was given as a 5-minute intra-arterial infusion without hydration just before pelvic radiation q.d. Dose escalation was performed. The starting dosage was 10 mg/m^2 q.d. At least three new patients were to be recruited for each dose level. If two of three patients at any dose level developed DLTs, the study was terminated. Three additional patients were treated at a dose level if one of the first three patients exhibited DLT. If at least four of six patients developed DLT at this level, then a MTD was said to have been reached The following dose levels were evaluated: 10, 15, 20 and 25 mg/m^2 Radiation: external pelvic irradiation was performed according to local standard schedules. The target volume was tumour and regional pelvic lymph nodes. External beam radiotherapy was given in daily fractions: 28 fractions of 1.8 Gy were given to the tumour and regional pelvic nodes; fractions were administered daily except for Saturday and Sunday Hyperthermia: after 20 Gy had been administered, the lesion was heated for 60 minutes with a Thermothron radio frequency-8 system (Yamamoto Vinita, Osaka, Japan), once a week for 4 weeks. Pelvic heating was performed with 30-cm electrodes operated anteroposteriorly or laterally. During the heating process, cold water (0–5 °C) was circulated in a cooling pool between the patient's skin and the electrodes. The treatment objective was the achievement of a tumour temperature ≥41 °C for a period of 30 minutes. The heat-up time was a max. of 60 minutes. If during heat up a temperature of 41 °C could not be achieved, treatment with the highest obtainable temperature was performed for 30 minutes. Power was applied to a max. wattage ranging from 600 W to 1200 W with a median of 900 W. Max. tumour indicative temperatures achieved ranged from 39 °C to 42 °C with a mean temperature of 40.6 ± 0.9 °C	NR
Virostek 1996[99]	30/30	Radical hysterectomy, 25; total hysterectomy abdominal, 3; total hysterectomy vaginal, 2	External beam irradiation: most patients were treated with the use of a four-field box technique; three patients were treated with a three-port perineal technique. The median dose given by the external beam was 50.4 Gy. All patients were treated at 1.8 Gy/day with the exception of two patients who received 2 Gy/day (12 patients) Brachytherapy: ovoids (four patients), vaginal cylinders (six patients), interstitial implant (three patients). Caesium-137 used in all patients treated with ovoids and five of six treated with vaginal cylinders. Iridium-192 used in all interstitial implants and one patient treated with a vaginal cylinder. Dose 0.5 cm when treating with vaginal cylinder; when treating with ovoids the dose was prescribed to 1.0 cm above the midplane between two colpostats; when treating with interstitial implant the dose was prescribed to a minimal peripheral dose encompassing 0.5 cm around all implant needles. Dose given with brachytherapy was then added to the external beam dose. Brachytherapy alone (one patient); external beam irradiation and brachytherapy (12 patients) Chemotherapy: therapeutic agents were either cisplatin or hydroxyurea concomitantly with radiotherapy (five patients), for persistence or recurrence after radiotherapy (15 patients)	NR

DLT, dose-limiting toxicity; i.v., intravenously; MTD, maximum tolerated dose; max., maximum; NR, not reported; PLND, pelvic lymph node dissection; q.d., every day; s.d., single dose; t.t.d., total tumour dose.

TABLE 47 Effectiveness results: chemoradiotherapy

Study	Total *N*/*n* analysed	Overall survival	Disease-free status	Recurrence	Mortality/ morbidity	Complications
Grigsby 2004[93]	22/22	5-year overall survival: 41% 10-year overall survival: 35% 15-year overall survival: 35%	NR	Recurrence: pelvic, 5; distant, 9	NR	Grade 3 in 18%; grade 4 in 9% Long-term complications: leg oedema, 7 (32%); DVT, 6 (27%); grade 3 cystitis, 27%
Haasbeek 2008[94]	35/35	2-year overall survival: all 35 patients, 66%; recurrence extending to the pelvic wall, 45%; central recurrence, 93% 5-year overall survival: all 35 patients, 43%; recurrence extending to the pelvic wall, 28%; central recurrence, 63% 10-year overall survival: all 35 patients, 33%; recurrence extending to the pelvic wall, 15%; central recurrence, 55% Median survival: all 35 patients 3.8 years; recurrence extending to the pelvic wall, 1.5 years; central recurrence, 12.8 years; tumour ≤5 cm, 8.2 years; tumour ≥5 cm, 2.4 years	2-, 5- and 10-year disease-free survival: 62%, 45% and 41% respectively Actuarial pelvic control rate 2, 5 and 10 years: 62%, 45% and 41% respectively	Recurrence: isolated local, 8; isolated distant metastasis, 9; combined local recurrence and distant metastasis, 2	NR	Grade 3 toxicity, 6 (17%; actuarial after 5 years 21%); ileus, 5
Ijaz 1998[95]	50/49	5-year overall survival: all 50 patients, 33%; curative intent, 39%; palliative intent, 25%; patient with central recurrence, 69%; central recurrence with pelvic wall extension, 18% Median survival: 8 (range 3–16) months	NR	NR	NR	Major late treatment complications, 3; small bowel obstructions, 2 (6 and 8 years after treatment with radiotherapy alone); partial left hydronephrosis ,1 (8 years after external beam irradiation for a left pelvic side wall recurrence)

Study	Total *N*/*n* analysed	Overall survival	Disease-free status	Recurrence	Mortality/ morbidity	Complications
Maneo 1999[96]	35/30	2-year survival: 44% 3-year survival rate: 25%; patients with vaginal or central pelvic relapse, 71% Median survival: all patients, 21 (range 18–90) months; alive with no evidence of disease, 31 (range 18–90) months; died of disease, 15 (range 3–33) months; alive with tumour, 15 (range 8–24) months	Alive with no evidence of disease, 13 (37%)	Partial response: 11 (31%); vagina, 1; central pelvis, 1; lateral pelvis, 7; pelvis and aortic nodes, 2 Complete response: 15 (43%); vagina, 3; central pelvis, 7; lateral pelvis, 4; aortic nodes, 1 Stable disease: 1 (3%); lateral pelvis, 1 Progression of disease: 8 (23%); central pelvis, 2; lateral pelvis, 2; para-aortic nodes, 3; pelvis and aortic nodes, 1	NR	Grades 3–4 toxicity, 11 (31%); grades 2–3 leucopoenia, 7 (20%); grade 3 thrombocytopenia, 2 (6%)
Thomas 1987[97]	17/17	5-year survival: 8 (47%) Median survival: alive 8, range 21–58 months; died 9, range 4–17 months	Disease free, 9 (53%)	NR	NR	NR
Tsuda 2003[98]	15/13	Median survival: 22.3 (range 7–70) months	Median progression-free interval: 8.9 (range 2–55) months	Recurrence: 9/14 (60%);[a] pelvic cavity, 7; liver, 1; lung, 1	NR	Grade 3/4 leucocytopenia/ neutrocytopenia, 10 (66.7%); grade 4 haematological toxicity, 3 (20%); grade 3 thrombocytopenia, 1 (6.67%); grade 3 diarrhoea, 3 (20.0%); haematuria (grade 1 or 2), 6 (40%); subcutaneous burns, 5 (33.3%)
Virostek 1996[99]	30/30	<1 year overall survival: 15 (50%) >2 years overall survival: 9 (30%) Median survival: central recurrence, 14.5 months; pelvic wall recurrence, 9 months	Disease-free 5-year survival: 3 (10%)	NR	NR	NR

DVT, deep-vein thrombosis; NR, not reported.

a One patient had no data.

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thrombocytopenia – 6.67%; grade 3 diarrhoea – 20.0%; haematuria (grade 1 or 2) – 40%; subcutaneous burns –33.3%. In Ijaz *et al.*,[95] major late treatment complications (small bowel obstructions, partial left hydronephrosis) were observed in 3 out of 49 patients. Long-term complications observed in Grigsby *et al.*[93] included leg oedema in 32% of patients, deep-vein thrombosis in 9% of patients and grade 3 cystitis in 27% of patients. In eight patients who survived beyond 5 years, the following grade 4 complications occurred: a vesicovaginal fistula (four patients), a rectovaginal fistula (three patients) and a life-threatening pelvic abscess (four patients) (see *Table 47*).

Surgery

Study selection

Included in this section are studies in which participants have recurrent or persistent cervical cancer that was initially treated with radiotherapy or chemoradiotherapy and who now have evidence of recurrence. The interventions are radical hysterectomy or Wertheim's operation and pelvic exenteration, and these two categories are described separately. The search found no relevant RCTs. Twenty-seven case series[100–126] fulfilled the inclusion criteria, most of which were retrospective, based on chart reviews. Most of the excluded papers were case series of gynaecological cancers as a whole without giving separate results for cervical cancer patients, or studies of cervical cancer patients with primary and recurrent tumour characteristics with the results described together. The results of the quality assessment are presented in *Appendix 16*. No measure of quality of life was provided in any of the included studies.

Radical hysterectomy population characteristics

Seven case series[100–106] gave information on radical hysterectomy (*Table 48*). They were published between 1965 and 1999 and were mostly from the USA, Canada and the European Union (Italy and Denmark). The number of participants ranged from 14 to 79. The mean or median age of patients was approximately 50 years. Most participants were classified at FIGO stage II and had squamous cell carcinoma.

Pelvic exenteration population characteristics

Twenty case series,[107–126] published between 1953 and 2009, presented results on pelvic exenteration, mostly from the USA (*Table 49*). The number of patients varied between 14 and 263. The mean or median age of the women was around 50 years (range 20–76 years). In many cases details about the baseline characteristics of the subpopulation of interest were incomplete but, in those publications in which the information was presented, most patients were classified as FIGO stage II and had squamous cell carcinoma.

Radical hysterectomy intervention

Descriptions of the interventions are provided in *Table 50*. In five studies,[100,101,103–105] radical hysterectomy was conducted as salvage surgery with curative intent. Tupper[106] described Wertheim's operation, and in Ibsen *et al.*[102] both Wertheim's operation and pelvic exenteration (which could be total, anterior or posterior) were combined with pelvic lymph node dissection. In all case series the primary therapy was radiotherapy. In Maneo *et al.*,[103] chemotherapy with cisplatin was also used postoperatively. The median time from previous therapy to salvage surgery in curative intention was between 7.5 and 19 months.

Pelvic exenteration intervention

Descriptions of the interventions are provided in *Table 51*. All patients in the case series had radiotherapy as their primary treatment. Total pelvic exenteration (TPE) was conducted most often compared with anterior or posterior pelvic exenteration. Reconstructive procedures were performed frequently as part of the operations or scheduled at a time when the patient's condition allowed it.

Radical hysterectomy results

The results of the radical hysterectomy case series are presented in *Table 52*. Operative deaths occurred in Rubin *et al.*[104] – 10% (from sepsis); postoperative deaths were analysed in four studies and occurred

TABLE 48 Population characteristics: radical hysterectomy case series

Study	Study location	Population	Total *N*/*n* assessed	Age (years)	FIGO stage	Histological type	Other disease specification
Adcock 1979[100]	University of Minnesota Hospitals, MN, USA	Persistent ($n = 31$) or recurrent ($n = 44$) CC	75/75	NR	Stage 0, 2; stage I, 40; stage II, 25; stage III, 5; unknown, 3	SCC, 62; ADC, 10; undifferentiated cancer, 3	Location of operative specimen tumour: none, 26; central, 41; central and nodes, 6; nodes only, 2
Coleman 1994[101]	Anderson Cancer Center, University of Texas, TX, USA	Centrally located and resectable CC. Recurrence: biopsy-confirmed lesions after NED >4 months from RT ($n = 32$); persistence: biopsy-confirmed tumours either grossly visible or growing up to 4 months after RT ($n = 18$)	50/50	Median 44 (range 23–70)	Stage IA, 2; stage IB, 14; stage IIA, 10; stage IIB, 7; stage IIIA, 2; stage IIIB, 2; unknown, 13	SCC, 46; ADC, 3; ASC, 1	Location of tumours: CC, 33; vagina, 6; vagina/cervix, 5; cervix, vagina and parametrium, 6 Nodes: negative, 34; positive, 5; not tested, 11
Ibsen 1988[102]	The Finsen Institute, Copenhagen, Denmark	Centrally located recurrent or persistent CC (no signs of invasion of the pelvic wall or distant metastases)	47/47	Median 56 (range 30–73, interquartile range 48–65)	Stage 0, 2; stage I, 14; stage II, 27; stage III, 3; unknown, 1	SCC, 40; ADC, 3; tumours from Gartner's duct, 2; cancer in situ, 2	Wertheim's operation: three patients had pelvic lymph node metastases; four did not have free resection edges Pelvic exenteration: six patients did not have free resection edges and one had pelvic lymph node metastases
Maneo 1999[103]	University of Bari, University of Milan, Italy	Centrally limited, invasive CC; 19 patients (56%) with recurrence (biopsy-confirmed lesions after NED >6 months after RT) and 15 (44%) with persistence (biopsy-confirmed tumours either grossly visible or growing within 6 months after RT)	34/34	Mean 49, median 51 (range 21–72)	Stage IB–IIA, 29; stage IIB, 4; stage IIIB, 1	SCC, 26; ADC, 8	Recurrence site: CC, 24; vaginal involvement, 4; parametrial involvement, 6; Lymph node involvement: pelvic, 6; pelvic and para-aortic, 1

continued

TABLE 48 Population characteristics: radical hysterectomy case series (*continued*)

Study	Study location	Population	Total *N*/*n* assessed	Age (years)	FIGO stage	Histological type	Other disease specification
Rubin 1987[104]	Memorial Sloan-Kettering Cancer Center, NY, USA	Small, central recurrence of CC	21/21	Mean 49 (range 27–67)	Stage IB, 4; stage IIA, 4; stage IIB, 11; stage IIIB, 1; stage IVA, 1	Epidermoid cancer, 17; ADC, 3; ASC, 1	21 patients with recurrence within 24 months of RT (13 of these within 1 year)
Terada 1987[105]	University of Michigan Medical Center, MI, USA	Centrally limited, invasive CC. Recurrence ($n = 13$) and one primary SCC of the upper vagina after pelvic irradiation for an endometrial ADC	14/14	Mean 54 (range 41–71)	Stage I, 8; stage II, 4; stage III, 1	NR	Regional metastatic disease at the time of SR, 6 (43%): pelvic lymph nodes, 5; unilateral ovarian, 1
Tupper 1965[106]	Victoria General Hospital, Dalhousie University, NS, Canada	Recurrent CC based on failure of the growth area to epithelialise within approximately 8 weeks of RT or the development of a dirty odorous ulcerative slough after previous epithelialisation with weight loss, as authors' indications	79/79	NR	NR	NR	40 patients: negative biopsy or no biopsy prior to SR Pre- and postoperative specimen: negative, 12; positive, 67

ADC, adenocarcinoma; ASC, adenosquamous carcinoma; CC, cervical cancer; NED, no evidence of disease; NR, not reported; RT, radiotherapy; SCC, squamous cell carcinoma; SR, surgery.

TABLE 49 Population characteristics: pelvic exenteration case series

Study	Study location	Population	Total *N*/*n* assessed	Age (years)	FIGO stage	Histological type	Other disease specification
Anthopoulos 1989[107]	University Hospital of the Pennsylvania State University, PA, USA	Primary, persistent or recurrent cancer of the cervix or vagina	20/14	NR	NR	NR	CC: primary, 1; persistent, 3; recurrent, 11
Barber 1971[108]	Memorial-James Ewing Hospitals, NY, USA	Recurrent or persistent CC	671/263	NR	NR	NR	Nodes: involved, 166; non-involved, 97 (10 patients had metastases to ovaries)
Beitler 1997[109]	Albert Einstein College of Medicine and Montefiore Medical Center, NY, USA	Recurrent CC	26/26	Mean 46.4, median 50.0 (range 29–76)	Stage I, 8; stage II, 9; stage III, 7; stage IV, 3	SCC, 1; ADC, 25	Seven patients had lymphovascular invasion or perineural involvement with clear margins. Two patients had microscopic nodal disease
Bricker 1960[110]	Washington University School of Medicine, St Louis, MO, USA	Persistent or recurrent pelvic malignancy	218/150	Range 20–70+	NR	NR	Cervix, 150
Brunschwig 1960[111]	Center for Cancer and Allied Diseases, USA	Gynaecological malignant neoplasms	592/161	NR	NR	NR	Recurrent CC, 161; pelvic lymph node metastases, 51
Chung 1983[112]	Milton S Hershey Medical Center, PA, USA	Recurrent CC	85/17	NR	NR	NR	CC treated with pelvic exenteration, 17
Deckers 1972[113]	National Cancer Institute, Bethesda, MD, USA	Recurrent CC	18/18	Mean age at the time of the second malignancy 53 (range 31–65)	NR	Primary epidermoid cancer, 17; primary sarcoma, 1	>5 years elapsed between initial irradiation and local recurrence

continued

TABLE 49 Population characteristics: pelvic exenteration case series (*continued*)

Study	Study location	Population	Total *N*/*n* assessed	Age (years)	FIGO stage	Histological type	Other disease specification
Hatch 1990[114]	University of Alabama at Birmingham, AL, USA	Recurrent CC	31/31	Median 47 (range 26–75)	Stage I, 13; stage II, 9; stage III, 4; stage IV, 2; unknown, 3	NR	Central recurrence, 28; complications from RT, 3
Ketcham 1970[115]	National Cancer Institute, National Institutes of Health, Bethesda, MD, USA	Primary or recurrent CC	162/94	NR	NR	SCC	Recurrent CC, 94
Kraybill 1988[116]	Ellis Fischel State Cancer Center (EFSCC), MO, USA	Advanced pelvic malignancy	99/58	NR	NR	NR	Recurrent CC, 58
Mikuta 1960[117]	University of Pennsylvania, PA, USA	Recurrent or persistent CC	28/18	Mean 43 (range 32–55)	Stage I, 7; stage II, 8; stage III, 3; stage IV, 0	NR	10 patients were found at laparotomy to be inoperative because of fixation in the pelvis or metastatic tumour in the aortic nodes and omentum
Mikuta 1967[118]	University of Pennsylvania, PA, USA	Recurrent or persistent CC	32/32	Mean 45 (range 32–67)	Stage 0, 1; stage I, 15; stage II, 10; stage III, 6; stage IV, 0	NR	
Palmer 1953[119]	Royal Society of Medicine, UK	Persistent or recurrent gynaecological malignancy	22/15	Range 38–70	NR	NR	Recurrent CC, 15
Pinelo 2002[120]	Instituto Português de Oncologia, Porto, Portugal	Recurrent or persistent gynaecological malignancy	21/14	Mean 52 (range 41–67)	NR	NR	CC: malignant lesions after RT, 13; side effects (inappropriate response), 1

Study	Study location	Population	Total *N*/*n* assessed	Age (years)	FIGO stage	Histological type	Other disease specification
Rutledge 1977[121]	University of Texas System Cancer Center, MD Anderson Hospital and Tumour Institute, TX, USA	Primary or recurrent gynaecological malignancy	296/196	NR	NR	NR	Recurrent CC, 196
Shingleton 1989[122]	University of Alabama at Birmingham, AL, USA	Recurrent CC	143/143	18% of patients <40 years, 19% of patients >60 years	Stage I and II, 66%; unknown, 21%	SCC, 133; ADC, 8; ASC, 2	Tumour involvement: bladder, 45; rectum, 16; pelvic nodes, 10
Stanhope 1990[123]	Mayo Clinic and Mayo Foundation, MN, USA	Recurrent CC	72/48	NR	NR	NR	48 patients were in non-palliative treatment after RT
Symmonds 1975[124]	Mayo Clinic, MN, USA	Recurrent or primary gynaecological malignancy	198/98	NR	NR	SCC, 98	Recurrent CC, 98
Teran-Porcayo 2006[125]	National Cancer Institute, Mexico	Recurrent or persistent gynaecological malignancy	76/42	Mean 45.1 (range 24–70)	Stage IA, 7; stage IIA, 2; stage IIB, 18; stage IIIB, 10; stage IVA, 1; non-classifiable, 4	SCC, 32; ASC, 9; ADC, 1	CC, 42
Viera 2009[126]	Universidade Federal do Piauí (UFPI), Brasil	Persistent or recurrent CC	16/16	Median 50 (range 26–76); 56.2% >50 years	stage IIA, 3; stage IIB, 10; stage IVA, 2	ADC, 1; cancer of the epidermis, 5	CC: persistent, 2; recurrent, 14

ADC, adenocarcinoma; ASC, adenosquamous carcinoma; CC, cervical cancer; NR, not reported; RT, radiotherapy; SCC, squamous cell carcinoma.

TABLE 50 Description of interventions: radical hysterectomy case series

Study	Total *N/n* assessed	Previous therapy	Surgery type	Interval between previous therapy and surgery
Adcock 1979[100]	75/75	External beam and intracavitary pelvic irradiation	Radical hysterectomy Note: Three patients also had resection of one distal ureter and the adjacent bladder with ureteroneocystostomy. Two patients had a radical cervicectomy for recurrence of the cervical stump. Bilateral pelvic lymphadenectomy was performed on 45 patients. Five patients had PLN biopsy only	Interval between original staging and SR: <6 months, 31; 6–12 months, 11; 12–24 months, 15; 24–60 months, 7; 5–10 years, 7; >10 years, 4
Coleman 1994[101]	50/50	RT: 40 (80%) 40–45 Gy external beam plus intracavitary irradiation; 6 (12%) only external beam irradiation; 4 (8%) only BT	Radical hysterectomy: class II, 11; class III, 28; class V, 6; and vaginal, 5. Note: 39 patients (78%) had either pelvic lymphadenectomy (33 patients) or PLN biopsy (six patients). Additionally, after radical hysterectomy, eight patients underwent curative pelvic exenteration	The disease-free interval for recurrence patients ranged from 4 to 301 months (median 16 months) and for diagnosis of persistence to SR was 2 months (range 1–4 months)
Ibsen 1988[102]	47/47	Vaginal or intracervical RT with 40 Gy external irradiation. Note: Two patients with stage 0 cancer had been hysterectomised 2 and 7 years before RT	Wertheim's operation with PLND, 23; pelvic exenteration (TPE 8, PPE 2, APE 13) combined with PLND, 23	Median 19 months (interquartile range 11–62 months)
Maneo 1999[103]	34/34	All patients received a mean dose of 50 Gy (range 45–64 Gy) delivered by linear accelerator (18 MeV) to the whole pelvis, encompassing the para-aortic area in case of radiological evidence of PLN involvement. In addition, 28 patients received BT to a mean total dose of 70 Gy to point A. Six non-responding cases to external irradiation did not receive BT and underwent radical hysterectomy	28 patients (82%): radical hysterectomy class III with pelvic lymphadenectomy and aortic node sampling (≥3 months after RT). Six patients: adjunctive procedure. Four patients: urological reconstruction. Four patients: bilateral transposition into the pelvis of the rectus abdominis muscle. Seven patients with cervical lesions >4 cm or early parametrial involvement: three cycles of cisplatin-based CH preoperatively. Ten patients with pathological risk factors received four to six cycles postoperatively	Mean 9 months, median 7.5 months (range 4–30 months)

Study	Total *N*/*n* assessed	Previous therapy	Surgery type	Interval between previous therapy and surgery
Rubin 1987[104]	21/21	All patients had internal and external RT. Mean 4340 rad to the whole pelvis with conventional BT with afterloading tandem and colpostats	Radical hysterectomy Note: 15 patients had PLND ± para-aortic node biopsy and two patients had only para-aortic biopsy. Additionally, six of the 13 survivors had urinary diversion and two also had a colostomy	Median interval from initial diagnosis to recurrence 10 months
Terada 1987[105]	14/14	Pelvic irradiation; external beam irradiation was used in combination with intracavitary sources	Radical hysterectomy. In addition, 11 patients underwent a pelvic lymphadenectomy and four patients underwent a total or near-total vaginectomy; and one patient also underwent a segmental resection of the ureter with ureteroneocystostomy to insure an adequate margin around the tumour	Median 14 months (range 4 months–25 years)
Tupper 1965[106]	79/79	RT	Wertheim's operation. In 10 patients in whom either the ureter or the bladder seemed to be involved, the bladder was removed, transplanting the ureters into the sigmoid	Range 1–38 months (over half <26 weeks)

APE, anterior pelvic exenteration; BT, brachytherapy; CH, chemotherapy; PLN, pelvic lymph node; PLND, pelvic lymph node dissection; PPE, posterior pelvic exenteration; RT, radiotherapy; SR, surgery; TPE, total pelvic exenteration.

TABLE 51 Description of interventions: pelvic exenteration case series

Study	Total *N*/*n* assessed	Previous therapy	Surgery type	Interval between previous therapy and surgery
Anthopoulos 1989[107]	20/14	External beam RT to the pelvis (3000–8600 cGy); 13 patients were also treated with BT	CC: TPE recurrence, 8; persistence, 3; APE recurrence, 3. Out of the whole group ($n = 20$), 18 patients underwent ileal conduits for their urinary diversions and two underwent sigmoid conduits	NR
Barber 1971[108]	671/263	RT	Involved nodes ($n = 97$): TPE, 61; APE, 36. Seven patients received additional X-ray therapy and two patients underwent planned postoperative RT	<6 months, 22 patients; 6–24 months, 58 patients; 2–5 years, 10 patients; 5–18 years, seven patients
Beitler 1997[109]	26/26	External RT (dose >39.6 Gy): yes, 25; no 1. Tandem and ovoid insertion: yes, 19; no, 6. 'Definitive' surgery, 3 (one patient was treated with a radical hysterectomy and never received curative RT)	TPE	NR
Bricker 1960[110]	218/150	Irradiation Note: three patients pelvic exenteration – initial treatment of advanced CC	TPE	NR
Brunschwig 1960[111]	592/161	RT	APE; TPE	NR
Chung 1983[112]	85/17	RT, 14; SR, 3	TPE, 12; APE, 3; PPE, 1; radical hysterectomy, 1	NR
Deckers 1972[113]	18/18	External irradiation, 18; total hysterectomy, 1	APE, 1; TPE, 17 One patient also had a simultaneous unilateral radical groin dissection and another underwent a partial pubic bone resection	Mean interval between treatment of the primary neoplasm and biopsy of the second malignancy, 11.5 years (range 5–19 years)
Hatch 1990[114]	31/31	Standard doses of RT	TPE with LRA, 29; PPE with LRA, 2. Anastomosis: hand-sewn, 1; automatic circular stapling device, 30. Protective colostomies, 12; omental wrap, 13. SR for central recurrence of CC, 28	NR
Ketcham 1970[115]	162/94	RT	APE, 9; TPE, 81	NR
Kraybill 1988[116]	99/58	RT	TPE. Reconstruction of the urinary tract (ileal loop) in all patients	NR

Study	Total *N*/*n* assessed	Previous therapy	Surgery type	Interval between previous therapy and surgery
Mikuta 1960[117]	28/18	Recurrence after irradiation, 9; resistance to irradiation, 6; radiation necrosis, 1; inadequate therapy, 2	TPE, 14; APE, 4	Time from previous therapy until diagnosis of recurrence or radioresistance, 3 months–14 years (average 3.7 years)
Mikuta 1967[118]	32/32	Recurrence after irradiation, 17; resistance to irradiation, 13; extensive radiation necrosis, 1; inadequate SR or RT, 1	TPE, 26; APE, 6	Time from previous therapy until evidence of tumour growth, 3 months–16 years (mean 4.3 years); mean time to recurrence, 6.9 years
Palmer 1953[119]	22/15	RT, 14; previous SR, 1 (failed Wertheim)	APE, 4; TPE, 11	Range 5 months–2 years 5 months
Pinelo 2002[120]	21/14	Malignant lesions after RT, 13; side effects (inappropriate response), 1	TPE, 7; APE, 6	NR
Rutledge 1977[121]	296/196	RT	Pelvic exenteration	NR
Shingleton 1989[122]	143/143	RT, 120; radical hysterectomy, 6; adjunctive pelvic irradiation after simple hysterectomy, 17	TPE, 78; APE, 63; PPE, 2	Time from initial RT to exenteration: ≤1 year, 63; >1 year, 79; unknown, 1
Stanhope 1990[123]	72/48	RT	Pelvic exenteration	NR
Symmonds 1975[124]	198/98	RT	APE, 59; TPE, 36; PPE, 3	NR
Teran-Porcayo 2006[125]	76/42	The mean RT dose was 50 Gy on opposite fields to the total pelvis	APE, 22; TPE, 20; 22 patients were left with a sigmoid duct	Time from RT until diagnosis of recurrence: ≤1 year, 24; >1 year, 18
Viera 2009[126]	16/16	RT, 15; radical hysterectomy, 1. All patients had undergone external beam RT with a median dose of 65 Gy (range 45–76 Gy), of whom seven were subjected to a strengthening of BT with low-dose rate (median of 43.1 Gy)	APE, 9; TPE, 7. Adjuvant CH was indicated by the lymph nodes in one patient and the SR margins in two patients	Mean time from initial RT to pelvic exenteration, 23 months

APE, anterior pelvic exenteration; BT, brachytherapy; CC, cervical cancer; CH, chemotherapy; LRA, low rectal anastomosis; NR, not reported; PPE, posterior pelvic exenteration; RT, radiotherapy; SR, surgery; TPE, total pelvic exenteration.

in 0%,[105] 2% (from sepsis),[101] 2%[102] and 7.6%[106] of patients. Survival results were presented in all publications. Five-year survival rates ranged between 32% and 72% and 5-year survival rates with no evidence of disease ranged between 27% and 65%. In Adcock[100] and Coleman *et al.*,[101] 5-year survival rates were also available for subpopulations of patients with persistent cervical cancer (52% and 82% respectively) and recurrent cervical cancer (65% and 75% respectively). Ten-year survival rates were presented in Coleman *et al.*[101] only and were 60% for the total population, 68% for the persistent subpopulation and 54% for the recurrent subpopulation. The rate of recurrence was between 32% and 59%. Major complications included fistulae, which required further surgical interventions.

Pelvic exenteration results

The results of the pelvic exenteration case series are shown in *Table 53*. Operative mortality ranged from 0% to 22% and postoperative mortality from 15% to 33%. The total percentage of complications varied between 50% and 69%. Three studies[103,107,124] gave 2-year survival rates: Stanhope *et al.*[103] for the complete population only (75%), Anthopoulos *et al.*[107] based on the type of surgery used (TPE 73%, anterior pelvic exenteration 75%) and Symonds *et al.*[124] according to pelvic lymph node status (positive 29%, negative 54%). Five-year survival rates ranged from 33% to 66% with one very low exception (12%) in Bricker *et al.*[110] The 5-year survival rates after specific types of exenteration were 58%[122] and 71.5%[125] for anterior exenteration and 42%[122] and 64.6%[125] for total exenteration. When there were metastases to pelvic lymph nodes (positive status), 2–25% of patients survived 5 years. For patients without metastases to pelvic lymph nodes (negative status), 5-year survival was between 17% and 73% (but 5-year survival for TPE was 7%). The 10-year survival rate was presented in only one study (23%).[124] The rate of recurrence varied by type of exenteration and whether there was local or distant spread. General information about the incidence of complications was very scarce.

Summary of accuracy and effectiveness results and inputs to economic evaluation

Statement of principal findings

Diagnostic studies and subjective elicitation

- Six studies[20, 48–52] evaluating conventional imaging plus PET-CT, two studies[53,54] evaluating MRI, three studies[55–57] evaluating CT and one study[58] evaluating both MRI and CT were included.
- The dates of the studies varied between 1981 and 2009.
- Most of the studies were small and several reported only a subset of results in a form that could be converted to a 2×2 table.
- The quality of the studies was poor. Although most probably included a representative spectrum of cervical cancer, very little clinical information about participants was given. Most studies did not report the time gap between the imaging test and the reference standard and most studies did not describe the reference standard clearly enough for replication.
- The later studies evaluated PET-CT, whereas the earlier studies evaluated CT and MRI. The technical imaging standards have changed since the early studies (reported in the 1980s) and so these are no longer valid. None of the MRI or CT studies used current standard methods.
- Five of the six PET-CT studies evaluated the whole body for recurrences and one reported extrapelvic recurrence only. Five of the six CT and MRI studies evaluated pelvic recurrences only and the newest evaluated whole-body recurrences, but this study included only 36 participants.
- Meta-analysis was conducted on PET-CT studies, which gave a combined sensitivity of 92.2% (95% CI 85.1% to 96.0%) and a specificity of 88.1% (95% CI 77.9% to 93.9%). Meta-analysis was not appropriate for the MRI and CT studies because of clinical heterogeneity.
- There was one study on the diagnostic and therapeutic impact of PET-CT,[20] which found that it had an impact on management in 12 (out of 52) patients and additional invasive diagnostic procedures in nine patients and assisted in planning therapy in nine patients.

TABLE 52 Results: radical hysterectomy case series

Study	Total *N*/*n* assessed	Survival data	Mortality data	Recurrence	Major complications
Adcock 1979[100]	75/75	5-year survival (NED): total, 49/75 (65%); persistent cancer, 16/31; recurrent cancer, 33/44	DOD, 22/75 (29%); dead of other causes, 4/75 (5%)	Recurrence or metastasis, 24/75 (32%)	Urinary tract or rectal or both: 31/75 (41%); three patients died as a result Fistulae: 12 patients (two multiple) Other complications: 23 patients (14 patients also urinary tract or rectal)
Coleman 1994[101]	50/50	5-year survival: total, 72%; persistence, 82%; recurrence, 65% 10-year survival: total, 60%; persistence, 68%; recurrence, 54% Median time to death: total, 93 months (mean 141 months, range 1–467 months); persistence, 148.5 months; recurrence, 87.5 months	Postoperative death (sepsis): 1/50 (2%)	Recurrence: 23/45 (49%) Location of the failure: central, 9; regional, 10; distant, 2; no information, 2 Median time to recurrence after SR: 13.5 months. For five patients the site of 'secondary' recurrence could not be monitored	Total: 32/50 (64%); temporary severe, 11; permanent severe, 21 Fistulae: persistent disease ($n = 18$), 2; recurrent disease ($n = 32$), 12 Required surgical procedure: bladder dysfunction, 12%; ureteral injury, 14% (three patients urinary conduits)
Ibsen 1988[102]	47/47	5-year survival: 32% (there was no difference in survival rate between Wertheim's operation and pelvic exenteration). Expected rate 94%. Total 5-year survival for stage I, 27%; for stage II, 39%	Postoperative death (3 months): 1/47 (2%) (APE)	NR	Complication free (after 3 months): Wertheim operation 4/23 (17%); TPE 3/8 (38%); APE 7/13 (54%) Complications requiring major SR (urinary fistula): Wertheim operation, 10/23 (43%); PPE, 2/2 (100%)

continued

TABLE 52 Results: radical hysterectomy case series (*continued*)

Study	Total *N*/*n* assessed	Survival data	Mortality data	Recurrence	Major complications
Maneo 1999[103]	34/34	5-year survival: 49%; alive NED, 15/34 (44%); median time alive NED, 81 months (range 33–192 months)	DOD (metastases): 18/34 (53%) Median time of survival (patients with recurrence), 24 months (range 7–106 months)	Recurrence, 20/34 (59%): local, 16; abdominal, 3; para-aortic lymph node, 1 Median time to recurrence, 37 months (range 4–56 months)	Major (grades III–IV), 15/34 (44%) Major, required surgical procedure, 4/34 (12%)
Rubin 1987[104]	21/21	Overall survival: 13/21 (62%); median time of overall survival 73 months 5-year survival (NED): patients with postoperative fistulae, 6/10 (60%); alive NED, 12/19 (63%)	Operative death (sepsis), 2/21 (10%) DOD (patients with recurrence), 6/7 (86%)	Recurrence, 7/19 (37%); median time to recurrence 6 months Two patients died of operative complications	Postoperative (fistulae), 10/21 (48%) Required surgical procedure, 9/21 (43%)
Terada 1987[105]	14/14	5-year survival: total (NED), 27%; regional metastases ($n = 6$), 100%; no regional metastases ($n = 8$), 54% Mean time of survival: 30.5 months. Alive NED, 4/14 (29%)	Postoperative death, 0 DOD, 10/14 (71%)	Regional metastases, 6/14 (43%)	Required major surgical procedure, 4/14 (29%)
Tupper 1965[106]	79/79	5-year survival: 34/79 (43%) Survival related to interval between RT and SR: 1–6 months, 19/55; 6–12 months, 11/27; 1–3 years, 4/9	Early postoperative death, 6/79 (7.6%)	NR	Fistulae: total, 17/79 (22%) Required major surgical procedure (colostomy), 4/17 (24%)

APE, anterior pelvic exenteration; DOD, dead of disease; NED, no evidence of disease; NR, not reported; PPE, posterior pelvic exenteration; RT, radiotherapy; SR, surgery.

TABLE 53 Results: pelvic exenteration case series

Study	Total *N*/*n* assessed	Survival data	Mortality data	Recurrence	Major complications
Anthopoulos 1989[107]	20/14	2-year survival: TPE ($n = 11$), 73%; APE ($n = 4$), 75%	NR	NR	NR
Barber 1971[108]	671/263	5-year survival: non-involved nodes, 29/166 (17.5%); involved nodes, 5/97 (5.2%)	2-year mortality (involved nodes): 86/97 (88.7%); hospital mortality (involved nodes), 21/97 (21.6%); DOD, 64/71 (90.1%); dead, NED, 2/71 (2.8%) Note: 21 patients with involved nodes died in hospital, and another five patients lived >5 years; they are not included	NR	NR
Beitler 1997[109]	26/26	Alive with disease, 1/26 (4%); alive, NED, 14/26 (54%); 5-year survival, 63%; locoregional control, 66%	DOD, 9/26 (35%); dead unrelated to disease, 2/26 (8%)	Recurrence: 10/26 (38%) Site of recurrence: local/regional, 7; local/regional and distant, 1; distant 1, none 1	One patient died of therapeutic complications
Bricker 1960[110]	218/150	5-year survival (based on those at risk at 5 years): 25%; alive, 68/150 (45%)	Postoperative death, 10/150 (15%); DOD, 64/150 (43%); dead unrelated to disease, 3/150 (2%)	NR	81 patients had none, 50 had one, and 19 had more than one complication 15 out of 150 patients (10%) died of complications
Brunschwig 1960[111]	592/161	5-year survival: 20/161 (12%); without PLN metastases ($n = 110$), 19; with PLN metastases ($n = 51$), 1	Operative mortality: total 30/161 (19%); without PLN metastases ($n = 110$), 14; with PLN metastases ($n = 51$), 16	NR	NR
Chung 1983[112]	85/17	Alive NED, 6/17 (35%) – five patients after TPE and one after APE	Dead, NED, 2/17 (12%) – two patients after TPE DOD, 9/17 (53%) – five patients after TPE, two after APE, one after PPE and one after radical hysterectomy	NR	NR
Deckers 1972[113]	18/18	5-year survival (NED or significant complications): 6/18 (33%)	Postoperative mortality: 6/18 (33%) – patients died prior to discharge from the hospital, 7–108 days postoperatively. All were NED at autopsy DOD (metastases), 5/18 (28%)	Local pelvic recurrence, 2/18 (11%)	NR

continued

TABLE 53 Results: pelvic exenteration case series (*continued*)

Study	Total *N*/*n* assessed	Survival data	Mortality data	Recurrence	Major complications
Hatch 1990[114]	31/31	Survival: total 68%; 1-year 86% Overall survival in patients with central recurrence (cervix and/or vagina, $n = 18$) 89% One patient died 5 months postoperatively from lung cancer and 16/17 were NED	Operative mortality, 0; postoperative mortality, 10/31 (32%)	Recurrence: total, 9/31 (29%); pelvis, 6; distant, 2; both, 1	NR
Ketcham 1970[115]	162/94	5-year survival: PLN positive, 21; PLN negative, 69; PLN total, 90 5-year survival for APE: PLN positive, 2; PLN negative, 7; PLN total, 9 5-year survival for TPE: PLN positive, 19; PLN negative, 62; PLN total, 81	Operative mortality: 21/94 (22%) – 12 cases were sepsis Mortality related to late complications (no recurrence): 9/94 (10%)	Mean time to recurrence: 14 months	NR
Kraybill 1988[116]	99/58	5-year survival (1966–75, $n = 33$): 36.3% 5-year survival (1976–81, $n = 25$): 61.5% 5-year survival ($n = 58$): PLN positive, 25%, PLN negative, 48.7%, margins positive, 25%, margins negative, 44.2%	Operative mortality (1966–75): 6/33 (19.5%) Operative mortality (1976–81): 2/25 (7.1%)	NR	NR
Mikuta 1960[117]	28/18	Alive NED: total, 8; <1 year, 0; 1–2 years, 3; 2–4 years, 2; 4–7 years, 3. Three patients died postoperatively	Postoperative mortality: 3/18 (16.6%) – two patients died within 30 days of operation, one after 30 days without leaving hospital; four patients who died had tumour recurrence and two had metastases Dead: total, 7; <1 year, 4; 1–2 years, 2; 2–4 years, 1; 4–7 years, 0	NR	Postoperative: total, 12/18 (67%); required surgical intervention, 3
Mikuta 1967[118]	32/32	Survival over 5 years (patients operated 5–14 years before publication) 8/24 (33%). Patients with PLN free of tumour	Mortality: total 6/32 (18.7%); operative, 0; surgical (within 30 days), 3; hospital (after 30 days), 3	NR	Complications (patients operated 5–14 years before publication): 15/24 (63%) – 15 patients had 18 complications
Palmer 1953[119]	22/15	Alive with recurrence, 3/15 (20%); alive and well, 3/15 (20%). One more patient was alive with complications with no recurrence	DOD (recurrence): 4/15 (27%) Dead with no recurrence: 4/15 (27%)	NR	NR

Study	Total *N*/*n* assessed	Survival data	Mortality data	Recurrence	Major complications
Pinelo 2002[120]	21/14	Alive, NED, 8/14 (57%). Overall survival: 5 (35.7%) Mean time overall survival: 14.6 months	NR	NR	NR
Rutledge 1977[121]	296/196	Survival: 83/196 (42%) 5-year survival: total, 33.8%, died due to recurrence, 48.3%	NR	NR	NR
Shingleton 1989[122]	143/143	5-year survival: total ($n = 142$), 50%; APE ($n = 63$), 58%; TPE ($n = 77$), 42%. Median time of survival after recurrence: APE, 5.2 months; TPE, 2.8 months	Operative mortality: total, 9/143 (6.3%); APE ($n = 63$), 1; PPE ($n = 2$), 0; TPE ($n = 78$), 8	Recurrence: total, 69/143 (48%); APE ($n = 63$), 29; PPE ($n = 2$), 1; TPE ($n = 78$), 39 Median time to recurrence: APE, 12 months; TPE, 9.6 months	NR
Stanhope 1990[123]	72/48	Survival: 1 year, 85%; 2 years, 75%; 5 years, 52%	NR	NR	NR
Symmonds 1975[124]	198/98	Survival: 5 years, 33%; 10 years, 23% 2-year survival: PLN positive ($n = 30$), 29%; PLN negative ($n = 68$), 54% 5-year survival: PLN positive ($n = 30$), 15%; PLN negative ($n = 68$), 42%	NR	NR	NR
Teran-Porcayo 2006[125]	76/42	5-year survival: total 66%; patients with recurrence <1 year ($n = 24$), 78%; patients with recurrence >1 year ($n = 18$), 57% 5-year survival (type of SR): APE ($n = 22$), 71.5%; TPE ($n = 20$), 64.6%	Mortality: patients with recurrence <1 year ($n = 24$), 33.3%; patients with recurrence >1 year ($n = 18$), 22.2% Operative mortality (TPE): 2/42 (5%)	NR	Complications: total 21/42 (50%); APE ($n = 22$), 12; TPE ($n = 20$), 9 Complications (time of occurrence): early, 4; intermediate, 7; late, 6 Required surgical intervention: 16/42 (38%)
Viera 2009[126]	16/16	Alive with disease, 2/16 (12.5%); alive NED, 7/16 (43.8%); survival, 64.3% Mean follow-up: 11 months	DOD (recurrence), 6/16 (37.5%); dead unrelated to disease, 1/16 (6.3%) – reason for death was necrotising fasciitis in the lower limbs	Recurrence: 8/16 (50%)	Perioperative or postoperative: total, 11/16 (68.8%); required reoperation, 7 Most common were pelvic infection, wound infection and fistulae

APE, anterior pelvic exenteration; DOD, dead of disease; NED, no evidence of disease; NR, not reported; PLN, pelvic lymph node; PPE, posterior pelvic exenteration; SR, surgery;

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- The subjective elicitation exercise obtained opinions from 21 clinical experts using a structured questionnaire. The results for accuracy in symptomatic women were similar to those from the published test accuracy studies. No comparison was possible for asymptomatic women.
- There was insufficient information in the published literature to use the results as the base case for the economic evaluation and so the subjective elicitation results were used, with the published information in sensitivity analyses.
- The subjective elicitation found that the elicited increase in accuracy from adding PET-CT to CT or MRI was less than the elicited minimum important difference in accuracy required to justify its routine addition in clinical practice.

Effectiveness

- A total of 19 RCTs[60–83] on chemotherapy (25 papers), 16 case series[84–99] on radiotherapy and chemoradiotherapy and 27 case series[100–126] on radical hysterectomy and pelvic exenteration were included.
- The dates of the publications varied between 1953 and 2010.
- For chemotherapy, the quality of the RCTs was variable, with little information on allocation concealment and none using blinding of patients and outcome measurement.
- There was no information on the effectiveness of cisplatin used as a single therapeutic agent. In comparisons of cisplatin with multiple chemotherapy, cisplatin was associated with either similar or shorter overall survival and progression-free survival, but with fewer side effects.
- For the other chemotherapy comparisons there was too little information to be able to determine the most effective chemotherapeutic options.
- For radiotherapy, 2-year survival rates ranged between 12% and 85% and 5-year survival rates varied between 2% and 82%, depending on type and location of recurrence and TNM status. For chemoradiotherapy, 2-year survival rates varied between 44% and 93% and 5-year survival rates varied between 30% and 71%.
- For radical hysterectomy, 5-year survival rates varied between 32% and 100%; for pelvic exenteration, 5-year survival rates varied between 12% and 63%. In general, the lower survival rates were in the earlier case series. Pelvic exenteration had high rates of complications, when results were given.

Accuracy and effectiveness inputs to the economic evaluation

Accuracy inputs

A key question of this project was whether PET-CT imaging would be useful as routine surveillance after primary cervical cancer treatment was successful in asymptomatic or symptomatic patients or whether or not it should be used at follow-up to plan management when patients become symptomatic. The systematic review of accuracy studies did not yield any information on routine follow-up of asymptomatic patients. Therefore, the subjective elicitation was used as the base case for the economic model. The test accuracy study results were used within sensitivity analyses for the symptomatic branch of the model and, when we had both, the published test accuracy results were similar to those from the subjective elicitation.

Effectiveness inputs

Assessment of the systematic review indicated that meta-analysis was not possible in almost all treatment areas. Key points were to ensure that recruitment of patients and treatment given occurred later than 1990 because of the changes in treatment since then. Other factors taken into account were the correct outcome measured and reported, the size of the study and the quality of the study. For some outcomes, little up-to-date information was available and so a pragmatic decision was made to use information from the best-quality studies for inputs to the economic model.

A wide range of chemotherapeutic agents was assessed in the systematic review, but not all are in current use. Clinical advice and the SIGN guideline[3] suggested that cisplatin used on its own would be the best chemotherapeutic agent to incorporate into the model. A recent IMS Oncology Analyser data set (from

October 2003 to September 2008) provides NHS clinical practice prescribing to women with recurrent or advanced cervical cancer (*Table 54*).[17]

Unfortunately, there were no RCTs investigating the effectiveness of cisplatin alone. The estimate of effectiveness was derived from an additional systematic review of cisplatin monotherapy compared with no treatment in any cervical cancer (as there was no evidence in recurrent cervical cancer). The methods and results from this systematic review can be found in *Appendix 17*. There was only one good-quality, relatively recent, RCT with a large sample size and a survival curve for ≥5 years.[127] This compared cisplatin (40 mg/m^2 weekly for 5 weeks) plus radiotherapy with radiotherapy alone in 259 women with cervical cancer of FIGO grades IB–IVA. The overall 5-year survival was approximately 63% in the cisplatin arm and 59% in the no cisplatin arm (log-rank test, $p = 0.53$) (estimate derived from enlarging survival curve to A3 size).

TABLE 54 NHS prescribed drugs for recurrent or advanced cervical cancer

Therapy	Number of patients	Percentage
5-Fluorouracil	1	2
5-Fluorouracil/cisplatin	1	2
5-Fluorouracil/mitomycin C	1	2
Bleomycin/cisplatin/folinic acid/methotrexate	2	4
Carboplatin	4	7
Carboplatin/epirubicin	1	2
Carboplatin/etoposide	1	2
Carboplatin/gemcitabine	1	2
Carboplatin/ifosfamide	1	2
Carboplatin/paclitaxel	10	18
Cisplatin	22	39
Cisplatin/etoposide	1	2
Cisplatin/ifosfamide	1	2
Cisplatin/methotrexate	2	4
Cisplatin/paclitaxel	2	4
Cisplatin/topotecan	1	2
Docetaxel/gemcitabine	2	4
Mitoxantrone/paclitaxel	1	2
Topotecan	2	4
Total	57	100

Chapter 7 Systematic review of economic evaluations

The database searches identified 409 citations. No identified studies were considered to be relevant to the economic evaluation of PET-CT for the diagnosis of recurrent cervical cancer.

There were six published economic evaluations that were close to being relevant,[128–133] but these were related to the diagnosis (using other methods) and treatment options for locally advanced cervical cancer and for the treatment of recurrent cervical cancer. Of the four studies[128–130,132] on the diagnosis of recurrent cervical cancer, two[129,130] investigated the surveillance of squamous cell carcinoma antigen levels, one[128] focused on routine cytological surveillance following treatment for cervical cancer and the other[132] investigated surveillance strategies after treatment for cervical intraepithelial neoplasia. Of the two studies[131,133] related to the treatment of cervical cancer, one study's objective was to compare the cost-effectiveness of various treatment options for recurrent and stage IVB carcinoma of the cervix[133] and the other's objective was to investigate the cost-effectiveness of concurrent chemoradiotherapy in comparison with the cost-effectiveness of radiotherapy alone in locally advanced cervical cancer.[131] These six studies[128–133] were reviewed in full, but no useful information was taken from them for the economic modelling.

Chapter 8 Economic evaluation methods and results

Objective

The objective of the economic evaluation was to compare the cost-effectiveness of adding PET-CT imaging to standard practice with MRI and/or CT with that of standard practice with MRI and/or CT alone in the diagnosis of recurrent or persistent cervical cancer. Currently in the UK, patients with suspected recurrence will undergo the following investigations:

1. history taking and clinical examination (rectovaginal and speculum examination, assessment of inguinal/supraclavicular lymph nodes)
2. cross-sectional imaging by MRI or CT of chest, abdomen and pelvis
3. examination under anaesthesia, histological confirmation of any vaginal vault mass by biopsy.

The economic evaluation is intended to inform current diagnostic policy for suspected recurrent or persistent cervical cancer, and the value of information (VOI) was intended to highlight future research needs.

Development of the model structure

To assess the cost-effectiveness of the various diagnostic procedures, a state transition (Markov) model was developed using TreeAge Pro 2011 software (TreeAge Software Inc., Williamstown, MA, USA). A Markov model was the appropriate modelling approach for this evaluation because the time horizons available for both the imaging and the interventions were relatively long and because patients changed health states or experienced recurrent events over a long period of time.[134]

In the model, two diagnostic strategies were examined:

1. clinical examination, MRI and/or CT scan (which represents the standard practice that women receive during follow-up assessment)
2. clinical examination, MRI and/or CT scan with the addition of a PET-CT scan.

The starting point for the patients in the model was women who have previously been treated for primary cervical cancer with either surgery or chemoradiotherapy based on the cancer stage that was defined at diagnosis (*Table 55*). It was assumed in the model that women who were initially diagnosed with cervical cancer could receive three different management strategies, based on original stage at diagnosis, current development of the malignancy, tumour characteristics and fitness of the patient.

At 3 months' follow-up, if the results of the history and examination suggested the presence of malignancy-related abnormalities (from symptoms such as pain, vaginal bleeding, weight loss, neuropathy or swelling of the abdomen or legs), women will have undergone a biopsy to confirm the presence of persistent or recurrent cervical cancer. This means that a modelled cohort of women following a pathway for the detection and treatment of potential recurrent cervical cancer cannot be considered to be homogeneous. The accuracy of detection and the probability of treatment success in the recurrent stage were affected by the primary diagnosis and the treatment received previously. To address this issue, the same model structure was used for four separate analyses, to account for the following four cohorts of women based on their primary treatment:

TABLE 55 Percentages of women receiving initial treatment strategies for cervical cancer

Management	Percentage of women receiving care	Explanation
Surgery	30–40%[a]	Surgery typically involves radical hysterectomy or trachelectomy
	Of these, 70–80% are cured	No further treatment needed
	The remaining 20–30% of women receive adjuvant postoperative chemoradiotherapy	This is because the histological examination of the tumour has shown positive margins or there are positive lymph nodes, or because of tumour size or volume, lymphovascular space invasion or stromal invasion
Chemoradiotherapy	50–60%[a]	
	Of these, 70% of the women are cured	No further treatment needed
	The remaining 30% of women are those who have not responded to first-line treatment (chemoradiotherapy) and may have persistent disease	Persistent disease can be detected at 3 months' follow-up after initial course of treatment has finished
Palliative treatment with chemotherapy or radiotherapy (or both)	<5%[a]	

a Source: personal communication, Dr S Sundar, University of Birmingham, April 2011.

1. women who had undergone surgery for early-stage primary cervical cancer
2. women who, in addition to surgery as per cohort 1, had postoperative chemoradiotherapy for early-stage primary cervical cancer because of positive margins, etc.
3. women who had chemoradiotherapy for early-stage (stages I and IIA) primary cervical cancer but not surgery
4. women who had chemoradiotherapy for late-stage (stages IIB, III and IV) primary cervical cancer but not surgery.

For all cohorts of women, the clinical pathways and model structure are identical. *Figure 28* shows the illustrative Markov model structure and the health-state transitions that are possible within the model. The full tree diagram is shown in *Figures 37–43* in *Appendix 18*. Health states in the illustrative Markov model structure (see *Figure 28*) are shown in ovals and the arrows represent the transitions that can occur between health states. These 11 health states are described in *Table 56*. All women who had undergone treatment for primary cervical cancer will start in one of the following four groups: asymptomatic cancer at 3 months, asymptomatic without cancer, symptomatic without cancer or symptomatic cancer at 3 months. The transitions are as follows:

1. asymptomatic women with cancer at 3 months will move to
    i. asymptomatic recurrence
    ii. symptomatic recurrence
    iii. post treatment: asymptomatic cancer at 3 months
    iv. death
2. asymptomatic women without cancer will remain or move to
    i. asymptomatic recurrence
    ii. symptomatic recurrence
    iii. symptomatic without cancer
    iv. death
3. symptomatic women without cancer will remain or move to
    i. asymptomatic without cancer

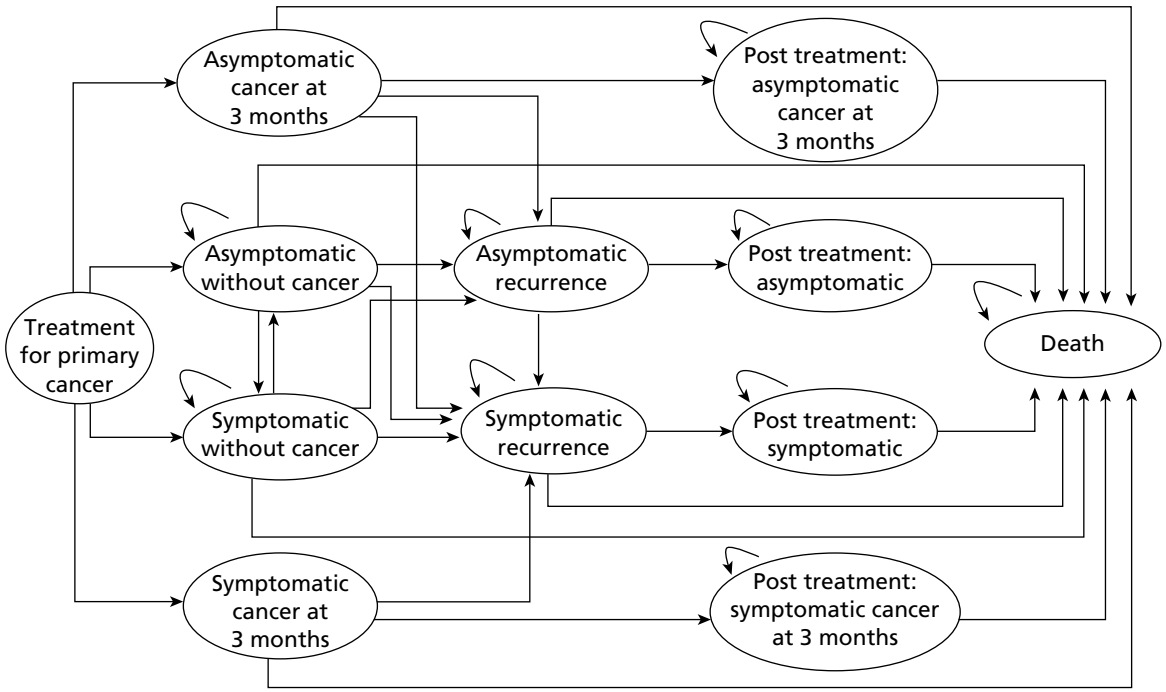

FIGURE 28 Markov model structure: health states and patient flow.

ii. asymptomatic recurrence
iii. symptomatic recurrence
iv. death

4. symptomatic women with cancer at 3 months will move to
   i. symptomatic recurrence
   ii. post treatment: symptomatic cancer at 3 months
   iii. death
5. asymptomatic women with recurrence will remain or move to
   i. post treatment: asymptomatic
   ii. symptomatic recurrence
   iii. death
6. symptomatic women with recurrence will remain or move to
   i. post treatment: symptomatic
   ii. death
7. post-treatment asymptomatic women with cancer at 3 months will remain or move to
   i. death
8. post-treatment symptomatic women with cancer at 3 months will remain or move to
   i. death
9. post-treatment asymptomatic women will remain then move to
   i. death
10. post-treatment symptomatic women will remain then move to
    i. death
11. death.

Model assumptions

A number of assumptions are required to develop a workable model structure and to enable the analysis to be carried out. These assumptions are:

TABLE 56 Definition of 11 health states for recurrent cervical cancer pathways

	Asymptomatic	Symptomatic
Cancer at 3 months	Women without symptoms of cancer who are likely to have recurrent or persistent cancer, which may or may not be detected at 3 months' follow-up	Women with symptoms of cancer who have been diagnosed with recurrent or persistent cancer, which may or may not be detected at 3 months' follow-up (i.e. symptoms may or may not be cancer)
Without cancer	Women who had previously been treated for initial cervical cancer and are receiving follow-up care, but are free of recurrent cervical cancer	Women who experience symptoms that they assume to be related to recurrent or persistent cervical cancer; however, on follow-up and confirmatory testing these women will be cleared of recurrent or persistent cervical cancer
Recurrence	Women without symptoms of cancer who have cancer that will not have been detected before a potential follow-up appointment; this may include women who may have had cancer not detected during the first 3 months' follow-up	Women with symptoms that are related to cancer who received follow-up care and who are confirmed as having recurrent or persistent cervical cancer
Post-treatment cancer at 3 months	Following diagnosis of cancer at first follow-up having been asymptomatic, women will receive new treatment (treatment type based on initial treatment and location of cancer recurrence or persistence)	Following diagnosis of cancer at first follow-up having been symptomatic, women will receive new treatment (treatment type based on initial treatment and location of cancer recurrence or persistence)
Post treatment	Following diagnosis of recurrent cervical cancer after being asymptomatic, women will receive new treatment (treatment type based on initial treatment and location of cancer recurrence or persistence)	Following diagnosis of recurrent cervical cancer after being symptomatic, women will receive new treatment (treatment type based on initial treatment and location of cancer recurrence or persistence)
Death	Women may die from natural causes or may die as a result of recurrent or persistent cervical cancer	

The model does not distinguish between recurrence and persistence. Women who had previously been treated for initial cancer with surgery and/or postoperative chemoradiotherapy or chemoradiotherapy are considered recurrent. Women who were originally treated with chemoradiotherapy who are detected at this stage are considered to have persistent disease.

Treatment for primary cancer is not included.

1. Women are followed up with examinations every 3 months for 2 years, then every 6 months for 2 years and then annually for 1 year, with the total follow-up being 5 years.
2. Women who were symptomatic at 3 months and whose cancer has not been detected cannot become asymptomatic.
3. Women with symptoms that they suspect are related to cervical cancer are usually given an urgent appointment or their pre-existing follow-up appointment is brought forward.
4. The sensitivity and specificity of the confirmatory biopsy test were 100% accurate.
5. Women who previously received chemoradiotherapy for primary cervical cancer and who are not diagnosed with persistence at 3 months' follow-up (i.e. not persistent or persistent cases missed) will be treated similarly to women with recurrent cervical cancer when detected.
6. The PET-CT procedure includes both the preparation and the scan of the patient; therefore, the preparation activity is implicit in the PET-CT scan resource use [NHS Reference Cost Team (anonymous) by email, pbrdatacollection@dh.gsi.gov.uk, 12 April 2011, personal communication].
7. Women who received treatment for primary cervical cancer and who have not survived at 5 years have died from recurrent cervical cancer only.
8. The utility for recurrent cervical cancer is equivalent to the average of the utilities for primary stage III and stage IV cervical cancer.
9. There is a constant hazard over 5 years for early-stage recurrent cervical cancer (i.e. the risk of recurrence is the same at 4 years as it is at 1 year).

10. Women treated for recurrent cervical cancer will have the same quality of life following treatment as they had after treatment for initial cervical cancer.

Data required for the model

Rates of recurrent cervical cancer

The model was populated with the rates of recurrent cervical cancer derived from the literature and in consultation with clinical experts. The rates of recurrence were calculated using a two-stage process. First, the survival following treatment for primary cervical cancer was derived from disease-free survival curves from Landoni *et al.*,[135] progression-free survival curves from Keys *et al.*[136] and overall survival curves following initial treatment from Landoni *et al.*[135] and Vale *et al.*[137] Information from these curves was used with the standard assumption of an exponential survival function. Three-month survival results were calculated for women who received surgical treatment, based on the disease-free survival curve presented in Landoni *et al.*[135] (*Figure 29*). Similar procedures were used to calculate survival following postoperative chemoradiotherapy and chemoradiotherapy. Second, the rates of recurrence were calculated, based on the initial survival of women in the branch of women who were symptomatic without cancer (see probabilities f1–f4 in *Tables 98–101* in *Appendix 18*), using the conditional probabilities following survival and the formulae presented in *Table 57. Table 58* shows the rates of recurrence used in the models.

Women enter the model at 3 months after initial treatment. If they have cancer at 3 months they enter the state 'Asymptomatic cancer at 3 months' or 'Symptomatic cancer at 3 months', but if they are free of cancer at this time they enter the state 'Asymptomatic without cancer' or 'Symptomatic without cancer'. In effect, the 3 months before entry in the model can be regarded as being represented by the probability tree shown in *Figure 30*.

Ideally, a separate data source would have been used to determine the proportions of women in each of these four states at the start of the model. In the absence of such a data source, it was necessary to make an assumption about these proportions. It was decided to use the probabilities for women moving from

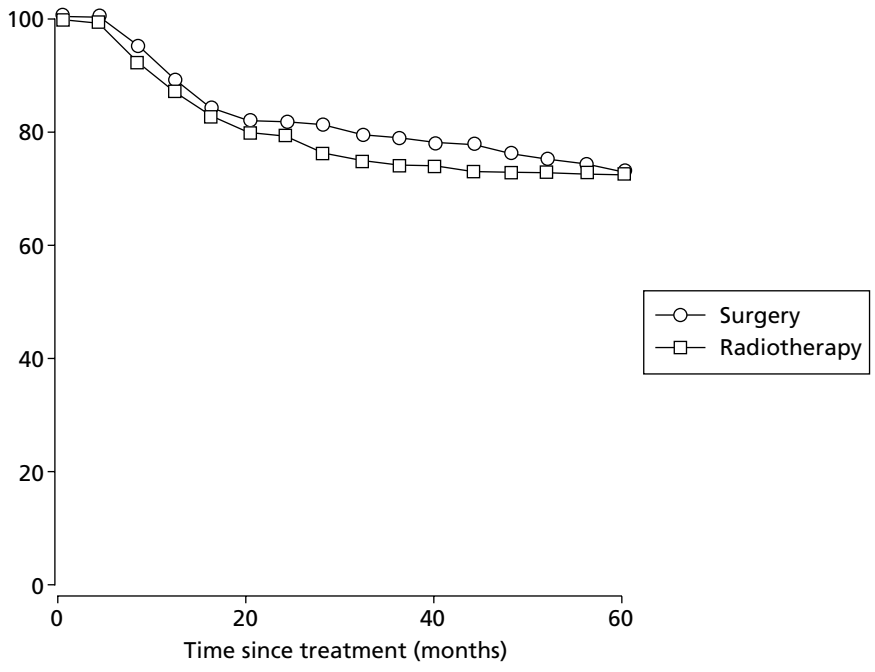

FIGURE 29 Disease-free survival from surgery and radiotherapy for stage IB–IIA cervical cancer (after Landoni *et al.*[135]).

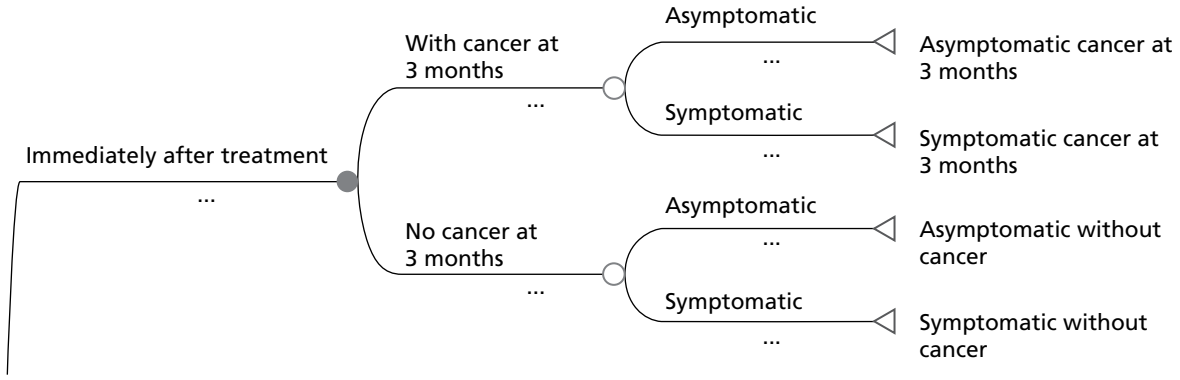

FIGURE 30 Initial 3 months following treatment (before entry into the model).

the state 'Symptomatic without cancer' (see *Tables 98–101* in *Appendix 18* for probabilities f2–f4) to give the necessary proportions. The way this was carried out is further detailed in *Table 57.*

Test accuracy results

Test accuracy results used in the model were based on the values estimated in the subjective elicitation exercise (see *Chapter 5* and *Table 14*). The predictive values, 95% CIs and probability distributions for MRI and/or CT and for PET-CT are shown in *Tables 59* and *60* respectively. Using the appropriate formulae, predictive values were converted to sensitivities and specificities to be used in the models. *Table 61* shows the accuracy data used in the base-case analysis. For sensitivity analysis, the uncertainty indicated in *Tables 59* and *60* was applied to the predictive values before conversion to sensitivity and specificity.

Survival following treatment

The results used in the model for survival following treatment for recurrence or persistence are shown in *Table 62.* Survival was reported in the systematic review in *Chapter 6*. From the systematic review, survival data from studies that followed up women following treatment for recurrent cervical cancer prior to 1990 were excluded. In cases in which 5-year survival after 1990 was not reported,[96] 2- and 3-year survival data were used. Note that these overall survival results are not given separately by the four FIGO stages.

From the results in *Table 62*, a weighted average of the 3-month survival following treatment was calculated, using weighting based on the percentages of people receiving the different treatments. *Table 63* shows the 3-month survival data used in the models.

Costs and resources

The costs of resources used were those that were directly incurred by the NHS. Costs for clinical examination, diagnostic imaging (PET-CT, MRI and CT), confirmatory biopsy and treatment were included (*Table 64*). Costs that were not considered were those incurred during the primary diagnosis and treatment of cervical cancer. Other costs not included were those for long-term and end-of-life care. In the models, recurrence was assumed to occur only once. Diagnostic procedure costs were taken from the *NHS Reference Costs 2009–2010*.[139] Cost estimates for chemotherapy and radiotherapy treatment were taken from Clark *et al.*,[140] and estimates for chemoradiotherapy were taken from Clark *et al.*[140] and were adjusted to 2010 prices using the Hospital and Community Health Services combined pay and price inflation index.[141] Estimated costs for the diagnosis of recurrent cervical cancer included costs for clinical examination, PET-CT, MRI and CT. These cost estimates were taken from the *NHS Reference Costs 2009–2010*[139] and published sources.[141] As a result of a paucity of cost-effectiveness studies comparing PET-CT as an adjunct with standard practice, an additive procedural cost of PET-CT as an adjunct to standard practice was assumed, as shown in *Table 64.* All costs were adjusted to 2010 prices and were discounted at 3.5% per annum.

TABLE 57 Formulae used to calculate the rates of recurrence of cervical cancer used in the models

Parameter	Written formula	Formula[a]
Asymptomatic at 3 months	(Probability of becoming recurrent having been symptomatic without cancer × probability of being asymptomatic recurrence conditional on recurrence)	(f2 × f3)
Asymptomatic without cancer	[(1 – probability of becoming recurrent having been symptomatic without cancer) × (probability of becoming asymptomatic without cancer conditional on no recurrence)]	[(1 – f2) × f4]
Symptomatic at 3 months	[Probability of becoming recurrent having been symptomatic without cancer × (1 – probability of being asymptomatic recurrence conditional on recurrence)]	[f2 × (1 – f3)]
Symptomatic without cancer	[(1 – probability of becoming recurrent having been symptomatic without recurrent cancer) × (1 – probability of becoming asymptomatic without cancer conditional on no recurrence)]	[(1 – f2) × (1 – f4)]

a See *Appendix 18* for tree diagram.

TABLE 58 Rates of recurrence of cervical cancer used in the models

	Surgery		Chemoradiotherapy		Postsurgery chemoradiotherapy		
Parameter	Early	Late	Early	Late	Early	Late	Source
Asymptomatic at 3 months	0.0041	–	0.0041	0.0041	0.0041	–	Derived from data from the literature and clinical experts
Asymptomatic without cancer	0.8907	–	0.8907	0.8907	0.8907	–	
Symptomatic at 3 months	0.0062	–	0.0062	0.0062	0.0062	–	
Symptomatic without cancer	0.0990	–	0.0990	0.0990	0.0990	–	

TABLE 59 Subjective elicitation summary accuracy results: MRI and/or CT

Characteristic	Predictive value	MRI and/or CT	95% CI	Probability distribution
Symptomatic	PPV	0.884 (SD 0.092)	0.8415 to 0.9265	Beta(188.77, 24.77)
	NPV	0.868 (SD 0.087)	0.8308 to 0.9112	Beta(226.38, 33.53)
Asymptomatic	PPV	0.856 (SD 0.098)	0.8107 to 0.9013	Beta(196.94, 33.13)
	NPV	0.900 (SD 0.077)	0.8644 to 0.9356	Beta(237.14, 26.35)

TABLE 60 Subjective elicitation summary accuracy results: MRI and/or CT with PET-CT

Characteristic	Predictive value	MRI and/or CT and PET-CT	95% CI	Probability distribution
Symptomatic	PPV	0.910 (SD 0.082)	0.8721 to 0.9479	Beta(295.75, 29.25)
	NPV	0.907 (SD 0.072)	0.8737 to 0.9403	Beta(299.31, 30.69)
Asymptomatic	PPV	0.902 (SD 0.077)	0.8664 to 0.9376	Beta(270.6, 29.4)
	NPV	0.934 (SD 0.055)	0.9086 to 0.9594	Beta(396.95, 28.05)

TABLE 61 Accuracy results used in the models

	Recurrent/persistent cervical cancer				
	Asymptomatic		Symptomatic		
Intervention	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Source
Recurrence after initial treatment					
Clinical follow-up and MRI ± CT	45.43	98.47	85.09	89.78	Elicitation exercise
Clinical follow-up, MRI ± CT and PET-CT	65.25	98.58	89.71	91.88	

TABLE 62 Overall survival for treatment options following recurrent or persistent cervical cancer

Treatment option	2-year survival (%)	3-year survival (%)	5-year survival (%)	Source
Radiotherapy	_	_	40.2 (95% CI 31.6 to 48.6) for whole group	Jain *et al.*[88]
Chemotherapy	_	_	64	Pearcey *et al.*[127]
Chemoradiotherapy	44	25	_	Maneo *et al.*[96]
Pelvic exenteration	_	_	63	Beitler *et al.*[109]
Untreated	_	_	3.1	Adriano *et al.*[138]

TABLE 63 Weighted 3-month survival data following recurrent cervical cancer

Model (initial treatment)	3-month survival	95% CI	Source
Model 1: Early stage, treated with surgery	0.9307	0.8842 to 0.9772	Derived from the survival literature and the proportions of women receiving treatment for recurrent cervical cancer
Model 2: Early stage, treated with chemoradiotherapy	0.9778	0.8526 to 0.9968	
Model 3: Late stage, treated with chemoradiotherapy	0.9779	0.8530 to 0.9969	
Model 4: Early stage, treated with surgery and postoperative chemoradiotherapy	0.9778	0.8526 to 0.9968	

TABLE 64 Cost data used in the model (all costs presented in 2010 UK pounds)

Description	Unit cost (£)	Source
Examination and imaging		
Clinical examination	28.17	Curtis 2010[141]
PET-CT	744.00	*NHS Reference Costs 2009–2010*[139]
MRI	366.00	*NHS Reference Costs 2009–2010*[139]
CT	162.00	*NHS Reference Costs 2009–2010*[139]
Confirmatory test		
Cone biopsy of cervix uteri NEC	968.00	*NHS Reference Costs 2009–2010*[139]
Treatment		
Surgical	6723.00	*NHS Reference Costs 2009–2010*[139]
Chemoradiotherapy	14,495.14	Brush *et al.*,[142] Curtis 2010[141]
Palliative		
Chemotherapy	356.56	Clark *et al.*,[140] Curtis 2010[141]
Radiotherapy	1167.79	Clark *et al.*,[140] Curtis 2010[141]
Weighted treatment costs		
Model 1	13,011.00	Derived from the literature and from consultation with clinical experts
Model 2	1629.85	
Model 3	993.20	
Model 4	1629.85	

NEC, neuroendocrine carcinoma.

Treatment of recurrent cervical cancer depends on the site and extent of recurrence, the type of previous treatment received, time elapsed since primary treatment and the patient's performance status. Treatment options for recurrent cervical cancer include surgery (radical hysterectomy or pelvic exenteration), chemoradiotherapy and palliative treatment (which can be chemoradiotherapy or radiotherapy). Treatment costs are presented in *Table 64.* In the models, a weighted mean cost of treatment was calculated based on the proportion of women who would receive each treatment. In model 1, for women who had previously received surgery for early-stage cervical cancer, treatment for recurrence was likely to be chemoradiotherapy in 85% of cases, exenteration in 10% of cases and chemotherapy for palliative care in the remaining 5%. The weighted treatment cost for model 1 was estimated at £13,011.00. In model 2, for women who had previously received chemoradiotherapy for early-stage cervical cancer, treatment for recurrence was likely to be chemotherapy alone for 80% of cases and exenteration for the remaining 20%. The weighted treatment cost for model 2 was estimated at £1629.85. In model 3, for women who had previously received chemoradiotherapy for late-stage cervical cancer, treatment for recurrence was likely to be chemotherapy alone in 90% of cases and pelvic exenteration for the remaining 10%. The weighted treatment cost for model 3 was estimated at £993.20. In model 4, for women who had previously received postoperative chemoradiotherapy for early-stage cervical cancer, treatment for recurrence was likely to be chemotherapy alone in 80% of cases and radical hysterectomy or pelvic exenteration for the remaining 20%. The weighted treatment cost for model 4 was estimated at £1629.85. (These percentage estimates were obtained in personal communication with Dr S Sundar, University of Birmingham, December 2011, as there was no published information available.) The proportions of women receiving treatment following recurrent cervical cancer, with their 95% CIs and probability distributions, are provided in *Tables 65–68* for models 1–4 respectively.

TABLE 65 Proportions of women receiving treatment following recurrent cervical cancer: model 1

Treatment following recurrence	Proportion	95% CI	Probability distribution
Chemotherapy	0.85	0.8075 to 0.8925	Beta(226.23, 39.99)
Surgery	0.10	0.0500 to 0.1050	Beta(44.65, 401.82)
Palliative care	0.05	0.0475 to 0.0525	Beta(1840.04, 34960.76)

TABLE 66 Proportions of women receiving treatment following recurrent cervical cancer: model 2

Treatment following recurrence	Proportion	95% CI	Probability distribution
Chemotherapy	0.80	0.7600 to 0.8400	Beta(309.98, 77.50)
Surgery	0.20	0.1900 to 0.2100	Beta(1183.93, 4735.74)

TABLE 67 Proportions of women receiving treatment following recurrent cervical cancer: model 3

Treatment following recurrence	Proportion	95% CI	Probability distribution
Chemotherapy	0.90	0.8500 to 0.9500	Beta(123.47, 13.72)
Surgery	0.10	0.0500 to 0.1050	Beta(44.65, 401.82)

TABLE 68 Proportions of women receiving treatment following recurrent cervical cancer: model 4

Treatment following recurrence	Proportion	95% CI	Probability distribution
Chemotherapy	0.80	0.7600 to 0.8400	Beta(309.98, 77.50)
Surgery	0.20	0.1900 to 0.2100	Beta(1183.93, 4735.74)

Outcomes

Three different effectiveness/outcome measures were used in the model: QALYs, recurrent case treated and death due to recurrent cervical cancer avoided. For the QALY calculations, utility weights for women who had been diagnosed with recurrent cervical cancer were obtained from Goldie *et al*.[143] The authors reported utility weights for women with invasive cancer by FIGO stage. An average weight based on stages III (0.56) and IV (0.48) was calculated, giving a utility for recurrent cervical cancer of 0.52. From the systematic review there were no studies that reported quality-of-life data following treatment for recurrent cervical cancer in a form that could be used in the model. It was assumed that women treated for recurrent cervical cancer would have the same quality of life as that following treatment for initial cervical cancer. Lang *et al.*[144] measured the health-related quality of life of Taiwanese women who have been treated for cervical cancer – this was associated with a quality of life of 0.87. In this paper the instruments used to measure health-related quality of life were the European Quality of Life-5 Dimensions (EQ-5D), Short Form questionnaire-8 items (SF-8) and the Karnofsky Performance Status (KPS). In the models, the results of the EQ-5D were used because it is recommended by NICE as the most appropriate measure to calculate QALY estimates. It is also useful because its responsiveness has been shown to be equal to that of the European Organisation for Research in the Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ C-30) global health status measure.[144] The utilities, 95% CIs and probability distributions used in the model are shown in *Table 69*.

Analysis

The recurrent cervical cancer model begins with a hypothetical cohort of women who have previously been treated for primary cervical cancer and who are now receiving follow-up assessment. The model estimates

TABLE 69 Utility data used in the model

Recurrence	Utility	95% CI	Probability distribution
Asymptomatic recurrence	0.87	0.8564 to 0.8836	Beta(2175, 325)
Symptomatic recurrence	0.52	0.3900 to 0.6500	Beta(28.6, 26.4)

the mean costs associated with the diagnostic procedure and assumes that women entering the model would be aged 50 years.

The model has a cycle length of 3 months. The follow-up pattern was every 3 months for 2 years and then twice a year for 3 years. This represents the follow-up pattern for women who were treated for initial cervical cancer. The model assumes a time period of 5 years; this represents the length of time that women are followed up after being diagnosed and treated and the time within which recurrent cervical cancer may be likely to occur.[32]

The model takes the form of a cost–utility analysis and was carried out from the UK NHS perspective in a secondary care setting. The primary outcome is cost per QALY, but a secondary outcome measure of cost per recurrent case treated was also estimated. The results of the cost–utility analysis are presented in terms of the incremental cost-effectiveness ratios (ICERs).

A deterministic sensitivity analysis was carried out on the 5-year survival rate for women who were untreated for recurrent cervical cancer (3.0%[138]–60%[127]). This wide range is because the estimate of 3% is from studies dated between 1906 and 1926 and it is likely that survival is now higher than this in untreated cervical cancer. As cervical cancer would now always be treated, it is unclear what the survival rate would be without treatment. The other inputs that were changed were the rates of symptomatic recurrence within 3 months of treatment and the utility values. Arbitrary values were used to explore the impact of changes on the results, given that the available data were poor. Rates of symptomatic recurrence within 3 months of treatment are given in *Table 99* (d1 = 0.9778) and *Table 100* (d2 = 0.9779) and these were changed to 0.9307, which is the lowest available estimate for surviving within 3 months of testing. The utility values used in the model were halved.

Probabilistic sensitivity analysis (PSA) was undertaken to determine the uncertainty in the model input parameters of prevalence, sensitivity and specificity, treatment costs and expected QALYs. PSA was carried out based on an outcome of cost per QALY only. In PSA, each model parameter was assigned a distribution reflecting the amount and pattern of its variation, and cost-effectiveness results were calculated by simultaneously selecting random values from each distribution. The process was repeated 10,000 times in a Monte Carlo simulation of the model to give an indication of how variation in the model parameters led to variation in the ICERs for a given test combination.

Value of information analysis

When a decision is not robust to plausible variation in the input parameters, it is possible to estimate a statistic known as the expected value of perfect information (EVPI). This is determined as a function of the threshold ICER, which allows a conversion from QALYs to monetary value. The preferred decision under uncertainty is determined by maximising the mean net benefit across the distribution of input parameter values. For any specific parameter set that leads to the same decision, there is no value of information attached to those parameters. If, however, a parameter set leads to a change in the decision, then the value attached to that parameter set is the difference in net monetary benefit between the decision made under uncertainty and the decision made knowing those parameter values. The EVPI is obtained by calculating the value attached to each parameter set used in the PSA and averaging across all parameter sets, taking into account the weightings determined by the probabilistic calibration described in the previous section.

Results of modelling

Results in terms of cost per quality-adjusted life-year

The base-case deterministic results of the strategies based on the cost per QALY are presented in *Tables 70–73*. The costs are adjusted to 2009/10 prices.

Model 1: women who have been treated for early-stage cancer by surgery

The results for model 1, women who have previously received treatment by surgery for early-stage cancer, are presented in *Table 70*. Standard practice had a mean cost of approximately £9169 with corresponding QALYs of 4.1086 compared with a mean cost of approximately £18,757 and 4.1096 QALYs for PET-CT together with standard practice. The estimated ICER for PET-CT together with standard practice compared with standard practice alone was £9,254,000 per QALY. This indicates that, for every additional QALY gained from the use of PET-CT as an adjunct to standard practice, there is an incremental cost of £9,254,000.

Model 2: women who have been treated for early-stage cancer by chemoradiotherapy

The results for model 2, women who have previously received chemoradiotherapy for early-stage cancer, are presented in *Table 71*. Standard practice had a mean cost of approximately £7695 with corresponding QALYs of 4.1501 compared with a mean cost of approximately £17,122 and corresponding QALYs of 4.1581 for PET-CT together with standard practice. The estimated ICER for PET-CT together with standard practice compared with standard practice alone was approximately £1,173,000 per QALY. This indicates that, for every additional QALY gained from the use of PET-CT as an adjunct to standard practice, there is an incremental cost of £1,173,000.

Model 3: women who have been treated for late-stage cancer by chemoradiotherapy and model 4: women who have been treated for early-stage cancer by postoperative chemoradiotherapy

Similarly, for models 3 and 4, the results are presented in *Tables 72* and *73* respectively. The mean costs for standard practice were £7612 and £7695 with QALYs of 4.1507 and 4.1501 respectively. The estimated ICERs for PET-CT together with standard practice compared with standard practice alone were approximately £1,065,000 per QALY for model 3 and £1,173,000 per QALY for model 4.

TABLE 70 Model 1 base-case results from the analysis based on cost per QALY

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (QALYs)	Incremental QALYs	ICER (£)
Standard practice	9169	–	4.1086	–	–
PET-CT together with standard practice	18,757	9588	4.1096	0.0010	9,254,000

TABLE 71 Model 2 base-case results from the analysis based on cost per QALY

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (QALYs)	Incremental QALYs	ICER (£)
Standard practice	7695	–	4.1501	–	–
PET-CT together with standard practice	17,122	9428[a]	4.1581	0.0080	1,173,000

a Apparent anomaly in subtraction is due to rounding effects.

TABLE 72 Model 3 base-case results from the analysis based on cost per QALY

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (QALYs)	Incremental QALYs	ICER (£)
Standard practice	7612	–	4.1507	–	–
PET-CT together with standard practice	17,031	9419	4.1595	0.0088	1,065,000

TABLE 73 Model 4 base-case results from the analysis based on cost per QALY

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (QALYs)	Incremental QALYs	ICER (£)
Standard practice	7695	–	4.1501	–	–
PET-CT together with standard practice	17,122	9428[a]	4.1581	0.0080	1,173,000

a Apparent anomaly in subtraction is due to rounding effects.

Results in terms of cost per recurrent case treated

The deterministic results for the cost per recurrent case treated were > £600,000 per case for all four models (*Tables 74–77*). In model 1 standard practice had a mean cost of approximately £9169 with corresponding cases treated of 0.1296 compared with a mean cost of approximately £18,757 and corresponding cases treated of 0.1436 for PET-CT together with standard practice. The estimated ICER for PET-CT together with standard practice compared with standard practice alone was £681,000 per case treated. This indicates that, for every additional case treated with PET-CT as an adjunct to standard practice, there was an incremental cost of £681,000. Similar results can be seen for models 2–4. PET-CT as an adjunct to standard practice was both more costly and more effective than standard practice alone, with an ICER of approximately £670,000 for each model.

Deterministic sensitivity analysis results

The deterministic results for the cost per recurrent case treated, presented in *Tables 74–77*, were > £600,000 per case for all four models. These results are summarised in *Table 78*.

Results of the probabilistic sensitivity analysis for the base-case cost per quality-adjusted life-year outcome

Figure 31 shows the Monte Carlo simulation for model 1. The scatterplot illustrates the uncertainty in the expected costs and QALYs based on PET-CT as an adjunct to standard practice compared with standard practice alone. For the 10,000 runs of the Monte Carlo simulation, the scatterplot shows considerable uncertainty about the additional expected costs and QALYs.

The scatterplots in *Figures 32–35* show the uncertainty surrounding the incremental expected costs and incremental expected QALYs for models 1–4, respectively, based on PET-CT as an adjunct to standard practice in comparison with standard practice alone. In each figure, for the 10,000 runs of the Monte Carlo simulation, the scatterplot shows considerable uncertainty about the additional expected incremental costs and QALYs.

The results for model 1 are presented in the form of cost-effectiveness acceptability curves (CEACs) in *Figure 36.* Analogous results were observed for models 2–4 (not shown). CEACs give the probability that a screening strategy is cost-effective given society's willingness to pay for a QALY. In other words, the CEAC shows the probability that PET-CT as an adjunct to standard practice is cost-effective compared with standard practice alone at different values for society's maximum acceptable cost-effectiveness

TABLE 74 Model 1 results from the analysis based on cost per recurrent case treated

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (cases treated)	Incremental cases treated	ICER (£)
Standard practice	9169	–	0.1296	–	–
PET-CT together with standard practice	18,757	9588	0.1436	0.0141[a]	681,000

a Apparent anomaly in subtraction is due to rounding effects.

TABLE 75 Model 2 results from the analysis based on cost per recurrent case treated

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (cases treated)	Incremental cases treated	ICER (£)
Standard practice	7695	–	0.1296	–	–
PET-CT together with standard practice	17,122	9428[a]	0.1436	0.0141[a]	670,000

a Apparent anomaly in subtraction is due to rounding effects.

TABLE 76 Model 3 results from the analysis based on cost per recurrent case treated

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (cases treated)	Incremental cases treated	ICER (£)
Standard practice	7612	–	0.1296	–	–
PET-CT together with standard practice	17,031	9419	0.1436	0.0141[a]	669,000

a Apparent anomaly in subtraction is due to rounding effects.

TABLE 77 Model 4 results from the analysis based on cost per recurrent case treated

Strategy	Mean cost per strategy (£)	Difference in costs (£)	Effectiveness (cases treated)	Incremental cases treated	ICER (£)
Standard practice	7695	–	0.1296	–	–
PET-CT together with standard practice	17,122	9428[a]	0.1436	0.0141[a]	670,000

a Apparent anomaly in subtraction is due to rounding effects.

ratio. The threshold used by NICE is between £20,000 and £30,000 per QALY, that is, society is willing to pay £20,000 per QALY for 1 year of life in full health. From *Figure 36* it can be seen that the use of PET-CT as an adjunct to standard practice alone is not likely to be cost-effective given the data used in the model. This is illustrated by no PET-CT (standard practice) having a probability of being cost-effective of approximately 100% and PET-CT (PET-CT as an adjunct to standard practice) having a probability of being cost-effective of approximately 0%. The implication of this result is that the VOI is necessarily zero across all thresholds, which means that further analysis of VOI was unnecessary.

TABLE 78 Summary of deterministic sensitivity analysis cost–utility results

	Incremental cost (£)	Incremental effectiveness	ICER (£)
Model 1			
Base case	9588	0.0010	9,254,000
1. Changing the 5-year survival following untreated cervical cancer (3.0% to 60%)	9528	–0.0072	(Dominance)
2. Halving the utility value for recurrent cervical cancer from 0.5200 to 0.2600	9588	0.0052	1,829,000
3. Changing the current follow-up schedule to annual follow-up	4974	0.0008	6,091,000
Model 2			
Base case	9428	0.0080	1,173,000
1. Changing the 5-year survival following untreated cervical cancer (3.0% to 60%)	9419	–0.0015	(Dominance)
2. Halving the utility value for recurrent cervical cancer from 0.5200 to 0.2600	9428	0.0122	771,000
3. Changing the current follow-up schedule to annual follow-up	4824	0.0069	697,000
Model 3			
Base case	9419	0.0088	1,065,000
1. Changing the 5-year survival following untreated cervical cancer (3.0% to 60%)	9413	–0.0007	(Dominance)
2. Halving the utility value for recurrent cervical cancer from 0.5200 to 0.2600	9419	0.0126	745,000
3. Changing the 3-month survival to 0.9307	9419	0.0027	3,527,000
4. Changing the current follow-up schedule to annual follow-up	4815	0.0072	673,000
Model 4			
Base case	9428	0.0080	1,173,000
1. Changing the 5-year survival following untreated cervical cancer (3.0% to 60%)	9419	–0.0015	(Dominance)
2. Halving the utility value for recurrent cervical cancer from 0.5200 to 0.2600	9428	0.0122	771,000
3. Changing the current follow-up schedule to annual follow-up	4824	0.0069	697,000

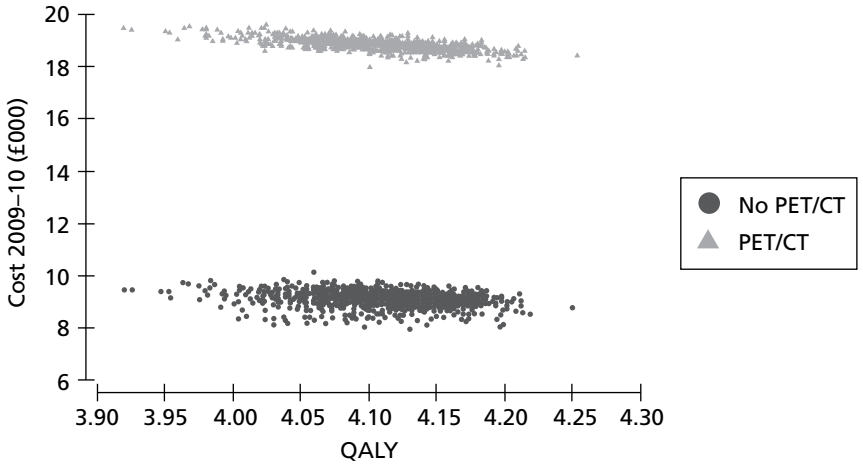

FIGURE 31 Scatterplot using distributions around the input parameters in model 1.

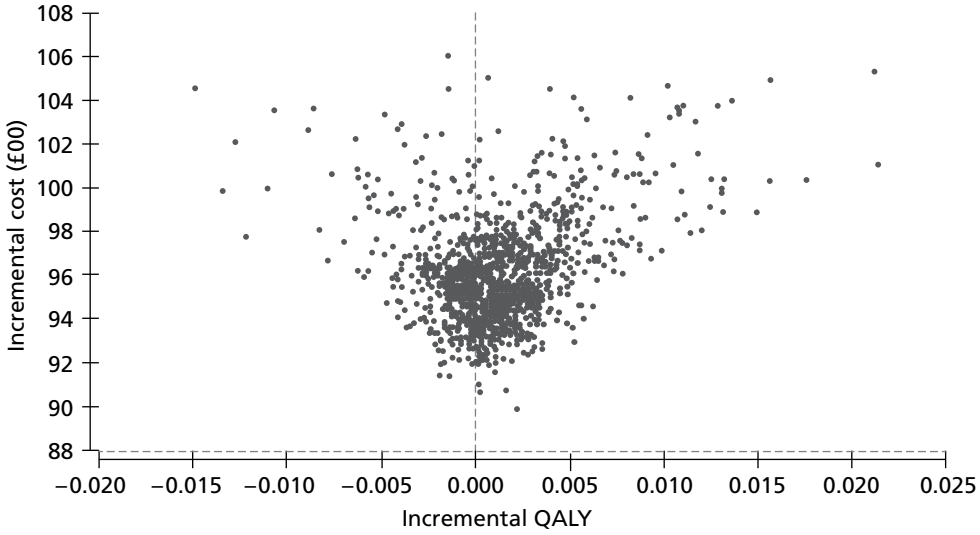

FIGURE 32 Scatterplot using distributions around the input parameters in model 1.

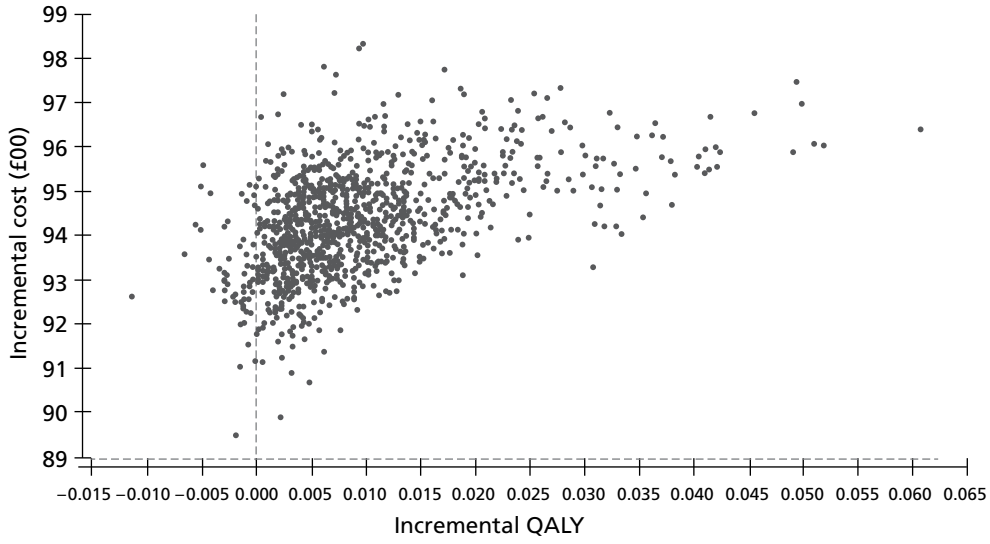

FIGURE 33 Scatterplot using distributions around the input parameters in model 2.

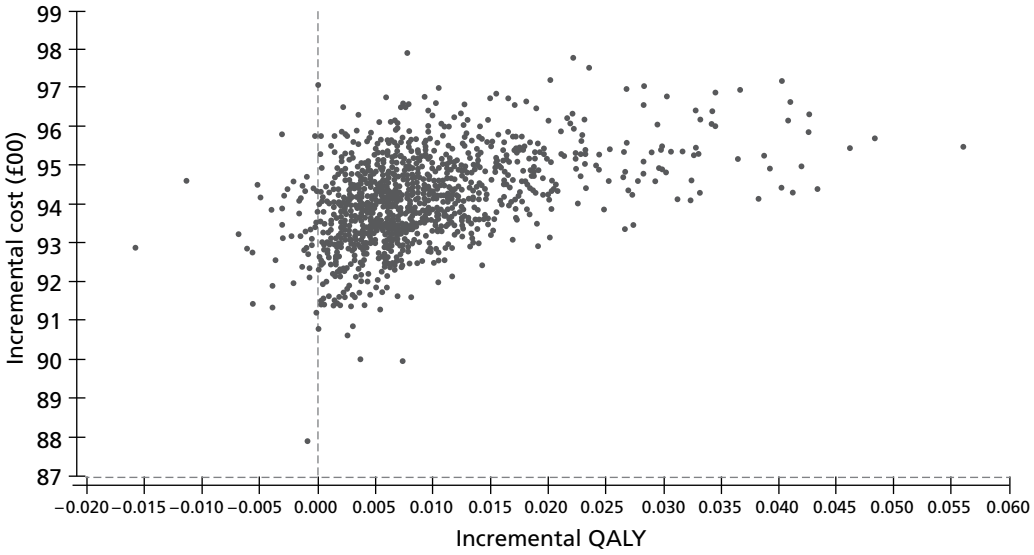

FIGURE 34 Scatterplot using distributions around the input parameters in model 3.

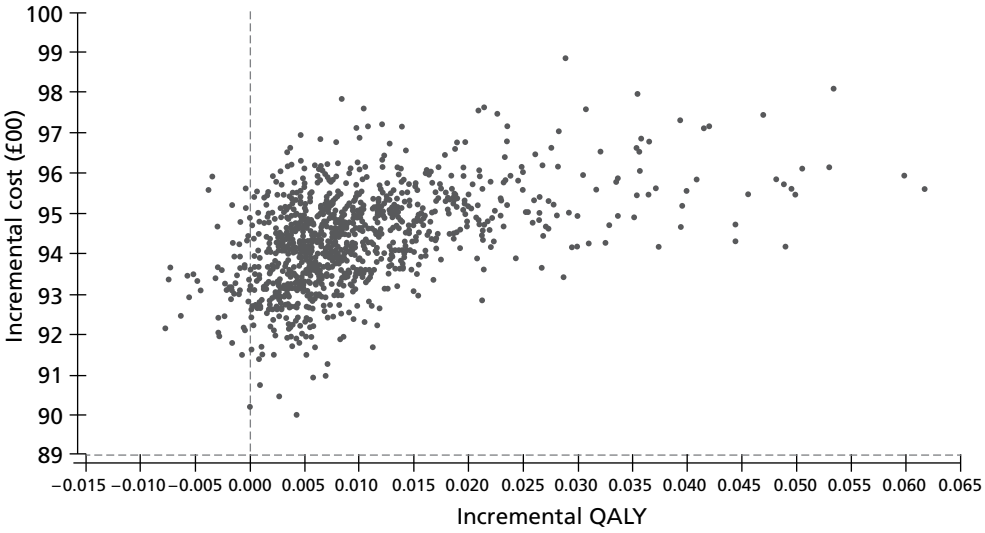

FIGURE 35 Scatterplot using distributions around the input parameters in model 4.

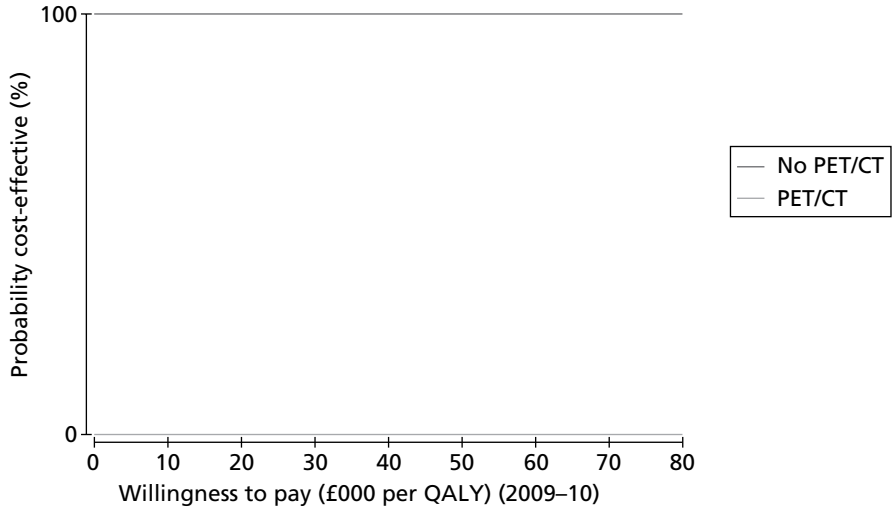

FIGURE 36 Cost-effectiveness acceptability curve using distributions around the outcomes.

Chapter 9 Discussion

Statement of principal findings

Test accuracy systematic review and subjective elicitation

Twelve test accuracy studies[20,48–58] were found that evaluated PET-CT ($n = 6$), MRI ($n = 3$), CT ($n = 2$) and MRI and CT ($n = 1$) compared with histology and/or clinical follow-up. Most of the studies were underpowered and of poor quality. Most of the later studies evaluated PET-CT and earlier studies evaluated MRI and CT. Imaging practice has developed since the earlier studies so the MRI and CT studies did not reflect current practice standards, making it difficult to ascertain the value of PET-CT when current practice for CT/MRI is based on outdated research. Both symptomatic and asymptomatic patients were to be investigated in this project, but there was very little information on imaging as routine follow-up for asymptomatic patients. The subjective elicitation exercise obtained the opinions of 21 clinical experts and the results were similar to the published estimates of accuracy for symptomatic women. There was information from one study comparing PET-CT and CT and/or MRI in the same patient group,[49] which suggested that PET-CT imaging found many more true-positives and fewer false-negatives than CT or MRI. The subjective elicitation results suggested that the estimated increase in accuracy of adding PET-CT to MRI and/or CT was less than the elicited minimum important difference in accuracy required to justify the routine addition of PET-CT for the investigation of women after completion of primary treatment for cervical cancer.

Effectiveness review

Chemotherapy, radiotherapy, chemoradiotherapy and surgery (radical hysterectomy and pelvic exenteration) were reviewed. There were 19 RCTs[60–83] on chemotherapy but none evaluated the effectiveness of cisplatin compared with no cisplatin, which is the most commonly used drug in recurrent or stage IV cervical cancer and was needed for the economic evaluation. Therefore, another review was carried out to find this information from a RCT. The best-quality RCT found compared cisplatin with no cisplatin with both groups receiving radiotherapy,[127] which gave an overall 5-year survival with cisplatin of 63% and without cisplatin of 59%. Only case series were found on radiotherapy (nine studies[84–92]), chemoradiotherapy (seven studies[93–99]), radical hysterectomy (seven studies[100–106]) and pelvic exenteration (20 studies[107–126]). The survival rates varied considerably, depending on the date of publication, characteristics of patients and type of treatment given. It was noticeable that the pelvic exenteration results showed particularly high rates of perioperative mortality and morbidity and very low survival rates.

Economic evaluation

The results of the base-case deterministic analyses based on the outcome of cost per QALY show that adding PET-CT to the current treatment strategy of clinical examination, MRI and/or CT is significantly more costly with only a minimal increase in effectiveness. This result holds true for all four models that were used in the analyses to represent the alternative treatment paths that women followed for their treatment of primary cancer. These previous treatment paths were differentiated to ensure that the results of the current analysis were not influenced by previous treatment for primary cervical cancer.

The ICER for the strategy of PET-CT as an adjunct to the standard treatment strategy, which included clinical examination, MRI and/or CT, compared with usual treatment alone was > £1M per QALY in all four models:

- for women who had been treated for early-stage cancer by surgery (model 1) the ICER was £9.3M per QALY
- for women who had been treated for early-stage cancer by chemoradiotherapy (model 2) the ICER was £1.2M per QALY

- for women who had been treated for late-stage cancer by chemoradiotherapy (model 3) the ICER was £1.1M per QALY
- for women who had been treated for early-stage cancer by postoperative chemoradiotherapy (model 4) the ICER was £1.2M per QALY.

For all models an exploration of the ICER based on the outcome of cost per additional case of recurrence treated was performed. For all four models, the additional cost per additional case of recurrence treated was in the region of £600,000 per case.

The acceptable ICER threshold used by NICE is £20,000–30,000 per QALY. This means that an ICER has to be below this for a technology to be currently considered cost-effective. The PSA suggests that the strategy of PET-CT as an adjunct to standard practice is not likely to be considered cost-effective given current willingness-to-pay thresholds for any of the models and data used in this analysis.

The sensitivity analysis showed that there was nothing, in terms of the data used in the models, that could be changed within plausible estimates, based on the current available evidence, that would change the direction of the results sufficiently to provide any doubt about the results of the current analysis. Thus, based on the current available data and expert opinion used in the models, there is little doubt that PET-CT as an adjunct to standard treatment has been shown to be not cost-effective in the diagnosis of recurrent or persistent cervical cancer at this time.

Strengths and limitations of the project

Strengths

- Well-established systematic review methods were used for this technology assessment, which lends considerable strength to its validity and reliability.
- Searches for the diagnostic and effectiveness studies were conducted systematically using a sensitive search strategy and so it is unlikely that any useful information will have been missed.
- Throughout the project the focus has been to investigate recurrent and persistent cervical cancer, rather than merge this evidence with that for primary cervical cancer, even if it was advanced when first diagnosed.
- Elicited estimates of accuracy of CT, MRI and PET-CT are plausible and reflect the fact that the accuracy of imaging tests is likely to be greater in symptomatic than in asymptomatic women because of the more advanced stage of disease in the former. Elicited estimates of accuracy also reflect a greater likelihood of an improvement in NPV than in PPV in both symptomatic and asymptomatic women, which is consistent with the probability of a larger number of false-positives with the addition of PET-CT to current imaging practice.
- Importantly, elicited estimates of prevalence and accuracy had face validity as judged by feedback to clinical experts who participated in the face-to-face elicitation exercise. Probabilities elicited with and without pre-elicitation training appeared similar.
- There have been four recent systematic reviews and narrative reviews on recurrent, persistent metastatic and advanced cervical cancer[59,145–147] and all have included RCTs on advanced primary cancer as well as cancer after primary treatment. They all investigated chemotherapy only and so the current project is the only one to incorporate information on radiotherapy, chemoradiotherapy and surgery in the same report.
- Considerable efforts were made to find appropriate input values for the decision-analytic model, for example conducting an additional systematic review on the effectiveness of single-agent cisplatin in (recurrent or primary) cervical cancer.
- The strength of the economic evaluation is that the analysis is based on the best available data. Systematic reviews showed that test accuracy evidence was severely limited.
- The subjective elicitation exercise was carried out using expert opinion before any economic analysis was undertaken. No assumption or item of data from the elicitation exercise was changed after the

analysis started apart from in the sensitivity analysis. All assumptions used in the model were agreed by the team based on expert advice a priori.

Limitations

- There was no information on the selective use of PET-CT to guide management of patients when considering surgical procedures such as exenteration, as suggested in guidelines on the use of PET-CT in recurrent cervical cancer.
- The diagnostic systematic review is limited by the quantity and quality of the included studies. The studies had few participants and were underpowered and the quality was frequently poor. The reference standard was different for test-positive patients (histology) and test-negative patients (clinical follow-up) in eight of the studies.[20,49–52,54–56] There was almost no information on the timing between the index tests and the reference standards. Also, imaging practice has changed and so the earlier studies do not reflect current practice; in particular, the CT and MRI studies were published between 1981 and 2000.
- There is a weakness in test accuracy studies in which the reference standard is not independent of the index text. In one study,[50] PET-CT was incorporated in the reference standard. For some patients the final diagnosis was based on the results of tumour marker level and PET-CT findings. This means that these studies are unlikely to give an accurate estimate of the test specificity.
- There was very little information from published studies comparing PET-CT in addition to MRI or CT with MRI or CT alone in order to determine whether or not PET-CT use would enhance test accuracy and improve therapeutic impact.
- In most of the existing studies the results for recurrent and persistent cancer, and in some cases (particularly RCTs) for primary advanced cervical cancer, were analysed together. When possible, results are presented for the subgroup of patients with recurrence and persistence only.
- There was little evidence on the effectiveness of single-agent cisplatin in recurrent or persistent cervical cancer, and other information required for the analysis was also scarce.
- It is debateable whether or not effectiveness evidence for patients who had undergone surgery with radiotherapy for their initial treatment should have been excluded. It is likely that further treatment will be chemotherapy. The additional systematic review on cisplatin as a single agent did not exclude these studies, so it is unlikely that this exclusion from the main effectiveness systematic review will have had any impact on the subsequent project.
- The main systematic review of effectiveness studies did not include any information on the effectiveness of the most commonly used chemotherapy regimen in recurrent and persistent cervical cancer, single-agent cisplatin.
- Effectiveness studies with long-term follow-up are the most useful but if they have a long follow-up it is inevitable that recruitment happened earlier and so the treatment given at the time may not be as effective as that given more recently. This limits the generalisability of these studies.
- The evidence on radiotherapy, chemoradiotherapy and surgery was all from case series; no RCT or comparative studies were available. Comparison of patient populations between studies was difficult because of a lack of information on baseline characteristics such as patient age, FIGO stage, histological cell type and site of disease. Many of the case series were published years ago (1950s to 1970s) and treatment effectiveness has improved over time. It is debateable whether or not the systematic reviews should have included these early data. However, the economic modelling required estimates for a number of parameters and it was not clear at the outset how early the inclusion criterion needed to be to find estimates for some parameters. On the one hand, basing estimates on early research means that they are not likely to be accurate; however, at least the parameter estimates are based on some research, even if early, rather than clinicians' opinions only.
- There was no information about quality of life in recurrent and persistent cervical cancer and so information had to be taken from a quality-of-life study in patients with advanced primary cervical cancer.[144]
- With regards to the economic evaluation, there are some major limitations in the analysis that must be considered when interpreting the results. Any economic model is limited by the availability of suitable data to populate it. In addition to the absence of PET-CT accuracy data, which was overcome

by the use of the preference elicitation exercise data, information on the effectiveness of appropriate treatments was also lacking. Thus, the data for the proportions of patients receiving treatment for recurrent cervical cancer were again provided by clinicians based on best clinical knowledge. Utility data for women diagnosed with recurrent cervical data were, with the approval of the clinicians on the team, calculated based on the average utility values for women who had been diagnosed with stage III and IV primary cervical cancer. Also, utility values for women treated were based on the utility values from Lang *et al*.,[144] which investigated primary cervical cancer but not recurrent or persistent cervical cancer. It is also worth clarifying that the data in the literature on survival did not report survival according to stage for women who have been treated for recurrent or persistent cervical cancer.

- When CIs were not reported in the literature, to conduct the PSA arbitrary ± ranges were used. Limited availability of data also meant that any correlations that may exist between the sensitivity and the specificity data, for the range of diagnostic tests, have been ignored.
- Cost data for tests were available in very few published studies and only unit costs for relevant resource use were available.

Uncertainties

There are a number of uncertainties in the results of the economic model, mainly due to uncertainties in the clinical parameters, such as the lack of test accuracy information for asymptomatic women. This is due in turn to the poor-quality evidence that is available for some parameters and the lack of evidence for others.

The use of differential reference standards leads to overestimation of diagnostic test accuracy.[148] However, on ethical grounds, clinical follow-up is an adequate way to evaluate test accuracy in patients with negative findings. Unfortunately, the different definitions of clinical follow-up in each study (from physical and gynaecological examination during at least 6 months to tumour marker levels and imaging findings) are problematic because it is uncertain whether or not the different studies are measuring the same imaging accuracy. When clinical follow-up is used as the reference standard it is inevitable that the condition of the patient will change. However, if no lesions are found on imaging it is unclear where biopsies for histology should be taken from.

There is a risk of under- or overestimation of diagnostic test accuracy depending on the change in a patient's condition, so information about the time period between the reference standard and the index test is important to be sure that the target condition did not change between the two tests.

With regard to the subjective elicitation, responses from individuals who received pre-elicitation education in the form of a lecture did not appear to differ from responses from those who did not. The data did not allow a formal investigation of the similarity of responses. Feedback from clinicians indicated that further disaggregation of women according to initial stage would have been ideal, reflecting variation in the prevalence of recurrence in women according to initial stage. However, this would have increased the number of accuracy elicitations from eight to 16 with an expected adverse impact on response rate and validity of responses.

Current practice in the UK does not include routine imaging surveillance of asymptomatic women post primary treatment for cervical cancer and therefore the elicited accuracy estimates for CT, MRI and PET-CT in this clinical population will not be based on the clinical experience of respondents, in contrast to the use of these imaging technologies in symptomatic women post primary treatment for cervical cancer. However, as discussed above, the pattern of estimates of accuracy in this population group is plausible given the lower prevalence and severity of any existing disease.

It is uncertain whether or not the addition of PET-CT is merited. One small published study[49] suggested that PET-CT found more true-positives and fewer false-negatives than MRI and/or CT but the subjective

elicitation suggested that the increase in accuracy was less than the minimum important clinical difference needed. PET-CT is recommended in the SIGN guidelines when CT or MRI has demonstrated recurrent or persistent disease,[3] but the evidence upon which this recommendation is based is unclear.

There is considerable uncertainty around the comparative effectiveness of cisplatin monotherapy and for radiotherapy, chemoradiotherapy, radical hysterectomy and pelvic exenteration in recurrent and persistent cervical cancer. These are the mainstays of current treatment and, therefore, the lack of evidence regarding their effectiveness is worrying.

No studies were identified that had considered the relative cost-effectiveness of available technologies for the diagnosis of recurrent or persistent cervical cancer and, therefore, appropriate comparisons with other existing studies are not possible. Consequently, it is uncertain whether or not the approach taken here would be robust if other studies were conducted.

In terms of the EVPI, given that the probability calculated in the modelling never went above zero for the range of willingness-to-pay values plotted, the EVPI is necessarily zero at any such willingness to pay. The EVPI reflects the parameter uncertainty in the elicitation exercise and would be different should the test accuracy of PET-CT be measured directly.

Chapter 10 Conclusions

Based on the current model and given the limitations that have been highlighted in terms of availability of data, the results of the current analysis suggest that the use of PET-CT in the diagnosis of recurrent or persistent cervical cancer is not cost-effective for symptomatic or asymptomatic women. The results are not even close to the current willingness-to-pay thresholds that are accepted in the UK by decision-making bodies such as NICE. The results reflect enormous uncertainty at many levels and so a better expression of our current understanding is that the cost-effectiveness of PET-CT combined with usual tests and treatment for detecting recurrent cervical cancer is not proven. Although PSA showed that the main conclusion about the cost-ineffectiveness of PET-CT was firm given the range of assumptions made, should more reliable information become available on accuracy, therapeutic impact and effectiveness, and the cost of PET-CT reduce, the conclusion may need revision. Current guidelines recommending imaging for diagnosis using expensive methods such as PET-CT need to be reconsidered in light of the above.

Implications for service provision

- A diagnosis of recurrent cervical cancer must be an extremely distressing situation for women and their families. Current evidence suggests that there are huge knowledge gaps about women's quality of life and survival given such a diagnosis. Also, missing an early diagnosis of recurrence is very distressing. Adding an additional PET-CT test to the toolkit to confirm diagnosis of recurrence, or not, might add something in terms of reassurance and hope. However, given that the additional accuracy of such a test is currently not clear, as well as the lack of other necessary evidence, a case for its implementation in current practice cannot yet be supported. Much more robust evidence on test accuracy, survival and quality of life is required before any such case can be made.
- It is uncertain whether or not the addition of PET-CT in routine surveillance of asymptomatic women and diagnosis of symptomatic women is good value for money, given the current state of knowledge. This lack of information around the usefulness of routine surveillance with PET-CT does not help the women concerned.
- Patients should be informed that the effectiveness of single-agent cisplatin in recurrent and persistent cervical cancer is uncertain.
- The pelvic exenteration results showed high operative and postoperative mortality rates and the complication rates were also high. Considering the morbidity of pelvic exenteration, it could be argued that the NHS care of these women should be further centralised into supraregional centres.

Implications for research

- The key clinical question is whether it is better to evaluate asymptomatic women following primary treatment or to wait until symptoms occur. A RCT could be conducted in which women who had completed treatment for primary cervical cancer would be randomised to a policy of routine surveillance or current practice of symptomatic follow-up.
- It is necessary to conduct larger, good-quality studies directly comparing the test accuracy of the addition of PET-CT to MRI and/or CT imaging alone in a population of women with recurrent and persistent cervical cancer in order to evaluate whether or not the additional expenditure on PET-CT is merited. Population groups need to be distinguished between symptomatic presentation and asymptomatic women undergoing routine follow-up.
- There is also a need to compare current practice with CT or MRI and the use of PET-CT in terms of change in diagnosis, work-up and change in the treatment plan by response to treatment in a way that permits continuation or alteration of treatment.

- To our knowledge this is the first example of the elicitation of test accuracy estimates. Use of predictive values and test errors resulted in consistent responses that had face validity in this sample. Further test accuracy elicitation exercises will be required to confirm the validity of this approach and for comparison of test accuracy elicitation using other test accuracy metrics.
- Investigation of the benefit of face-to-face pre-elicitation education for the validity of responses is warranted as this has an impact on the methods of elicitation that are possible (e.g. the use of postal- and internet-based questionnaires), the resources required and the response rate.
- Generally, to obtain more reliable results for radiotherapy, chemoradiotherapy or surgery, there is a need to conduct prospective studies with a comparative group, preferably RCTs, that are sufficiently powered to present definitive results in the subpopulations of persistent and recurrent patients separately. These studies should collect information about long-term overall survival, disease-free status, recurrence, morbidity, hospital stay, late complications and, most importantly, generic quality of life using, for example, the EQ-5D, the assessment of which is crucial for the evaluation of the full impact of therapies on patients' well-being.
- It would be useful to have a UK register of pelvic exenterations for recurrent/persistent cervical cancer. This is a major operation with considerable implications for morbidity. Our searches demonstrate that current published data on outcomes from pelvic exenteration for cervical cancer are outdated. In the systematic review most pelvic exenteration case series were published before the year 2000 and the only one from the UK was published in 1953.[119] This makes it impossible for the effectiveness of diagnostic work-ups or indeed exenterative surgery to be provided accurately. Such surgery – resulting in the loss of the bladder and/or bowel – has the potential for significant morbidity and mortality as well as having an impact on the patient's emotional well-being and body image. It is vital that we collect prospective good-quality data that can be used to improve care and establish standards and outcomes for women who require such surgery. Furthermore, this register may also help promote the rationalisation of service use by concentrating such services at centres that establish expertise in the preoperative, postoperative and long-term supportive care of these women.

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Contribution of authors

Catherine Meads	Supervised and co-ordinated the project and rewrote and edited the manuscript.
Peter Auguste	Designed the decision model and inputs, conducted the analysis, interpreted the results and provided detailed comments on the economic evaluation chapter.
Clare Davenport	Carried out the systematic review of test accuracy and subjective elicitation and commented on the final report.
Sylwia Małysiak	Carried out the systematic review of test accuracy studies and commented on the final report.
Sudha Sundar	Provided clinical orientation, contributed to the project design, interpreted the results and commented on the final report.
Monika Kowalska	Carried out the systematic review of test accuracy studies and commented on the final report.
Anna Zapalska	Carried out the systematic review of effectiveness and commented on the final report.
Peter Guest	Carried out the quality assessment of test accuracy studies and had radiological input.
Shakila Thangaratinam	Preparation of the grant application and review of the final report.
Pierre Martin-Hirsch	Provided clinical comments on the final report.

Ewa Borowiack	Management of the original systematic reviews and the effectiveness systematic review.
Pelham Barton	Provided advice on all aspects of the economic evaluation and detailed comments on the economic evaluation chapter.
Tracy Roberts	Management of the economic evaluation, designed and supervised the economic evaluation and wrote the first draft of the economic evaluation chapter and the discussion.
Khalid Khan	Design of the HTA and overall supervision of the project and commented on the final report.

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Appendix 1 Protocol

CLINICAL EFFECTIVENESS OF PET-CT IMAGING IN RESTAGING RECURRENT CERVICAL CANCER: SYSTEMATIC REVIEW OF EVIDENCE AND ECONOMIC MODELLING

1. Clinical background

Cervical cancer is the most common gynaecological malignancy in the world with an estimated 493,000 new cases diagnosed worldwide each year.[1] In the United Kingdom, approximately 2,800 patients are diagnosed with cervical cancer per year, accounting for around 2% of all female cancer cases[2]. In 2007 there were 941 deaths from cervical cancer which translates to a European age-standardised death rate of 2.4 per 100 000 females. Early stage (stage 1A2–IB1) cervical cancer is treated with either surgery or chemo radiotherapy with equal survival rates whereas advanced stage cervical cancer (stage IB2–IV) is usually treated with chemo radiotherapy or chemotherapy alone[3]. Survival rates depend on stage at presentation and histology of tumour and the all-stage five-year survival rate is 64.1%[4]. The risk of recurrence after primary treatment depends on the extent of the primary cancer at presentation. Approximately 10–20% of patients with stage IB–IIA cervical cancer with negative lymph nodes will recur, while those with nodal metastasis or locally advanced disease have an up to 70% risk of recurrence[1–3].

Recurrences can be central at the cervix or vaginal vault, pelvic in the lymph nodes of the pelvic side wall or distant metastases (for e.g. lung, supraclavicular lymph nodes and para aortic lymph nodes). Recurrences are common within the first 24 months after the initial diagnosis and can be symptomatic or asymptomatic. Symptom status at time of recurrence is a significant predictor of survival; the median survival is 11 months for symptomatic recurrence and 42 months for asymptomatic recurrence detected at follow-up[5]. Routine clinical examination is not accurate in detecting recurrent disease as a high proportion of patients are found to be symptomatic at the time of detecting recurrence. Patients with pelvic recurrence usually present with vaginal bleeding, discharge, pelvic pain, and sciatic pain. Patient with disseminated recurrence will develop systemic symptoms associated with cachexia. Unfortunately 5-year survival for recurrent or persistent cervical cancer evaluated with current imaging practices is between 3.2% and 13%[6]. Identification of incurable metastases eliminates unnecessary salvage procedures and suffering, while more accurate delineation of tumour extent increases the probability of successful treatment. Survival with distant disease is poor[3]. The key issue is to correctly identify recurrent disease that is amenable to curative treatment, while also correctly identifying cases for palliation.

1.1 Existing clinical practice

Currently in the United Kingdom, patients with suspected recurrence will undergo[4]

- clinical examination (rectovaginal and speculum examination, assessment of inguinal/ supraclavicular lymph nodes)
- cross sectional imaging by MRI (Magnetic Resonance Imaging) or CT (Computed Tomography) of chest, abdomen and pelvis
- examination under anaesthesia, histological confirmation of any vaginal vault mass by biopsies.

In preparing this proposal, we have established that current imaging practice in England for the diagnosis and management of recurrence involves an MRI or CT scan of the chest or abdomen and pelvis[4]. A search of the cancer network guidelines of practice in South West, West Midlands and Lancashire confirms that this is standard practice; this is also supported by the evidence based Scottish intercollegiate network (SIGN) guidance governing practice in Scotland. Our conceptualisation of this bid (*Fig 1*) is therefore an assessment of the effectiveness of PET-CT over current practice.

1.2 Applications of PET-CT

CT and MRI are high-resolution anatomical imaging techniques that are commonly used in cancer to detect potential tumours. MRI and CT are currently considered first when recurrence is suspected[4] but have limitations in differentiating recurrent tumour from post-radiotherapy or surgical fibrosis. CT and MRI also have limitations in accurately identifying the extent of recurrence as small volume metastatic nodal disease and distant recurrence may not be identified. They can also be unreliable in determining the presence or absence of recurrent disease in the pelvis after radiotherapy as radiotherapy induced fibrosis makes tissues indurated thus potentially concealing recurrent disease. Incomplete excision of disease is associated with significantly reduced survival after surgery. Similarly, CT and MRI may not identify disease spread to regional and distant lymph nodes and other organ sites.

PET is an imaging method that can be used to establish the functional parameters of tissue allowing it to detect metabolically active tumours.[7] ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most widely used radiotracer in the management of cancer patients. It is a glucose analogue and is taken up and actively trapped in the enhanced glycolytic pathway of cancer cells in particular. Positron emission tomography (PET) imaging utilises a coincidence camera system to detect the high energy photons emitted as a result of annihilation of positrons emitted by the radioisotope with nearby negatively charged electrons, thus providing anatomical localisation of the source i.e. area of pharmaceutical accumulation. PET provides anatomical image resolution of the order of 4–6 mm, significantly better than conventional gamma-cameras, but inferior to the 1–2-mm resolution of CT or MRI. The size of lesion that can be detected by PET is limited by several factors, including the physics of positron emission, the spatial resolution of the scanner (typically 4.5–6 mm in the centre of the axial field) and safe dosing limits of ^{18}F-FDG.[7] PET-CT precisely aligns and combines metabolic PET mages with anatomical CT images obtained immediately consecutively on the same machine without patient movement, and is being increasingly preferred over PET scanning alone – almost universally, as it allows precise localisation of active disease foci and recognition of normal variants.

The combination of PET-CT rather than PET alone is therefore used in cervical cancer in order to overcome limitations of either neuro-imaging technology alone. PET-CT detects metabolically active disease in primary tumours and metastatic lesions, and can demonstrate disease in normal sized nodes, and in post surgical or radiotherapy fibrosis. False positives are recognised following radiation and surgery as a result of radiotherapy and surgery induced inflammation and the general advice is to wait for 3 to 6 months after treatment. False positives can also occur in sepsis that cannot be always differentiated by PET-CT. False-negatives can also occur soon after chemotherapy and the advice is preferably to wait for 6 weeks with a minimum of 2 weeks. After allowing for important treatment effects, the detection capability of PET-CT is believed to be similar for detection of primary lesion and recurrence of tumour.

The applications of PET-CT in cervical cancer patients include: identification of persistent/recurrent disease, assessing local tumour extension, evaluating pelvic nodal involvement, detection of distant metastases (for example lung, supraclavicular lymph nodes and para-aortic lymph nodes, radiation therapy planning (in patients with PET scans positive for lymph nodes) and in assessing response to therapy[8].

1.3 Current treatment options for management of recurrent cervical cancer

Treatment of recurrent cervical cancer depends upon the site (central, pelvic, distant), extent of recurrence, type of previous treatment received (surgery, chemoradiation, radiation), time elapsed since primary treatment and the patient's performance status. Treatment is usually curative or palliative in intent. Potentially curative disease is defined as a) confirmed recurrent disease confined to the pelvis, if the patient had not received previous primary or adjuvant pelvic RT (Radiotherapy) b) disease confined to the central pelvis, without pelvic side wall or extrapelvic involvement, if RT had been administered before recurrence c) distant recurrences at a single site (such as para aortic lymph node) that could be completely resected or encompassed by a curative RT procedure[9]. The treatment is palliative in intent if distant or multiple site recurrence. It is critical that the therapeutic intent (curative or palliative) is preceded by accurate diagnosis.

The treatment options for recurrent cervical cancer varies according to the mode of treatment provided for primary cervical cancer and the extent of recurrence.

1.3.1 Previous surgical treatment:

In women who have had primary radical surgery and who have had a pelvic relapse, radiation is the treatment of choice[3]. This project will evaluate any evidence on whether early diagnosis of persistent or recurrent disease influences outcomes and whether clearly defining the extent of disease influences management and patient outcomes.

1.3.2 Previous chemoradiation or radiation only:

Salvage surgery is generally considered in women who have undergone chemoradiation or radiation treatment alone as primary treatment for cervical cancer and who have evidence of localised recurrence and surgery has a high chance of completely removing the disease[4]. Surgery for relapsed disease after radiation therapy is often associated with high morbidity as radiation fibrosis makes surgery difficult and to enhance cure rates surgical excision of disease often involves removal of bladder, uterus, cervix, and various amounts of the vagina (anterior exenteration) or uterus, vagina and portions of the rectosigmoid colon and anus (posterior exenteration) or a complete pelvic clearance (exenteration). In a small number of patients radical hysterectomy will suffice, if the disease is highly localised. As exenterations are morbid surgical procedures resulting in alteration of body image, patients require extensive preoperative psychosocial counselling.

The evidence base for outcomes after exenterative surgery is based on retrospective case series since the first advocate of this surgery by Alexander Brunschwig in 1946. With appropriate selection of patients, better pre- and postoperative care and improved operative techniques, the operative mortality varies from 16% to 2%[7–8]. The 5-year survival of patients treated with pelvic exenteration is around 30%–60%[8,10,11]. Many of these reports vary in case selection, operative philosophy and technique. The objective of this aspect of the project will be to identify all published reports of salvage surgery after radiation and chemoradiation therapy for cervical cancer. Reports that include surgery for recurrent disease from other organs will be excluded. We will also endeavour to contact all cancer centres in the UK in case unpublished audits of salvage surgery have been undertaken. Once the evidence base has been established, we will endeavour to identify the optimum surgical approach from the evidence and quantify short and long term outcomes.

1.3.3 Early Palliative Treatment

For multiple site or distant recurrence, chemotherapy can be administered with a palliative intent. Treatment options must be balanced with good supportive care and often palliative care alone is appropriate to maintain quality of life towards the end of life. The project team will also review the evidence if early recognition of unresectable persistent or recurrent disease by imaging after chemoradiation influences patient outcomes.

2. Work leading to the proposal

We have conducted systematic reviews of accuracy PET, CT and MRI in primary cervical cancer staging with respect to diagnosis of lymphadenopathy through an MRC research training fellowship awarded under Prof Khalid Khan's supervision. In particular we have developed test accuracy studies comparing PET-CT and sentinel node technique with current imaging standards of CT and MRI to detect lymph node metastases in cervical cancer[12]. In our work, we have developed literature searching, data extraction procedures, and analytic strategies for this topic. We are familiar with the literature and the gaps therein.

There are only a few attempts to incorporate test accuracy evidence into therapeutic decision-making in cancer research. We have identified the need for and developed a decision analytical model for managing patients with vulval cancer which incorporates the accuracy of imaging techniques with the therapeutic

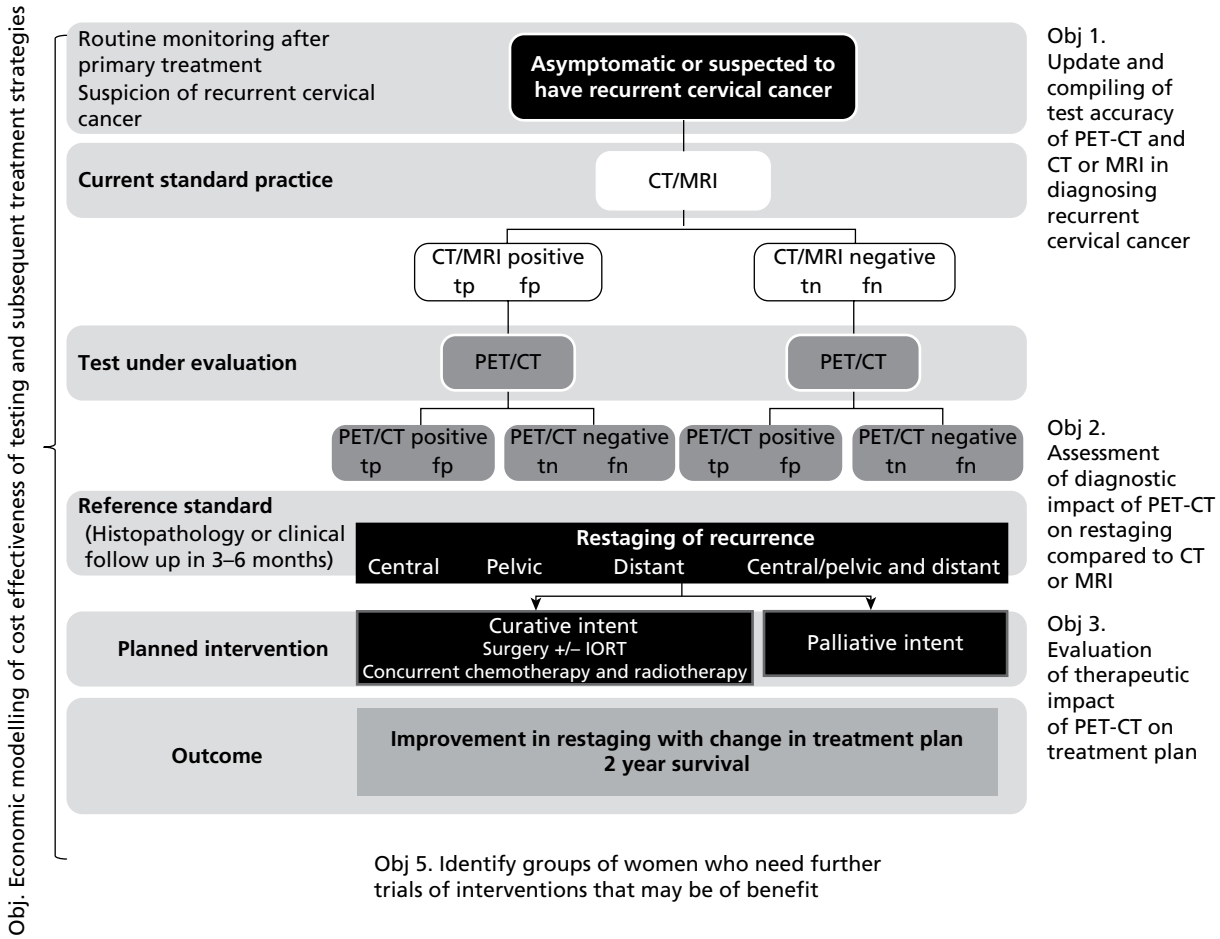


FIGURE 1 Imaging modalities and treatment strategies in women with recurrent cervical cancer.

evidence. A summary of data on accuracy of PET, CT and MRI for accurately staging primary cervical cancer from our published review is provided in *Appendix 1*.

We have also developed analytical techniques to compensate for the absence of gold standard histopathology for verification of test accuracy previously[13]. We are now in a position to use the above as the basis for developing a robust decision analytic model for recurrent cervical cancer. We have also conducted model based health economics evaluations in obstetrics using output from systematic review[14]. Therefore, we welcome the opportunity to bid for this call for proposals, which will allow us to consolidate and advance the work we have already undertaken in this field.

We are confident that given our knowledge and expertise in the relevant clinical and methodological fields, we can with appropriate resources, deliver a high quality HTA report.

3. Research Objectives

The commissioning brief is for an evidence synthesis of the added value of PET/CT for restaging women with recurrent cervical cancer. Our project will follow the key steps involved in health technology assessment and will meet the commissioned brief by fulfilling the following objectives:

1. To determine the diagnostic accuracy of PET-CT compared to CT or MRI (current imaging) in women with suspected or confirmed recurrent cervical cancer in identifying (restaging) locoregional recurrence, nodal and distant metastasis
2. To evaluate the diagnostic impact of PET-CT resulting in change in diagnosis or restaging compared to CT or MRI
3. To assess the therapeutic impact of PET-CT in changing planned treatment improving mortality and morbidity through systematic review of effectiveness of various interventions (surgery, radiotherapy, chemotherapy, early palliative care) in the management of recurrent cervical cancer detected by current practice (CT or MRI) and PET-CT
4. To evaluate the cost-effectiveness of using PET-CT (in addition to standard practice) for the detection and restaging of recurrent disease and treatment response assessment and consequent treatment strategies in terms of both human and financial costs using decision-analytic modelling.
5. To identify groups of women with recurrent cervical cancer in whom it is possible to undertake future powerful trials of interventions to reduce mortality and morbidity, and to identify key areas and research questions requiring further primary research (in addition to identifying areas where evidence is strong enough to generate recommendations for clinical practice) using Value Of Information (VOI) analysis.

The relationship of our objectives to the clinical process is shown in *Fig 1.*

4. Relevance to Commissioning Brief

The title of the HTA commissioning brief (09/29) refers to 'The added value of PET-CT for restaging in recurrent cervical cancer'. It goes on to include the following in the scope of the work to be carried out: effect of staging on treatment planned, decision analysis and cost effectiveness of added value of PET-CT compared to current imaging practice. From this, we take it that the scope of the work is to be broad.

There is substantial literature on the diagnostic accuracy of PET-CT in primary diagnosis of cervical cancer but literature on recurrent disease is limited. In order to determine the value of PET-CT, information on diagnostic accuracy alone will not be sufficient. In addition information on diagnostic impact, therapeutic and patient outcomes will be needed. Thus, it is crucial to review effectiveness of various interventions in patients with recurrent cervical cancer in addition to accuracy of PET-CT and CT or MRI (current practice) in restaging to inform decision analytic modelling. The project team's interpretation of the scope of this commissioning brief is the added value of PET-CT in restaging in recurrent cervical cancer and not detection of recurrence alone. However the added value of PET-CT in detecting recurrence in asymptomatic women is being promoted as recommended best practice[4] and the project team propose broadening the scope to include an assessment of the added value of PET-CT as surveillance for asymptomatic patients. Surveillance populations will be restricted to patients with advanced stage cervical cancer (IB2–IV) treated previously with chemoradiation as a sub-group in whom recurrence is most likely. We will obtain information on the treatment for primary cervical cancer for modelling as the mode of initial treatment will influence the accuracy of the test and subsequent treatment for recurrence.

We believe that it is feasible to undertake this work within the time scale with the resources we have requested. Our team has the necessary experience and expertise for fulfilling all the requirements in the HTA brief. We have a very strong, internationally renowned, group knowledgeable in systematic reviews of diagnostic and effectiveness data and in economic modelling. We have recently undertaken a large number of reviews for tests and treatments in cancer including primary cervical cancer and have developed a decision-making framework[12,15,16]. This background provides the basis for us to rapidly undertake the review work and the modelling within the time constraints specified in the brief.

5. Plan of research

The plan of research will be to undertake a novel systematic review of the accuracy of PET-CT in recurrent cervical cancer and a systematic review of the effectiveness of treatments for recurrent cervical cancer. Simultaneously a decision analytic model will be developed and additional rapid systematic reviews will be undertaken as necessary to populate the emerging model. A scoping search of the literature on the test accuracy of PET-CT has been undertaken. This has identified 2 reviews in the literature at various levels of currency (2004–2005)[17,18]. Searches for these 2 reviews were conducted in 2004 and 2005 respectively and yielded a total of 14 citations of potential relevance to the assessment of accuracy of PET-CT in recurrent cervical cancer. On this basis we expect the volume of test accuracy literature to be small and we therefore propose to include triangulation of subjective probabilities of test accuracy elicited from clinical experts and information on the test accuracy of PET-CT in primary cervical cancer where appropriate[12].

This project team will address the following structured question:

Population

1. Clinical suspicion of recurrence: women suspected to have persistent or recurrent cervical cancer after primary treatment, on the basis of one or more of clinical history, clinical examination, tests (including imaging and histology).
2. Surveillance in asymptomatic patients: patients with advanced stage cervical cancer (IB2–IV) treated previously with chemoradiation with a minimum gap between completion of treatment and imaging of 3 months.

Tests

PET-CT using FDG in addition to current imaging (CT or MRI) in comparison with current practice (CT or MRI) alone.

Reference standard

Disease status determined by histopathological findings, clinical follow up.

Interventions

Surgery, chemo radiation, radiation, palliative treatment.

Outcomes

Test accuracy: confirmation of stage of recurrence; incremental accuracy above existing tests in identifying potentially curable disease.

Diagnostic impact: change in diagnosis and/or staging after PET-CT compared to existing tests.

Therapeutic impact: change in treatment plan after PET-CT compared to existing tests by response to treatment that permits continuation or alteration of treatment.

Patient outcomes: morbidity, mortality, Quality of Life.

Costs: Use of resources.

Study design

Test accuracy studies.
Diagnostic before after studies investigating diagnostic and therapeutic impact with or without concurrent assessment of test accuracy.
Randomised controlled trials and non randomised controlled studies assessing effectiveness of interventions.
Economic evaluations.

Exclusions

Women within 3 months of completion of treatment for primary disease due to the problems associated with distinguishing treatment complications such as oedema and inflammatory response from recurrence in this patient group.

Systematic reviews of test accuracy, diagnostic and therapeutic impact and effectiveness will be carried out using established systematic review methodology in line with the recommendations of the NHS Centre for Reviews and Dissemination and the Cochrane Collaboration including those of Cochrane Methods Working Group on Screening and Diagnostic tests[19,20]. The systematic review of diagnostic test accuracy will be registered as a Cochrane review and as such will receive support from the Cochrane Methods Working Group on Screening and Diagnostic Tests based at the University of Birmingham. Inclusion, data extraction and quality assessment will be carried out in duplicate with differences resolved by consensus and/or arbitration involving a third reviewer.

5.1 Reviews of diagnostic studies

5.1.1 Study identification and selection

Evidence on the diagnostic accuracy of PET-CT, diagnostic impact of PET-CT and therapeutic impact of PET-CT in recurrent cervical cancer will be identified from a database of published and unpublished literature which will be assembled. Language restrictions will not be applied to electronic searches. The following databases will be searched: MEDLINE, EMBASE, Science Citation Index, and Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA). MEDION database has not been updated since 1998 and so would be irrelevant in these update searches. Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including Clinical Trials.com and UK Clinical Research Network Portfolio. A draft MEDLINE strategy is included in *Appendix 2*. This strategy was devised in consultation with the information specialist at the Cochrane Methods Working Group on Screening and Diagnostic tests and consideration of the strategy compiled by Mijnhout[21]. Electronic searches will be supplemented by hand searching, contacting manufacturers and consultation with experts in the area. In addition authors of included studies will be contacted for information on relevant published or unpublished studies. Citations identified by the search will be selected for inclusion in the review in a two-stage process using predefined and explicit criteria regarding populations, tests, outcomes and study design. These criteria will be pilot tested using a sample of papers and agreement between reviewers will be measured.

Due to anticipated small numbers of studies we also plan to update existing reviews of the accuracy of PET-CT in primary cervical cancer using the search strategy outlined above, removing the terms for recurrent cervical cancer.

5.1.2 Study quality assessment and data extraction

Methodological quality of the selected primary studies will be assessed based on elements of study design, conduct and analysis included in a validated assessment tool, QUADAS, which will be adapted to the topic area as necessary[22]. No quality assessment tool exists for the assessment of diagnostic before after studies but members of the project team have experience of devising quality checklists for this particular study design based on existing knowledge in the area[23]. Data extraction will be performed using pre-designed, piloted data extraction forms, drawing on existing pro-formas used by the project team in previous, completed reviews in the topic area[12]. Missing information will be obtained from investigators if is crucial to subsequent stages of analysis and modelling. To avoid introducing bias, unpublished information will be treated in the same fashion as published information. In addition to using double data extraction to ensure the reproducibility of the overview, sensitivity analyses around important or questionable judgements regarding quality assessment and data extraction will be performed.

5.1.3 Data synthesis

Sensitivity, specificity and likelihood ratios for individual studies comparing PET-CT and current imaging methods (CT or MRI) will be derived. Presence of a threshold effect will be examined by plotting sensitivity against 1 – specificity in a receiver operating-characteristic analysis (ROC analysis) and by calculating Spearman correlation coefficients[24]. Heterogeneity of results between studies will be investigated qualitatively by examining the distribution of sensitivities and specificities in (ROC) space and variability of estimates of diagnostic odds ratios (DOR) across studies using the forest plot[24]. In addition heterogeneity will be investigated quantitatively using meta-regression and subgroup analyses if the volume of studies allow. Multivariable analysis will be undertaken to identify those criteria that have the most effect on our data set. Quantitative investigation will be undertaken based on variables defined a priori and including population characteristics, index and reference test characteristics and study quality[25]. It is anticipated that the following will be important sources of variation in test accuracy estimates:

- Population characteristics: initial staging of primary tumour, primary treatment received, interval between initial treatment and recurrence, symptomatic and asymptomatic recurrence.
- Index test characteristics: technical details of the PET CT scanner including imaging methodology and sequences used, skill and experience of the operator, healthcare setting (2y or 3y), timing of scan post injection of tracer, does of tracer used.
- Reference test: histology or clinical follow up.
- Study quality: study design (prospective or case–control) and study quality (high: meeting all assessment criteria; medium: meeting at least one assessment criteria; low: meeting no quality criteria). High quality studies will be used as the reference category to determine whether medium and low quality studies have biased estimates of test accuracy.

Based on an investigation of heterogeneity summary estimates of sensitivity, specificity and likelihood ratios (LRs), and summary ROC curves will be derived as appropriate using recognised methods for meta-analysis of test accuracy[26]. Direct comparisons are more robust and will be distinguished from indirect comparisons[27,28]. LRs are considered more clinically meaningful as measures of test accuracy and they allow estimation of probabilities for economic modelling. Post test probabilities can be used to tailor the absolute effectiveness estimates according to test results.

The risk of publication and related biases is expected to be high in reviews of test accuracy[29,30]. Publication bias will be investigated using funnel plots of DOR against corresponding variances. Qualitative investigation will be based on the premise that large gaps in the funnel indicate possible 'missing' publications. These omissions are usually due to small studies showing limited accuracy and are unlikely to be missing at random. Statistical investigation of publication bias will be undertaken in STATA based on templates of commands and instructions already developed by the project team.

5.2 Reviews of effectiveness of interventions

Once accurate imaging modality has identified the women with potentially curable disease by restaging, these patients may benefit from interventions effective in reducing mortality and morbidity. Existing reviews will be assessed for their quality and currency follow existing guidelines QUOROM and MOOSE[30,31]. Through this process we will identify gaps where reviews do not exist and where they need updating. Where necessary effectiveness reviews of RCTs of treatments for recurrent cervical cancer will be undertaken follow existing guidelines[32] ensuring the output complies with the QUOROM statement[30].

5.2.1 Study identification and selection

For evidence on the of effectiveness of treatments for recurrent cervical cancer we will begin by searching for exiting systematic reviews using the ARIF search protocol[33]. Any existing reviews will be examined for relevance and currency in order to inform further searching for primary studies. Searches for further primary studies will be performed. The following databases will be searched: MEDLINE, EMBASE, Science Citation Index and the Cochrane Library (all databases). On-going studies will be sought by searching Clinical Trials.com and the UK Clinical Research Network portfolio. Draft searches for MEDLINE are included

in *Appendix 2*. Studies will be selected for inclusion in the review in a two-stage process using predefined and explicit criteria regarding populations, interventions and outcomes using procedures similar to the ones outlined in the previous section 5.1.1.

5.2.2 Study quality assessment and data extraction

The quality of included reviews will be assessed against a validated tool and a reporting checklist, QUOROM[30]. Methodological quality of randomised and non-randomised trials will be assessed based on accepted criteria. Information on the adequacy of randomisation, sequence generation, concealment, blinding, description of withdrawals, and follow-up rates would be sought as these are elements most likely to have a direct relationship to bias in a RCT[34]. Procedures for obtaining missing information and resolving disagreements will be similar to the ones outlined in section 5.2.1.

5.2.3 Data synthesis

Revman and Stata softwares will be used to conduct analyses. The former will allow uniformity with Cochrane reviews and the latter will allow the data analytic flexibility that we will need to examine issues not included in the Revman software. Heterogeneity of results between studies and investigation for publication bias will be statistically and graphically assessed using methods outlined in section 5.1.3. The decision to proceed to meta-analysis will depend on the degree of heterogeneity in the data set. It is anticipated that the following will be important sources of variation in the estimates of effectiveness:

- Population characteristics: initial staging of primary tumour, primary treatment received, interval between initial treatment and recurrence, symptomatic and asymptomatic recurrence, extent of recurrence, physical performance status of patient.
- Treatment characteristics: Type of intervention (surgery, radiotherapy or chemoradiotherapy), intention of treatment (curative or palliative) duration of therapy, healthcare setting (2y or 3y), timing of intervention.
- Outcome measures: Mortality, morbidity, Quality of life.

Conclusions regarding the typical estimate of an effect size of the intervention will be interpreted cautiously if there is significant heterogeneity.

5.3 Eliciting subjective probabilities

In anticipation of small numbers of test accuracy studies subjective probabilities will be elicited, using a group interview, from between 10 and 15 clinical experts in the fields of gynaecological cancer and radiology with no conflict of interest in the area, identified by clinicians in the project team and project advisors. The aim of the elicitation process will be to gather subjective views about the size and probability of incremental changes in test accuracy (true positives, false positives, true negatives and false negatives) from the addition of PET-CT to current imaging practice in the detection (surveillance in asymptomatic women) and restaging of recurrent cervical cancer.

Subjective probability estimates will be elicited concerning:

- The diagnostic accuracy of the addition of PET CT to current imaging practice (CT or MRI) and current imaging practice alone in recurrent cervical cancer.
- The diagnostic impact of the addition of PET CT to current imaging practice in recurrent cervical cancer (changes in diagnosis and treatment planning).
- The therapeutic impact of the addition of PET CT to current imaging practice in recurrent cervical cancer (the effects of changes in treatment).

Eliciting subjective probabilities from clinicians has three roles:

1. Providing data to populate the economic model in the absence of information found in the literature.

2. Supplementing information found in the literature. Literature may be sparse, of poor quality or not transferable to the UK setting. Information gained from clinicians in the form of subjective probabilities may be used to supplement information found in the literature to enable sensitivity analyses to be performed as part of the economic model. For example subjective estimates of the therapeutic impact of the addition of PET-CT from clinicians in the UK may be different to results obtained by combining test accuracy and effectiveness evidence estimated in research settings (effectiveness versus efficacy).
3. Planning the dissemination strategy for the results of the research. If it is not possible for clinicians to reach agreement about their subjective estimates of the accuracy, diagnostic impact and therapeutic impact of PET-CT this information can be useful when developing a dissemination plan for this research project.

The process of eliciting probabilities

Subjective probabilities will be elicited using group interviews with between 10 and 15 clinical experts in the fields of gynaecology, oncology and radiology with no conflict of interest in the area. Experts will be identified by clinicians in the project team and project advisors. Based on experience of eliciting probabilities in other clinical topics it is anticipated that 2, half day interviews or one whole day interview will be necessary to elicit all the required information: test accuracy, diagnostic impact and therapeutic impact.

A face-face group interview (behavioural aggregation) will be used in preference to individual interviews as this facilitates a common understanding of the problem and task from experts and will allow us to benefit from group discussion and interaction leading to a consensus of opinion[35]. The expert group will be facilitated by both a clinical and non-clinical expert drawn from the project team with sufficient statistical expertise to provide probabilistic training to experts, validate their results and provide feedback. The expert group interview(s) will be facilitated by both a clinical and non-clinical expert drawn from the project team with sufficient statistical expertise to provide probabilistic training to experts, validate their results and provide feedback. The interview(s) will briefly comprise:

- Training of experts (probability, probability distributions, judgement heuristics and biases)
- Practising elicitations

In this part of the workshop participants will be presented with a non-related topic to allow evaluation of their understanding of the task to be completed (subjective probability estimates of the accuracy, diagnostic impact and therapeutic impact of the addition of PET-CT in recurrent cervical cancer) and a rehearsal of the process. In addition the results of the practice example will be fed back to participants to demonstrate how the outcome of the workshop will be integrated with the findings from the systematic review. Attachment: practice probabilities.xls provides an example of a practice elicitation exercise used successfully in previous research with clinicians.

Eliciting probabilities about the use of PET-CT in recurrent cervical cancer

Following completion of the practice exercise participants will be asked to provide separately their subjective estimates of the size and probability of test accuracy outcomes, diagnostic impact outcomes and therapeutic impact outcomes. The following sections detail how subjective probabilities about test accuracy will be elicited as an illustrative example. Participants will be presented with the prevalence of recurrent cervical cancer in the population of interest (the prior probability of having recurrent cervical cancer). The probability of recurrent cervical cancer will be modified by the results of the test(s) under investigation: CT or MRI versus CT or MRI and PET-CT. Respondents will be asked for their subjective estimates of the accuracy (expressed as the probability of true positives (TP) and true negatives (TN)) for each of the tests/test combinations under investigation. Uncertainty regarding estimates of test accuracy will result in a distribution of possible test accuracy estimates instead of a precise figure (see *Appendix 3* in the illustrative example below). In *Appendix 5 Tables 1–3* in the illustrative example a range of probabilities between 50 and 100% have been used. In practise in the workshop we plan to begin by asking

respondents for their single most likely estimates of TP and TN and then present a range of probabilities around these estimates.

Presentation of results back to experts.
It is planned that the elicitation of subjective probabilities will be a paper based exercise and results will be analysed immediately following the elicitation exercise. In previous research it has been possible to analyse results from small numbers of participants in the period of one hour. The subjective probabilities of all participants will be combined and fed-back to participants. A combined probability distribution will be constructed (for example, see *Appendix 3*) by summing the frequency of points awarded to each probability presented to participants and presenting this graphically. If there is substantial disagreement within the group, individual subjective estimates will be presented and examination of agreement within sub-groups of respondents, for example according to speciality will be explored (for example see *Appendix 4* in the illustrative example).

Repeat elicitation of probabilities
The elicitation process will be repeated following feedback of results from round 1 to ensure reliability. In the event of substantial variation suggesting construction of a combined probability would be inappropriate, a repeat of the exercise may result in greater agreement. In the event that it is not possible to construct a combined probability distribution for participants the degree of variability of estimates of test accuracy, diagnostic impact and therapeutic impact will be useful in informing the dissemination strategy for the results of the research.

Updating the prior probability of disease (prevalence) using subjective probabilities and findings from the systematic review
The probability of disease prior to testing (prevalence of cervical cancer) will be updated using the combined test accuracy distribution derived from respondents using a Bayesian updating formula to produce a posterior distribution of disease probability. This posterior distribution of disease derived from the elicitation process will be further updated with the results of the systematic review, again using a Bayesian updating formula to provide a final posterior distribution for use in probabilistic sensitivity analysis. In the event that it is not possible to derive a combined probability distribution from respondents the prior probability of disease (prevalence) will be updated using estimates from the systematic review only.

The elicitation process also aims to generate subjective probabilities concerning the diagnostic and therapeutic impact of the addition of PET-CT. Findings from the elicitation process will be triangulated with findings from the systematic reviews and probability distributions will assist with populating the decision analytic model. As well as expertise within the project team[36] we have access to experts in the field, based at the University of Birmingham[37].

5.4 Model Based Economic Evaluation

The objective of the economic evaluation is to compare the relative cost effectiveness of adding PET-CT imaging as an adjunct to standard practice against standard practice alone in re-staging recurrent cervical cancer.

5.4.1 Perspective and data collection

If PET-CT screening is shown to be an effective adjunct to the standard practice in re-staging recurrent cervical cancer then it is likely that important cost implications will be imposed on the health care sector. For example, PET-CT may detect additional evidence of the extent of metastasis compared to standard investigations which could increase the number and extent of subsequent tests and treatment required by the individual. But the additional associated costs associated with more accurate re-staging of the re-current cancer may lead to a reduction in costs associated with unnecessary or ineffective subsequent treatments and also prolong the life of the woman. Thus, if available data allow, the economic evaluation

will be based on an outcome of cost per QALY and/or Cost per recurrent case treated; and/or cost per 'death due to recurrent cancer' avoided. The analysis will adopt the perspective of the NHS.

Therefore data collection required for the model based economic evaluation will include:

- The equipment, other resource use and costs associated with PET-CT
- Knock-on costs associated with further tests and treatments that are required as a result of the re-staging
- Equipment, resource use and costs associated with current practice
- Accuracy of the PET-CT test and current practice package compared to the accuracy of current practice tests alone
- Effectiveness of alternative intervention pathways that are followed as a result of the diagnosis
- Outcomes such as quality of life associated with cervical cancer at various disease stages; probability of death associated with various stages of the disease diagnosed.

A scoping search has already been undertaken to identify economic evaluations of cervical cancer. This search used terms for 'cervical cancer' in conjunction with an economic search filter in MEDLINE. The search identified 360 references. A systematic search for economic evaluations and any other data needed to populate the model will be undertaken in NHS EED, MEDLINE and EMBASE. The objective of searching the economic literature is to identify studies reporting costs and consequences associated with recurrent cervical cancer, which will provide estimates for a comparison with current practice. The review of economic studies will also try to identify quality-of-life information that could be used to estimate the proposed outcome of cost per QALY although our initial scoping search has not found many studies of this type. If relevant QALY data is unavailable for this type of recurrent cancer we will infer QALY values from other cancer studies.

Cost data will be collected from two principal sources. First, once the clinical evidence has been synthesised into the main strategies of diagnosis and treatment, relevant studies will be examined for their data on costs and resource use. These data will be subject to relevant quality criteria. Additional cost data will be available from other sources such as the National Schedule for Reference Costs. If necessary, primary cost and resource data will be collected from the Pan-Birmingham Gynaecology Cancer Network to complete any gaps in the information required for the modelling process.

Additional searches will be undertaken to help populate the decision model. The Information Specialist will work in close liaison with the health economist to identify the model questions. Information to answer these questions will be provided by focused searching of appropriate databases, including reference cost databases, statistical sources and other sources of relevant information.

The evidence found in the clinical accuracy and effectiveness reviews will provide the majority of the parameters required to carry out the economic evaluations of alternative test and treat packages. If information on the correlation between a package of tests and correlation between a package of treatments is available from the reviews, the framework will allow these more complex strategies to be evaluated as well as strategies that allow alteration in the form of repeated testing.

5.4.2 Model and analysis

The economic evaluation will involve the development of a decision analytic simulation model as a framework for conducting cost-effectiveness and associated value of information analyses[38,39]. The economic evaluations will inform current treatment policy in this clinical area, whilst the value of information component will serve to highlight future research needs and agendas, and inform possible future research funding decisions. A modelling framework is ideally suited to demonstrate and explore the importance of the inherent uncertainty.

The risk of recurrence after primary treatment depends on the extent of primary cancer at presentation. Treatment of recurrent cervical cancer depends on the site and extent of recurrence, the type of previous treatment received, time elapsed since primary treatment and the patient's performance status. A Markov model is the appropriate modelling approach for this evaluation because the time horizons available for both the imaging and the interventions are relatively long. Markov models are also able to represent clinical situations where patients change health states or experience recurrent events over a long period of time[40]. The Markov model will be constructed using TreeAge Pro software. This is a widely-used and highly user-friendly package ideally suited to the construction and analysis of decision trees and Markov models.

An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from current practice to alternative test and treatment strategies. Using discounting, adjustments will be made to reflect the differential timing of costs and outcomes in terms of the extension to the length of life extend associated with the test and treat strategies. The base-case analysis will follow Treasury recommendations for public sector projects.

5.4.3 Presentation of results and sensitivity analysis

The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness values.

For the Value of Information analysis we shall quantify the total uncertainty in terms of the value of removing that uncertainty. As appropriate, we shall include partial value of information analysis calculations. We shall also use both deterministic and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

6. Expertise in the team

The applicants have a wide and appropriate range of expertise in systematic reviews, gynaecological oncology, medical oncology, radiology, clinical epidemiology, health measurement, medical statistics, information science and health technology assessment.

SK has successfully completed many HTA projects on systematic reviews of test and treatments including systematic reviews of tests for pre-eclampsia, systematic reviews of tests and treatment in pre term labour. In addition he has experience of the process of eliciting subjective probabilities[36]. He has been awarded MRC studentship fellowship to undertake systematic reviews of accuracy of tests and treatment in gynaecologic cancer[12,15,16,41] including cervical cancer and for undertaking modelling and decision analytic economic evaluation and a grant on the methodology of evaluation of tests without gold standards by the NHS Research Methodology Programme. KSK and TR have a grant on evaluation of accuracy and cost effectiveness of intrapartum rapid tests for Group B streptococcus infection. TR has experience in cost-effectiveness analyses of tests and interventions in cancer. ST has undertaken many systematic reviews on tests and treatment in women with pre-eclampsia, preterm labour and epilepsy. SS and PM are both members of the gynaecological cancer clinical studies group of the NCRI (National Cancer Research Institute) – the national group responsible for selecting national trials for inclusion in the NCRI portfolio and supporting and directing clinical research in gynaecological cancer.

SS and PM are gynaecological oncologists involved in managing women with cervical cancer. PM has published systematic reviews on management in cervical pre cancer and compiled the evidence base for the Improving Outcomes Guidance (IOG) document in gynaecological cancer issued by the Department of Health. CD has considerable experience of undertaking and managing health technology assessments as part of the West Midlands Health Technology Assessment Collaboration (WMHTAC). Her experience includes HTAs concerned with diagnosis, and effectiveness, as well as a methodological review concerned with the use of on-going trials in health technology assessments HTA 8(24). Recent, relevant research

includes development of a tool for assessment of quality in diagnostic before–after studies, identification of reviews of test accuracy and she is nearing the end of a programme of doctoral research concerned with communication of test accuracy outcome measures and evaluation of their diagnostic impact. AF has extensive experience as an information specialist in providing support to a diagnostic and effectiveness technology assessments as a member of the West Midlands Health Technology Assessment Collaboration and the Aggressive Research Intelligence Facility based at the University of Birmingham. She is currently undertaking a systematic review on PET and PET/CT in breast cancer recurrence (HTA no 08/34) concerned with the incremental diagnostic accuracy of PET and PET/CT compared to existing diagnostic strategies in recurrent breast cancer. PG is a consultant radiologist with expertise in PET CT in patients with gynaecological cancers. RM is the chair of Jo's Trust Fighting Cervical Cancer, the only UK dedicated to women, their families and friends affected by pre-cancer and cancer of the cervix.

The applicants will be supported in an advisory capacity by Dr Chris Hyde, Dr Jon J Deeks and Dr Chris Williams. JJD is an expert in test evaluation leading the NIHR funded Diagnostic evaluation and review support unit, and will provide input into the study design and in its output as a Cochrane review. CW is a Medical Oncologist (specialising in gynaecological cancer), with a particular interest in clinical trials methodology and systematic reviews. He is the Co-ordinating Editor of the Cochrane Gynaecological Cancer Review Group and a past Chair of the Cancer Therapy Committee and the Gynaecological Cancer Working party of the Medical Research Council. CH has been involved in projects like CASP (Critical Appraisal Skills for Purchasers) and the Cochrane Group on Effective Practice and Organisation of Care (EPOC). Through ARIF, his aim is to facilitate the use of research information, particularly systematic reviews of effectiveness in population level health care decision making within the West Midlands.

7. Contribution to Collective Research Effort:

This systematic review on the added value of PET-CT and cost effectiveness analysis of PET-CT imaging in comparison with current imaging fits comfortably with previously published HTA evaluations of PET-CT in other cancers. This research application complements existing NCRN (National cancer research network) portfolio research in gynaecological cancer. Members of the research team (PM, SS, KK, TR, AT, PG) are co-applicants in an NCRN endorsed primary investigation of PET-CT in endometrial cancer.

Due to the multiple methods employed by the proposed evidence synthesis the project team expect that the outputs of the work would be of interest to a broad research and clinical community including experts in the areas of evidence synthesis and in particular synthesis of test accuracy, gynaecological cancer, and decision making. Outputs would be submitted for presentation at national and international conferences such as Health Technology Assessment international, Medical Decision Making, European Society of Gynaecological Oncology (EGSO) and Society of Gynaecological Oncology (SGO). Similarly the outputs of this work would be of interest to a variety of peer reviewed journals and the project team would aim for a minimum of 3 peer reviewed publications in addition to publication as an HTA monograph. One of the outputs of this project would be a Cochrane review to be added to the Cochrane database of systematic reviews of test accuracy.

The project team have involved members of Jo's trust, a reputed national charity in cervical cancer and user representatives of the Pan Birmingham cancer research network (PBCRN) and the Lancashire cancer networks. Users will be represented in study conduct and planning of dissemination strategies. Experience from previous research conducted by the team (HTA no 01/64/04: Methods of prediction and prevention of pre-eclampsia: Systematic review of accuracy and effectiveness literature with economic modelling in preterm labour) has already indicated that publication and dissemination needs careful consideration from the outset. Publication strategy will also need to anticipate early the need for versions of the report, which can be, used by women themselves. For this we will seek input from relevant consumers.

8. Please provide details about any related (planned or active) grants held by any member of your research team in this or similar research areas.

KSK has been awarded MRC studentship fellowship to undertake systematic reviews of accuracy of tests and treatment in gynaecologic cancer including cervical cancer. The information from the review on accuracy of PET CT over CT or MRI in diagnosing primary cervical cancer will be integrated in the modelling. We have also undertaking modelling and decision analytic economic evaluation for tests in vulval cancer and the experience will be utilised in modelling for this project. PM has been successfully awarded a NHS Cochrane grant application as a joint editor of the Cochrane Gynaecological Review Group for £380K to support the generation of updated evidence based gynaecological oncology guidelines March 20007. He has also developed a joint project with the departments of epidemiology and psychology at UCLAN investigating the impact of cancer symptoms and being referred to secondary care. SS has 1 PhD student funded by the department of Health investigating the epigenetic changes induced by HPV in cervical cancer. The ongoing work by SS and PM in gynaecologic oncology will be of use in providing subjective probabilistic estimates for test accuracy and effectiveness. AF (information specialist) is currently working on an HTA assessing the value of PET-CT for recurrent breast cancer and her expertise in devising the search strategy and database management will be of benefit to this proposal.

9. Summary for the non expert

Every year in the UK, over 2,800 women are diagnosed with cervical cancer and 1,000 women will die from the disease. After breast cancer, cervical cancer is the second most common cancer in women aged 35 and under. Early stage cervical cancer is treated with either surgery or chemo radiotherapy with a cure rate of 80%. Advanced stage cervical cancer is usually treated with chemo radiotherapy or chemotherapy alone and 30–50% of patients will have persistent or recurrent disease after treatment. The prognosis for recurrent cervical cancer is generally poor. The reported 5 year survival rates in recurrent cervical cancer are between 3.2% and 13% and the time to recurrence is short with 75% occurring before 3 years.

An accurate restaging of the extent of recurrent cancer (confined to the pelvis, spread to the lymph nodes or spread to distant organs) helps to plan subsequent treatment. Accurate identification of incurable spread of cancer avoids unnecessary treatment which itself is unpleasant and carries considerable risk, while more accurate delineation of tumour extent (restaging) increases the probability of receiving treatments appropriate to the extent of spread which may lead to improvements in survival and quality of life.

In current clinical practice, patients are monitored at regular intervals after primary treatment to detect persistent or recurrent disease. Present techniques of clinical examination and CT or MRI scans can be unreliable in detecting persistent or recurrent disease in the pelvis after radiotherapy as radiotherapy induced scarring can potentially conceal recurrent disease. Similarly, CT and MRI may not identify disease spread to lymph nodes and other organs. PET CT (Positron Emission Tomography with anatomical CT images) is an imaging method using radio labelled molecules to detect metabolically active tumours in the management of cancer patients. PET CT has been shown to improve the detection of cancer and its spread from 8% to 43% over conventional testing in patients with lung, colorectal cancer, lymphoma, melanoma, breast cancer, and thyroid cancer and it may have similar benefits for patients with recurrent cervical cancer.

For the proposed project our objectives are as follows:

In women who had undergone treatment for cervical cancer, under routine surveillance or with suspicion of recurrence

- To assess if the addition of PET-CT to existing scans (CT or MRI) improves the detection of recurrent cervical cancer
- To evaluate if the use of PET-CT results in change in (re)staging i.e. extent of recurrence compared to CT or MRI
- To assess the impact of performing PET-CT on the planned treatment after diagnosis of recurrence and during subsequent monitoring
- To summarise the effectiveness of available treatments in women with recurrent cervical cancer
- To estimate the impact of PET CT findings patient outcomes and the costs associated with its routine use in this patient group.

We plan to fulfil the above objectives by systematically identifying the available evidence on the diagnostic accuracy of PET CT in recurrent cervical cancer compared to the diagnostic accuracy of exiting diagnostic tests used in this patients group and the effectiveness of treatments for recurrent cervical cancer. The evidence found will be used in an economic evaluation comparing existing testing and treatment strategies with PET CT guided treatment strategies. This evaluation will inform current treatment policy in this clinical area and highlight future research need.

10. Project Timetable and Milestones

Fig 2 shows the project timetable and milestones for the accuracy and effectiveness reviews and economic modelling. We have carefully evaluated the ongoing work and the level of staffing within our departments and feel that we would be able to commence the work in January 2010 for a period of 18 months, if funded.

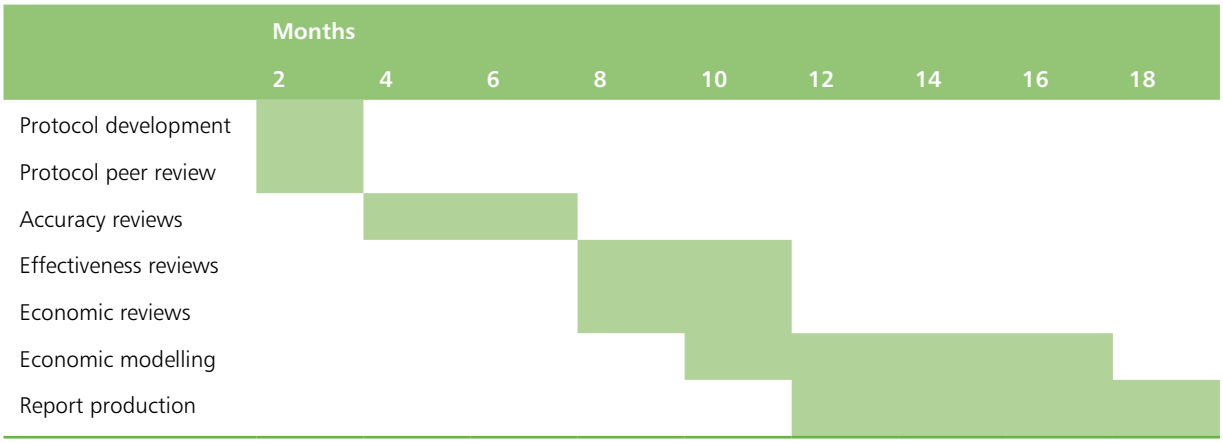


FIGURE 2 Timetable.

11. Justification for the support required

Staff:

- Supervisor, also providing support for researchers, for example: double data extraction, assisting with inclusion decisions and being the lead for producing the final report – 1 day per week for the duration of the project.
- Researcher to perform systematic review of accuracy and effectiveness studies and to identify additional epidemiological and background information for input into the modelling exercise– 1 wte for 18 months.
- Health economist to perform systematic review of cost-effectiveness literature and modelling – 1wte for 12 months.
- Information support for searching and document retrieval – 20 days.

Equipment and consumables:

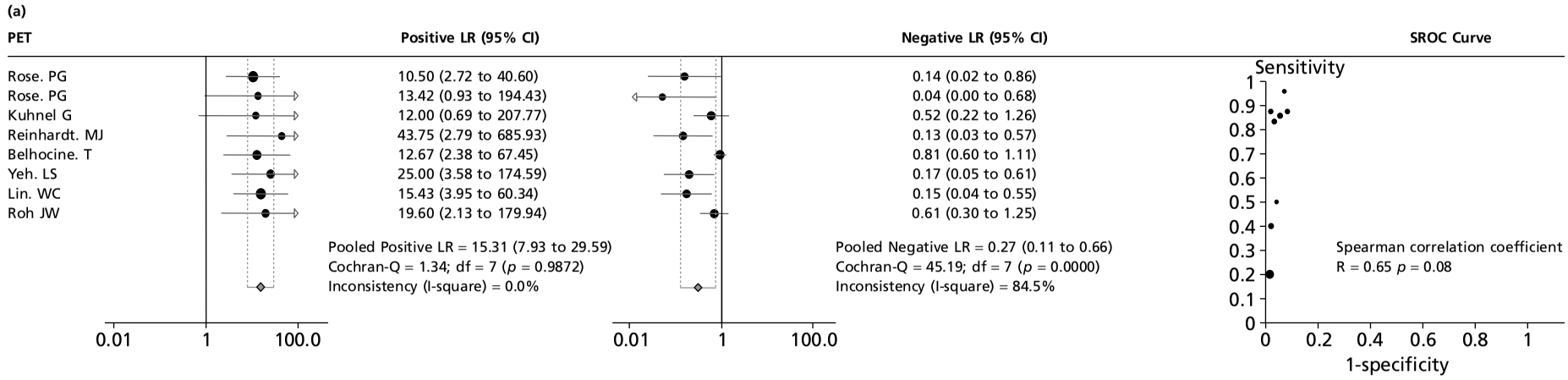
- two standard specification computers, printing cartridges, paper and photocopying,
- telephone and fax calls, postage,
- estimated 200 interlibrary loans.

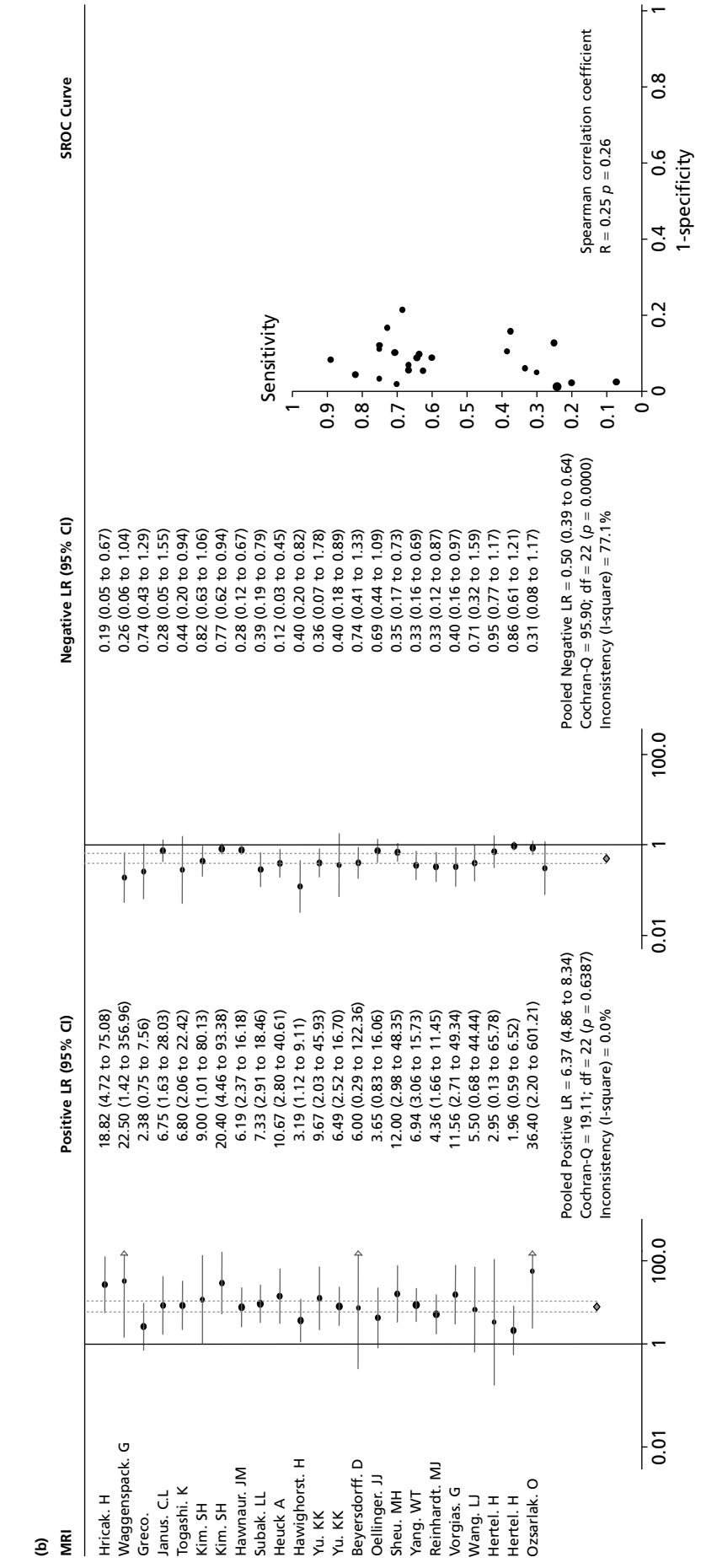
Support:

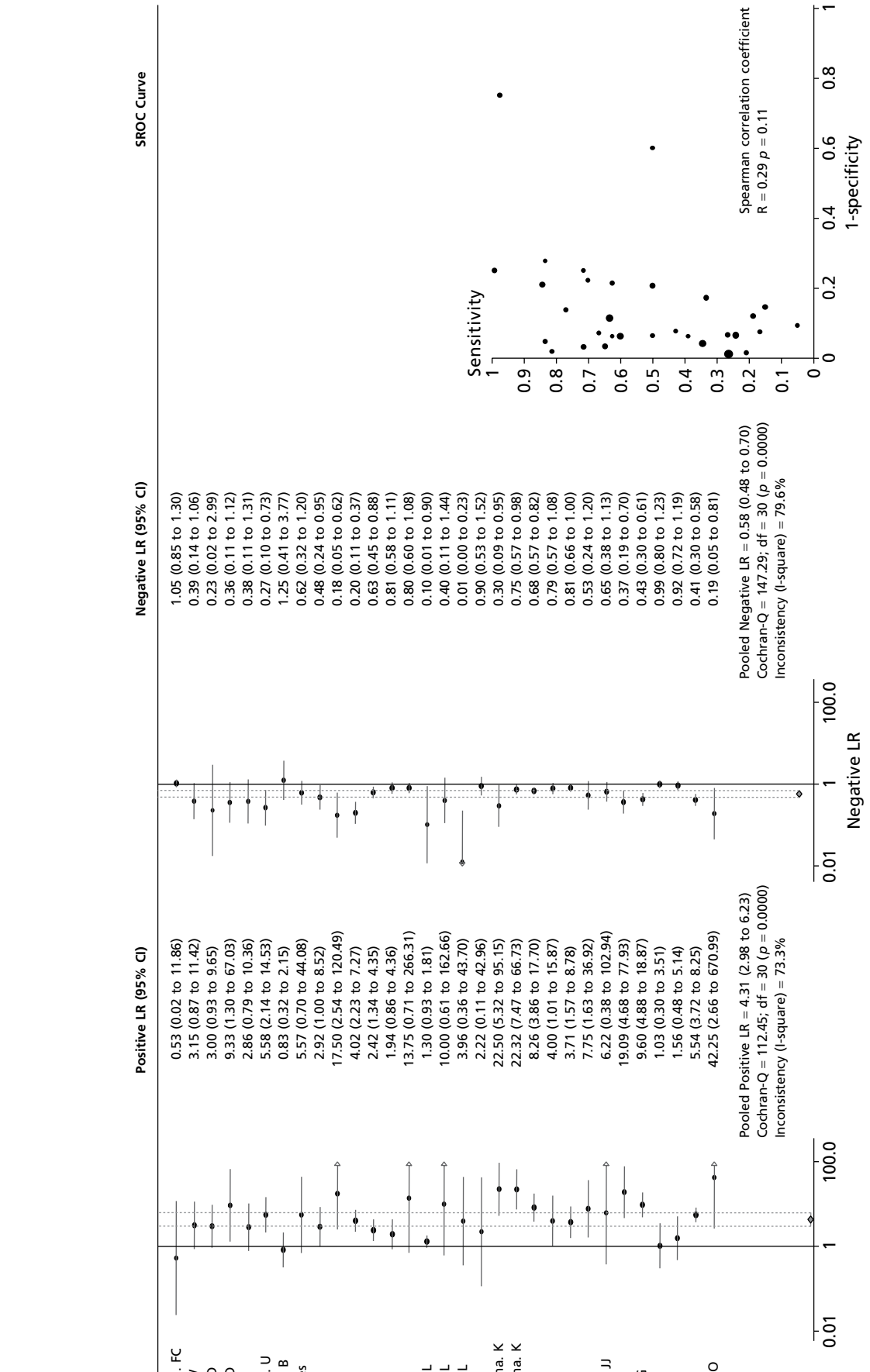
- meeting room, refreshments and travel for the project team and consultants based on 4 face to face meetings over 12 months.
- administrative support, for steering group and preparation of final report – 10 days over 12 months.

We are in an excellent position to gauge the level of resources required to deliver this type of project (systematic review and cost-effectiveness analysis) with several years experience in their delivery. We are able to draw on additional in-house expertise if necessary. Travel costs are not estimated to be high.

Appendix 1 SROC curves and forest plots of likelihood ratios for studies in a systematic review to determine lymph node status in primary cervical cancer with a) PET; B) MRI; c) CT






(c)
CT
Positive LR (95% CI)
Negative LR (95% CI)
SROC Curve
Grumbine. FC 0.53 (0.02 to 11.86) 1.05 (0.85 to 1.30)
Walsh. JW 3.15 (0.87 to 11.42) 0.39 (0.14 to 1.06)
Brenner. D 3.00 (0.93 to 9.65) 0.23 (0.02 to 2.99)
Brenner. D 9.33 (1.30 to 67.03) 0.36 (0.11 to 1.12)
Jing. BS 2.86 (0.79 to 10.36) 0.38 (0.11 to 1.31)
Villasanta. U 5.58 (2.14 to 14.53) 0.27 (0.10 to 0.73)
Marincek. B 0.83 (0.32 to 2.15) 1.25 (0.41 to 3.77)
Van Engles 5.57 (0.70 to 44.08) 0.62 (0.32 to 1.20)
Vas. W 2.92 (1.00 to 8.52) 0.48 (0.24 to 0.95)
Vas. W 17.50 (2.54 to 120.49) 0.18 (0.05 to 0.62)
King. LA 4.02 (2.23 to 7.27) 0.20 (0.11 to 0.37)
King. LA 2.42 (1.34 to 4.35) 0.63 (0.45 to 0.88)
Raber G 1.94 (0.86 to 4.36) 0.81 (0.58 to 1.11)
Feigen. M 13.75 (0.71 to 266.31) 0.80 (0.60 to 1.08)
Camilien. L 1.30 (0.93 to 1.81) 0.10 (0.01 to 0.90)
Camilien. L 10.00 (0.61 to 162.66) 0.40 (0.11 to 1.44)
Camilien. L 3.96 (0.36 to 43.70) 0.01 (0.00 to 0.23)
Janus. C.L 2.22 (0.11 to 42.96) 0.90 (0.53 to 1.52)
Matsukuma. K 22.50 (5.32 to 95.15) 0.30 (0.09 to 0.95)
Matsukuma. K 22.32 (7.47 to 66.73) 0.75 (0.57 to 0.98)
Heller. PB 8.26 (3.86 to 17.70) 0.68 (0.57 to 0.82)
Kim. SH 4.00 (1.01 to 15.87) 0.79 (0.57 to 1.08)
Kim. SH 3.71 (1.57 to 8.78) 0.81 (0.66 to 1.00)
Subak. LL 7.75 (1.63 to 36.92) 0.53 (0.24 to 1.20)
Oellinger. JJ 6.22 (0.38 to 102.94) 0.65 (0.38 to 1.13)
Yang. WT 19.09 (4.68 to 77.93) 0.37 (0.19 to 0.70)
Vorgias. G 9.60 (4.88 to 18.87) 0.43 (0.30 to 0.61)
Hertel. H 1.03 (0.30 to 3.51) 0.99 (0.80 to 1.23)
Hertel. H 1.56 (0.48 to 5.14) 0.92 (0.72 to 1.19)
Kokka. F 5.54 (3.72 to 8.25) 0.41 (0.30 to 0.58)
Ozsarlak. O 42.25 (2.66 to 670.99) 0.19 (0.05 to 0.81)
Pooled Positive LR = 4.31 (2.98 to 6.23)
Cochran-Q = 112.45; df = 30 (p = 0.0000)
Inconsistency (I-square) = 73.3%
Pooled Negative LR = 0.58 (0.48 to 0.70)
Cochran-Q = 147.29; df = 30 (p = 0.0000)
Inconsistency (I-square) = 79.6%
0.01
1
100.0
Negative LR
Sensitivity
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Spearman correlation coefficient
R = 0.29 p = 0.11

Appendix 2 Proposed MEDLINE search strategy to identify the relevant studies

Test accuracy search – proposed MEDLINE strategy

Ovid MEDLINE(R) – 1950 to June week 1 2009

1. exp tomography, emission-computed/ (53449)
2. (emission adj2 comput$ adj2 tomograph$).tw. (9829)
3. (tomograph$ adj2 emission adj2 comput$).tw. (10061)
4. (radionuclide-comput$ adj2 tomograph$).tw. (19)
5. (radionuclide adj2 cat scan$).tw. (4)
6. (radionuclide adj2 ct scan$).tw. (29)
7. (scintigraph$ adj2 comput$ adj2 tomograph$).tw. (375)
8. (positron adj2 emission adj2 tomograph$).tw. (21619)
9. (pet or petct).tw. (30569)
10. or/1-9 (66680)
11. (recur$ or relaps$ or metasta$ or restag$ or re-stag$).mp. (638721)
12. uterine cervical neoplasms/ (47784)
13. ((cervix or cervical) adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (44525)
14. 12 or 13 (59939)
15. 11 and 10 and 14 (259)

Effectiveness search (systematic reviews) – proposed MEDLINE strategy

Ovid MEDLINE(R) – 1950 to June week 1 2009

1. (recur$ or relaps$ or metasta$ or restag$ or re-stag$).mp. (638721)
2. uterine cervical neoplasms/ (47784)
3. ((cervix or cervical) adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (44525)
4. 2 or 3 (59939)
5. 1 and 4 (11331)
6. limit 5 to "reviews (specificity)" (66)

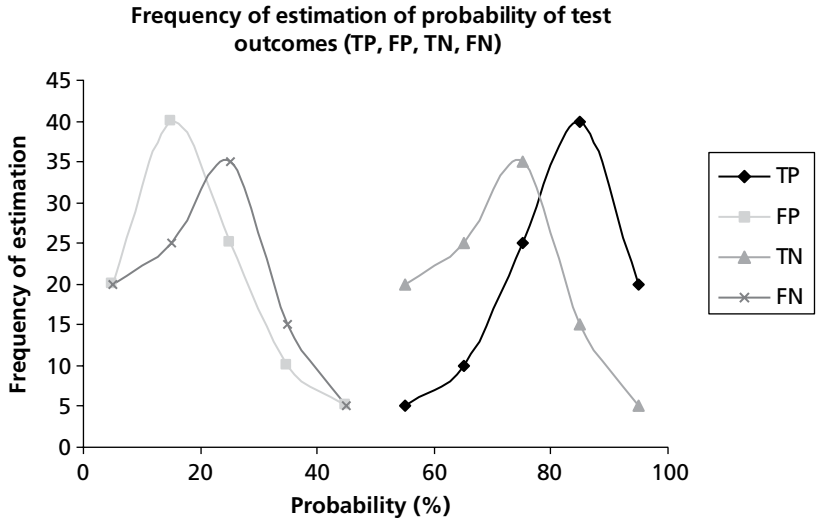
Effectiveness search (RCTs) – proposed MEDLINE strategy

Ovid MEDLINE(R) –1950 to June week 1 2009

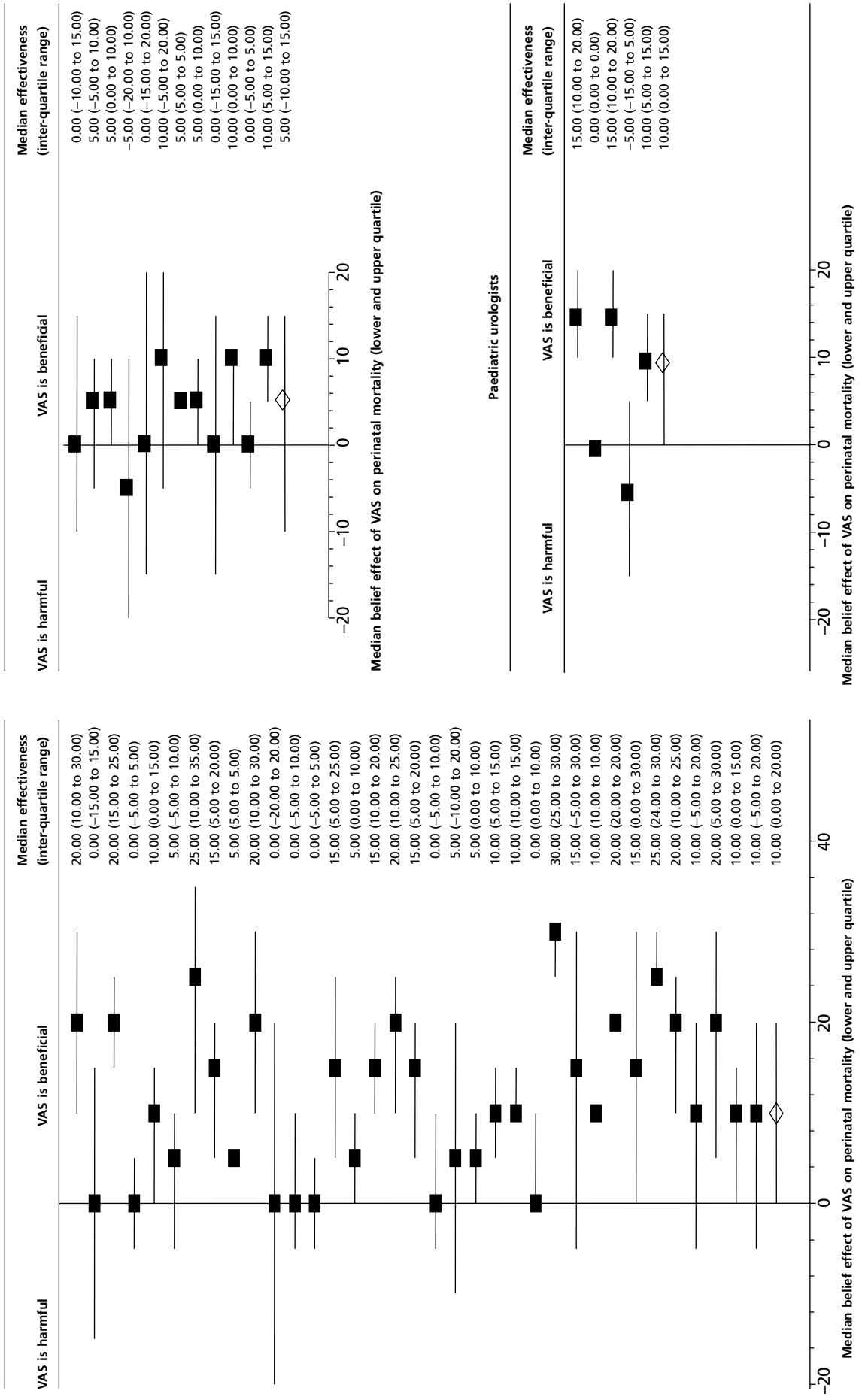
1. (recur$ or relaps$ or metasta$ or restag$ or re-stag$).mp. (638721)
2. uterine cervical neoplasms/ (47784)
3. ((cervix or cervical) adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (44525)
4. 2 or 3 (59939)
5. 1 and 4 (11331)
6. limit 5 to "therapy (specificity)" (191)

Appendix 3 Probability distributions of TP, TN, FP, FN derived from *table 3* for CT or MRI used to detect recurrence of cervical cancer (stage IB2–IV)

The attached excel work sheet demonstrates an exercise in eliciting subjective probabilities on the estimated distance between London and Birmingham.



Appendix 4 Forest plots demonstrating variations in probability estimations



Appendix 5 Illustrative example: eliciting subjective probabilities on test accuracy scenario 1

Accuracy of CT/MRI in patients with a primary diagnosis of stage IB2–IV who are suspected to have recurrence on the basis of being symptomatic (assuming prevalence of recurrence of cervical cancer of 15% in this patient group)

Please indicate by allocating points to a sum of 100 how likely each estimate of the % of true-positives (as a % of all those with confirmed recurrent cervical cancer) and similarly how likely each estimate of the % of true-negatives (as a % of those with no recurrence confirmed) is to be true when CT or MRI are used in the detection of recurrent cervical cancer in this population.

	Recurrence confirmed D+	No recurrence confirmed D–
	True positive (TP) result	False positive
CT or MRI +ve	Percent of TP detected: 50–60% of 150	
	Percent of TP detected: 61–70% of 150	
	Percent of TP detected: 71–80% of 150	
	Percent of TP detected: 81–90% of 150	
	Percent of TP detected: 91–100% of 150	
	Total: 100 points	
CT or MRI –ve		True negative (TN) result
		Percent of TN detected: 50–60% of 850
		Percent of TN detected: 61–70% of 850
		Percent of TN detected: 71–80% of 850
		Percent of TN detected: 81–90% of 850
		Percent of TN detected: 91–100% of 850
		Total: 100 points
	150	850

TABLE 2 Example of completed table

	Recurrence confirmed D+		No recurrence confirmed D–	
	True positive (TP) result		False positive	
CT or MRI +ve	Percent of TP detected: 50–60% of 150	5		
	Percent of TP detected: 61–70% of 150	1		
	Percent of TP detected: 71–80% of 150	25		
	Percent of TP detected: 81–90% of 150	40		
	Percent of TP detected: 91–100% of 150	20		
		Total: 100 points		
CT or MRI –ve			True negative (TN) result	
			Percent of TN detected: 50–60% of 850	20
			Percent of TN detected: 61–70% of 850	25
			Percent of TN detected: 71–80% of 850	35
			Percent of TN detected: 81–90% of 850	15
			Percent of TN detected: 91–100% of 850	5
				Total: 100 points
	150		850	

TABLE 3 Assuming the probability distribution of FP is the inverse of the TP distribution and the probability distribution of TN is the inverse of the FN distribution

	Recurrence confirmed D+		No recurrence confirmed D–	
	True positive (TP) result		False positive (FP) result	
CT or MRI +ve	Percent of TP detected: 50–60% of 150	5	Percent of FP detected: 40–49% of 850	5
	Percent of TP detected: 61–70% of 150	10	Percent of FP detected: 30–39% of 850	10
	Percent of TP detected: 71–80% of 150	25	Percent of FP detected: 20–29% of 850	25
	Percent of TP detected: 81–90% of 150	40	Percent of FP detected: 10–19% of 850	40
	Percent of TP detected: 91–100% of 150	20	Percent of FP detected: 0–9% of 850	20
		Total: 100 points		Total: 100 points
CT or MRI –ve	False negative (FN) result		True negative (TN) result	
	Percent of FN detected: 40–49% of 850	20	Percent of TN detected: 50–60% of 850	20
	Percent of FN detected: 30–39% of 850	25	Percent of TN detected: 61–70% of 850	25
	Percent of FN detected: 20–29% of 850	35	Percent of TN detected: 71–80% of 850	35
	Percent of FN detected: 10–19% of 850	15	Percent of TN detected: 81–90% of 850	15
	Percent of FN detected: 0–9% of 850	5	Percent of TN detected: 91–100% of 850	5
		Total: 100 points		Total: 100 points
	150		850	

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Appendix 2 Scoping search strategies and results

The objective was a scoping search to identify published systematic reviews (for diagnostic accuracy, yield and effectiveness). Searches were undertaken between May 2010 and August 2010. The following databases would be searched: MEDLINE, EMBASE, Science Citation Index, The Cochrane Library (all databases), UK Clinical Research Network Study Portfolio and ClinicalTrials.gov.

The search terms used are shown below.

In total, 468 citations for published studies and 12 citations for ongoing research were found. Of these, 50 full-text articles were assessed for eligibility and one systematic review was found.[59] This was assessed using the form below.

Searches

MEDLINE (Ovid Gateway) (May 2010)

One hundred and thirty records were retrieved in MEDLINE.

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Recurrence/ or exp Neoplasm Recurrence, Local/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp Neoplasm Metastasis/
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 and 25
27. ("review" or "review academic" or "review tutorial").pt.
28. (scisearch or psychinfo or psycinfo).tw,sh.
29. cinahl.tw,sh.
30. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
31. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.

32. (pooling or pooled or mantel haenszel).tw,sh.
33. (retraction of publication or retracted publication).pt.
34. (peto or dersimonian or der simonian or fixed effect).tw,sh.
35. (medline or medlars or embase or pubmed).tw,sh.
36. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. meta-analysis.pt.
38. meta-analysis.sh.
39. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
40. (systematic$ adj5 review$).tw,sh.
41. (systematic$ adj5 overview$).tw,sh.
42. (quantitativ$ adj5 overview$).tw,sh.
43. (quantitativ$ adj5 synthesis$).tw,sh.
44. (methodologic$ adj5 review$).tw,sh.
45. (methodologic$ adj5 overview$).tw,sh.
46. (integrative research review$ or research integration).tw.
47. (quantitativ$ adj5 review$).tw,sh.
48. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. 27 and 36
50. 48 or 49
51. 26 and 50

EMBASE (Ovid Gateway) (May 2010)

Two hundred and three records were retrieved in EMBASE.

1. exp uterine cervix tumor/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 malignan$).mp.
7. (cervi$ adj5 tumor$).mp.
8. (cervi$ adj5 tumour$).mp.
9. (cervi$ adj5 neoplas$).mp.
10. (cervi$ adj5 metasta$).mp.
11. (cervi$ adj5 cyst$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp recurrent disease/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp metastasis/
22. restag$.mp.
23. re-stag.mp.
24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 12 and 24
26. exp review/
27. (medline or medlars or embase or pubmed).ti,ab,sh.
28. (scisearch or psychlit or psyclit).ti,ab,sh.
29. (psycinfo or psychinfo).ti,ab,sh.

30. cinahl.ti,ab,sh.
31. ((electronic adj database$) or (bibliographic adj database$)).tw.
32. ((pooled adj analys$) or pooling).tw.
33. (peto or dersimonian or (fixed adj effect) or mantel haenszel).tw.
34. RETRACTED ARTICLE/
35. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 26 and 35
37. exp meta analysis/
38. meta?analys$.tw,sh.
39. (systematic$ adj5 review$).tw,sh.
40. (systematic$ adj5 overview$).tw,sh.
41. (quantitativ$ adj5 review$).tw,sh.
42. (quantitativ$ adj5 overview$).tw,sh.
43. (methodologic$ adj5 review$).tw,sh.
44. (methodologic$ adj5 overview$).tw,sh.
45. ((integrative adj5 research adj5 review$) or (research adj5 integration)).tw.
46. (quantitativ$ adj5 synthesi$).tw,sh.
47. 37or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48. 36 or 47
49. 25 and 48

The Cochrane Library (all databases) (May 2010)

Six hundred and eleven records were retrieved in The Cochrane Library (all databases).

1. MeSH descriptor Uterine Cervical Neoplasms explode all trees
2. cervi* near/5 neoplas*
3. cervi* near/5 carcinom*
4. cervi* near/5 malignan*
5. cervi* near/5 tumor*
6. cervi* near/5 tumour*
7. cervi* near/5 cancer*
8. cervi* near/5 adenocarcinom*
9. cervi* near/5 carcinogen*
10. cervi* near/5 metasta*
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. recur*
13. relaps*
14. repeat*
15. reappearance*
16. reoccurence*
17. return
18. MeSH descriptor Neoplasm Metastasis explode all trees
19. restag*
20. re-stag
21. metasta*
22. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #21
23. #12 AND #23

Review assessment form: effectiveness part

Review Assessment Form – Effectiveness Part

Ongoing review title .....

Date ..... **(dd/mm/yy)**

Reviewer ID .....

Assessed review ID .....

Assessed review title	
First author	
Source of publication Journal yy;vol(iss):pp	
Publication type	journal □ abstract other (s*pecify*): …….

Inclusion criteria/PICOS Scheme	
Population	women with persistent or recurrent cervical cancer after primary treatment Description *(for example primary treatment)* ……..
Intervention	surgery chemo radiation radiation palliative treatment other
Comparators	no comparators comparators used *(specify):* …… comparison within the same group of participants over time
Outcomes	morbidity mortality Quality of Life other
Study design	RCT non-randomized controlled study *(specify):* …….. other *(specify):* ……..

Searching for primary studies	
Search strategy	Strategy is reproducible Strategy is not reproducible No strategy is presented
Databases searched	MEDLINE EMBASE Cochrane Library Science Citation Index Clinical Trials.com UK Clinical Research Network Portfolio other
Hand searching	Yes No Not stated
Search restrictions	language publication date no restrictions no stated

Quality assessment of included studies	
Select the parameters which are included in quality assessment of particularly trials? method of randomization allocation concealment information about excluded patients intention-to-treat analysis blinding no quality assessment was conducted other parameters (*specy*):……	
Data extraction	
Was extraction prepared independently by at least 2 reviewers?	Yes No Not stated
Data synthesis	
Select the activities performed in data synthesis: proper presentation of results (effect size and confidence intervals) presentation of results for each treatment group in each trial for ich primary outcomes presentation of results as intention-to-treat analysis assessment of heterogeneity sensivity testing biases assessment	
Specify the method of combining results: ……..……	

Reviewer's assessment
Do results and conclusions presented in the review need for: updating? filling gaps in information? correction? The review presents current, correct and valid information regarding clinical problem being concern.

Reviewer's comments

Appendix 3 Diagnostic review data extraction form

Data Extraction Form – Diagnostic Part

Review title.....

Date..... **(dd/mm/yy)**

Reviewer ID .....

Study ID .....

Study title	
First author	
Source of publication Journal yy;vol(iss):pp	
Country of publication	
Publication type	journal □ abstract other (*specify*): ……

Study eligibility

Population	women suspected to have persistent or recurrent cervical cancer after primary treatment patients with advanced stage cervical cancer (IB2-IV) treated previously with chemoradiation with a minimum gap between completion of treatment and imaging of 3 months other
Index test	PET-CT other
Comparator	MRI CT other lack of comparator
Reference standard	histopatology clinical follow-up other

Study characteristics

Population	
Trial inclusion criteria	
Trial exclusion criteria	
Number of enrolled patients, N	
Number of patients who completed the study, n (%)	
Age, in years; mean (range)	
Type of initial treatment, n (%)	
Initial staging, n (%)	
Other main baseline parameters	
Tests	
Type of index test used (short description)	

Type of alternative test/comparator (short description)	
Type of reference standard (short description)	
Duration of follow up in months (range)	
Methods	
Method of enrolment	consecutive arbitrary random not reported
Data Collection	prospective retrospective not reported
Information about drops out	precise information inaccurate information lack of information
Statistical technique used	
Sample size calculation	
Funding source	

Quality assessment	
Representative spectrum?	Yes No Unclear
Acceptable reference standard?	Yes No Unclear
Acceptable delay between tests?	Yes No Unclear
Partial verification avoided?	Yes No Unclear
Differential verification avoided?	Yes No Unclear
Incorporation avoided?	Yes No Unclear
Reference standard results blinded?	Yes No Unclear
Index test results blinded?	Yes No Unclear
Relevant clinical information?	Yes No Unclear
Uninterpretable results reported?	Yes No Unclear
Withdrawals explained?	Yes No Unclear

Results

		Reference standard		
		Positive	Negative	Total
PET- CT	Positive			
	Negative			
	Total			

		Reference standard		
		Positive	Negative	Total
Comparator CT	Positive			
	Negative			
	Total			

Reviewer's comments

……

Appendix 4 Effectiveness review data extraction forms

Data Extraction Form – Effectiveness Part

Review title.....

Date..... **(dd/mm/yy)**

Reviewer ID..... **Study ID** .....

Study title	
First author	
Source of publication Journal yy;vol(iss):pp	
Language	
Publication type	journal □ abstract other (s*pecify*): ……

Study eligibility/PICOS Scheme

Population	women with persistent or recurrent cervical cancer after primary treatment: radiation, chemoradiation women with persistent or recurrent cervical cancer after primary treatment: radical surgery women with multiple site or distant reccurence (treatment in palliative intent) other
Intervention	Curative intent: surgery chemo radiation radiation Palliative intent: palliative treatment other
Comparison	no comparators comparators used (specify)…… comparison within the same group of participants over time
Outcomes	morbidity mortality Quality of Life none of the above
Study design	RCT non-randomized controlled study (specify): …… other (specify): ……

If included study is comparative experimental study, then go to the point A ,

If included study is comparative observational study, then go to the point B,

f included study is non- comparative study, then go to the point C

PART A

Comparative Experimental Studies:

1. Study characteristics

Methods/methodological quality	
Study design	RCT NRS
RCT	
Method of randomization	specify and assess the method: …… adequate inadequate unclear not reported
Allocation concealment	adequate inadequate unclear not reported Describe……..
Blinding	select blinded subjects: patients investigators/clinicians outcomes assessors no blinding used assess the method: adequate inadequate unclear not reported
Information about drop outs	precise information (number of patients and reasons) inaccurate information lack of information
Rate of loss to follow-up	
Patients lost to follow-up analyzed for adverse events	
Was the follow-up adequate to ascertain adverse effects?	Yes No Unclear If "yes", specify……
Statistical technique used	
Was adequate statistical analysis of potential confounders performed?	Yes No Unclear
Intention-to-treat analysis What was the definition of ITT in the study?	implemented not implemented …… …… …… ……
Sample size calculation	
Was the sensitivity analysis performed?	Yes No Not applicable
How problem with missing data was resolved?	
Were missing data accounted for in the analyses?	Yes No

Post hoc analysis	
Funding source	
NRS	
Control group selection	specify and assess the method: …… ……..... adequate inadequate unclear not reported
Allocation concealment	adequate inadequate unclear not reported Describe……..
Blinding	select blinded subjects: patients investigators/clinicians outcomes assessors no blinding used assess the method: adequate inadequate unclear not reported
Information about drop outs	precise information (number of patients and reasons) inaccurate information lack of information
Rate of loss to follow-up	
Patients lost to follow-up analyzed for adverse events	
Was the follow-up adequate to ascertain adverse effects?	Yes No Unclear If "yes", specify……
Statistical technique used	
Was adequate statistical analysis of potential confounders performed?	Yes No Unclear
Intention-to-treat analysis What was the definition of ITT in the study?	implemented not implemented ……
Sample size calculation	
Was the sensitivity analysis performed?	Yes No Not applicable
How problem with missing data was resolved?	
Were missing data accounted for in the analyses?	Yes No
Post hoc analysis	
Funding source	

Population		
Trial inclusion criteria		
Trial exclusion criteria		
	Intervention group	Comparator/control group
Number of enrolled patients		
Number of patients randomized, N_R		
Number of patients who completed treatment, n (%)		
Number of patients available for follow up, n (%)		
Age, in years *specify the measure*: ……		
Other baseline characteristics (stage: % recurrent, metastatic, persistent, prior therapy, site of disease: pelvic, distant, both)		
Were treatment groups comparable at baseline?	Yes No *If "no" specify the reasons:* ……	
Treatment		
Type of treatment used (technique, no. of sessions)		
Treatment duration		
Duration of follow up		
Outcomes		
Definition and unit of measurement		

Results

Dichotomous data

Outcome:……. Follow up:……			
Intervention group N_R / $N_=$		Control group N_R / $N_=$	
N’	n (%)	N’	n (%)
Effect estimate RR OR (95% CI SE p)			
Blinding	*select blinded subjects:* patients investigators/clinicians outcomes assessors no binding used *assess the method:* adequate inadequate unclear not reported		
Incomplete outcome data addressed			

N’ – number of evaluated patients; n – number of patients with outcome

DOI: 10.3310/hta17120

Time-to-event data

Outcome:…….. Follow up:……			
Intervention group N_R / N =		Control group N_R / N =	
N'	Median	N'	Median
Effect estimate HR (95% CI SE p)			
Blinding	*select blinded subjects:* patients investigators/clinicians outcomes assessors no binding used *assess the method:* adequate inadequate unclear not reported		
Incomplete outcome data addressed			

N' – number of evaluated patients

Continuous data

Outcome:…….. Follow up:……							
Intervention group $N_R / N_=$				Control group $N_R / N_=$			
N’	Mean value at baseline (SD / SE / other)	Mean endpoint value (SD / SE / other)	Mean change from baseline (SD / SE / other)	N’	Mean value at baseline (SD / SE / other)	Mean endpoint value (SD / SE / other)	Mean change from baseline (SD / SE / other)
Blinding	*select blinded subjects:* patients investigators/clinicians outcomes assessors no binding used *assess the method:* adequate inadequate unclear not reported						
Incomplete outcome data addressed							

N’ – number of evaluated patients

PART B

B) Comparative Observational Studies:

1. Study characteristics

Methods/methodological quality	
Study design	Case – control Cohort
Case – Control	
Is case definition adequate?	independent validation record linkage self reported none
Are the cases representative?	all cases arising from same population or group not known
Selection of controls	same population as cases not known or no
Definition of controls	outcome of interest not present in history no mention of history of outcome
Comparability of cases and controls	Yes No Unclear
Ascertainment of exposure to intervention	secure record structured interview where blind to case/control status interview not blinded to case/control status written self report of medical record only no description
Was the method of ascertainment of exposure for cases and controls the same?	Yes No Unclear
Non-response rate	same for both groups… non respondents described rate different and no designation
Cohort	
Is the cohort representative	Yes No Unclear
Selection of non–exposed cohort	same population as exposed cohort not known or no
Ascertainment of exposure	secure record structured interview written self report no description
Demonstration that outcome of interest wasn't present at start of study?	Yes No Unclear
Comparability of cohorts on the basis of the design or analysis	Yes No Unclear
Assessment of outcome	independent or blind assessment record linkage self-report no description
Was follow-up long enough for outcomes to occur?	Yes No Unclear *If "yes", specify*……

Was follow-up of cohorts adequate?	complete follow-up subjects lost to follow-up unlikely to introduce bias, small number lost (…..%) follow-up rate ….%, and no description of this lost no statement	
Population		
Trial inclusion criteria		
Trial exclusion criteria		
Is the target population defined?	Yes No	
	Intervention group	Comparator/control group
Number of included patients, N		
Number of patients who completed treatment, n (%)		
Age, in years *specify the measure*:		
Other baseline characteristics (stage: % recurrent, metastatic, persistent, prior therapy, site of disease: pelvic, distant, both)		
Were treatment groups comparable at baseline?	Yes No Not applicable *If "no" specify the reasons:* ……	
Treatment		
Type of treatment used (technique, no. of sessions)		
Treatment duration		
Duration of follow up		
Outcomes		
Definition and unit of measurement		

DOI: 10.3310/hta17120

Results

Dichotomous data

Outcome:……. Follow up:……			
Intervention group N_R / $N_=$		Control group N_R / $N_=$	
N'	n (%)	N'	n (%)
Effect estimate RR OR (95% CI SE p)			
Blinding	*select blinded subjects:* patients investigators/clinicians outcomes assessors no binding used *assess the method:* adequate inadequate unclear not reported		
Incomplete outcome data addressed			

N' – number of evaluated patients; n – number of patients with outcome

Time-to-event data

Outcome:……. Follow up:……			
Intervention group N_R / $N_=$		Control group N_R / $N_=$	
N’	Median	N’	Median
Effect estimate HR (95% CI SE p)			
Blinding	*select blinded subjects:* patients investigators/clinicians outcomes assessors no binding used *assess the method:* adequate inadequate unclear not reported		
Incomplete outcome data addressed			

N’ – number of evaluated patients

Continuous data

Outcome:…… Follow up:……							
Intervention group N_R / N =				Control group N_R / N =			
N'	Mean value at baseline (SD / SE / other)	Mean endpoint value (SD / SE / other)	Mean change from baseline (SD / SE / other)	N'	Mean value at baseline (SD / SE / other)	Mean endpoint value (SD / SE / other)	Mean change from baseline (SD / SE / other)
Blinding	*select blinded subjects:* patients investigators/clinicians outcomes assessors no binding used *assess the method:* adequate inadequate unclear not reported						
Incomplete outcome data addressed							

N' – number of evaluated patients

Reviewer's comments

……

PART C

Non-Comparative Studies:

Quality assessment according checklist from "Methods for the development of NICE public health guidance (second edition)"

Type of study,

methodology_decription……

……

……

Population	
Trial inclusion criteria	
Trial exclusion criteria	
Number of enrolled patients	
Number of patients who completed treatment, n (%)	
Number of patients available for follow up, n (%)	
Age, in years *specify the measure*:	
Other baseline characteristics (stage: % recurrent, metastatic, persistent, prior therapy, site of disease: pelvic, distant, both)	
Treatment	
Type of treatment used (technique, no. of sessions)	
Treatment duration	
Duration of follow up	
Outcomes	
Definition and unit of measurement	

Results

Dichotomous data

Outcome:…….. Follow up:……	
Intervention group	
N	n (%)
(95% CI SE p)	
Incomplete outcome data addressed	

N' – number of evaluated patients; n – number of patients with outcome

Time to event data

Outcome:…….. Follow up:….	
Intervention group	
N	Median
(95% CI SE p)	
Incomplete outcome data addressed	

N' – number of evaluated patients; n – number of patients with outcome

Continuous data

Outcome:…….. Follow up:……			
Intervention group			
N	Mean value at baseline (SD / SE / other)	Mean endpoint value (SD / SE / other)	Mean change from baseline (SD / SE / other)
p			
Incomplete outcome data addressed			

N' – number of evaluated patients; n – number of patients with outcome

Appendix 5 Case series quality assessment form

Checklist used for quality assessment of case series

Study identification (Include full citation details)		
Study design: Refer to the glossary of study designs and the algorithm for classifying experimental and observational study designs to best describe the paper's underpinning study design **Guidance topic:**		
Assessed by:		
Section 1: Population		
1.1 Is the source population or source area well described? Was the country (e.g. developed or nondeveloped, type of health care system), setting (primary schools, community centres etc.), location (urban, rural), population demographics etc. adequately described?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
1.2 Is the eligible population or area representative of the source population or area? Was the recruitment of individuals/clusters/areas well defined (e.g. advertisement, birth register)? Was the eligible population representative of the source? Were important groups under-represented?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
1.3 Do the selected participants or areas represent the eligible population or area? Was the method of selection of participants from the eligible population well described? What % of selected individuals/clusters agreed to	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:

participate? Were there any sources of bias? Were the in-/exclusion criteria explicit and appropriate?		
Section 2: Method of Allocation to intervention (or comparison)		
2.1 Allocation to intervention (or comparison). How was selection bias minimised? Was allocation to exposure and comparison randomised? Was it truly random ++ or pseudo-randomised + (e.g. consecutive admissions)? If not randomised, was significant confounding likely (-) or not (+)? If a cross-over, was order of intervention randomised?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
2.2 Were interventions (and comparisons) well described and appropriate? Were intervention/s & comparison/s described in sufficient detail (i.e. enough for study to be replicated)? Was comparison/s appropriate (e.g. usual practice rather than no intervention)?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
2.3 Was the allocation concealed? Could the person(s) determining allocation of participants/clusters to intervention or comparison groups have influenced the allocation? Adequate allocation concealment (++) would include centralised allocation or computerised allocation systems.	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
2.4 Were participants and/or investigators blind to exposure and comparison? Were participants AND	☐ ++ ☐ +	Comments:

investigators – those delivering and/or assessing the intervention kept blind to intervention allocation? (Triple or double blinding score ++) If lack of blinding is likely to cause important bias, score -.	☐ - ☐ NR ☐ NA	
2.5 Was the exposure to the intervention and comparison adequate? Is reduced exposure to intervention or control related to the intervention (e.g. adverse effects leading to reduced compliance) or fidelity of implementation (e.g. reduced adherence to protocol)? Was lack of exposure sufficient to cause important bias?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
2.6 Was contamination acceptably low? Did any in the comparison group receive the intervention or vice versa? If so, was it sufficient to cause important bias? If a cross-over trial, was there a sufficient wash-out period between interventions?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
2.7 Were other interventions similar in both groups? Did either group receive additional interventions or have services provided in a different manner? Were the groups treated equally by researchers or other professionals? Was this sufficient to cause important bias?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
2.8 Were all participants accounted for at study conclusion? Were those lost-to-follow-up (i.e. dropped or lost pre-/during/post-intervention) acceptably low (i.e. typically	☐ ++ ☐ + ☐ - ☐ NR	Comments:

<20%)?		
Did the proportion dropped differ by group? For example, were drop-outs related to the adverse effects of the intervention?	☐ NA	
2.9 Did the setting reflect usual UK practice? Did the setting in which the intervention or comparison was delivered differ significantly from usual practice in the UK? For example, did participants receive intervention (or comparison) condition in a hospital rather than a community-based setting?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
2.10 Did the intervention or control comparison reflect usual UK practice? Did the intervention or comparison differ significantly from usual practice in the UK? For example, did participants receive intervention (or comparison) delivered by specialists rather than GPs? Were participants monitored more closely?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
Section 3: Outcomes		
3.1 Were outcome measures reliable? Were outcome measures subjective or objective (e.g. biochemically validated nicotine levels ++ vs self-reported smoking -). How reliable were outcome measures (e.g. inter- or intra-rater reliability scores)?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:

Was there any indication that measures had been validated (e.g. validated against a gold standard measure or assessed for content validity)		
3.2 Were all outcome measurements complete? Were all/most study participants who met the defined study outcome definitions likely to have been identified?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
3.3 Were all important outcomes assessed? Were all important benefits and harms assessed? Was it possible to determine the overall balance of benefits and harms of the intervention versus comparison?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
3.4 Were outcomes relevant? Where surrogate outcome measures were used, did they measure what they set out to measure? (e.g. a study to assess impact on physical activity assesses gym membership – a potentially objective outcome measure – but is it a reliable predictor of physical activity?)	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
3.5 Were there similar follow-up times in exposure and comparison groups? If groups are followed for different lengths of time, then more events are likely to	☐ ++ ☐ + ☐ - ☐ NR	Comments:

occur in the group followed-up for longer distorting the comparison. Analyses can be adjusted to allow for differences in length of follow-up (e.g. using person-years).	☐ NA	
3.6 Was follow-up time meaningful? Was follow-up long enough to assess longterm benefits/harms? Was it too long, e.g. participants lost to follow-up?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
Section 4: Analyses		
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted? Were there any differences between groups in important confounders at baseline? If so, were these adjusted for in the analyses (e.g. multivariate analyses or stratification). Were there likely to be any residual differences of relevance?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
4.2 Was Intention to treat (ITT) analysis conducted? Were all participants (including those that dropped out or did not fully complete the intervention course) analysed in the groups (i.e. intervention or comparison) to	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:

which they were originally allocated?		
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)? A power of 0.8 (i.e. it is likely to see an effect of a given size if one exists, 80% of the time) is the conventionally accepted standard. Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
4.4 Were the estimates of effect size given or calculable? Were effect estimates (e.g. relative risks, absolute risks) given or possible to calculate?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
4.5 Were the analytical methods appropriate? Were important differences in follow-up time and likely confounders adjusted for? If a cluster design, were analyses of sample size (and power), and effect size performed on clusters (and not individuals)? Were subgroup analyses pre-specified?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
4.6 Was the precision of intervention effects given or calculable? Were they meaningful? Were confidence intervals and/or p-values for effect estimates given or	☐ ++ ☐ + ☐ - ☐ NR	Comments:

possible to calculate? Were CI's wide or were they sufficiently precise to aid decision-making? If precision is lacking, is this because the study is under-powered?	☐ NA	
Section 5: Summary		
5.1 Are the study results internally valid (i.e. unbiased)? How well did the study minimise sources of bias (i.e. adjusting for potential confounders)? Were there significant flaws in the study design?	☐ ++ ☐ + ☐ -	Comments:
5.2 Are the findings generalisable to the source population (i.e. externally valid)? Are there sufficient details given about the study to determine if the findings are generalisable to the source population? Consider: participants, interventions and comparisons, outcomes, resource and policy implications.	☐ ++ ☐ + ☐ -	Comments:

Appendix 6 Diagnostic systematic review search strategies

MEDLINE (Ovid Gateway) (May 2010)

Two thousand, five hundred and eighty-six records were retrieved in MEDLINE.

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Recurrence/ or exp Neoplasm Recurrence, Local/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp Neoplasm Metastasis/
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 and 25
27. exp Diagnostic Imaging/
28. exp Imaging, Three-Dimensional/
29. exp magnetic resonance imaging/ or exp diffusion magnetic resonance imaging/ or exp magnetic resonance imaging, cine/
30. exp Magnetic Resonance Spectroscopy/
31. magnetic resonance imaging.mp.
32. magnetic resonance.mp.
33. mri.mp.
34. mr imaging.mp.
35. mri scan$.mp.
36. exp Radionuclide Imaging/
37. exp tomography, emission-computed/ or exp positron-emission tomography/
38. (emission adj2 comput$ adj2 tomograph$).mp.
39. (tomograph$ adj2 emission adj2 comput$).mp.
40. (radionuclide adj2 cat scan$).mp.
41. (scintigraph$ adj2 comput$ adj2 tomograph$).mp.

42. (positron adj2 emission adj2 tomograph$).mp.
43. (radionuclide adj2 ct scan$).mp.
44. (positron adj2 tomograph$).mp.
45. (pet or petct).mp.
46. fdg-pet.mp.
47. exp tomography, x-ray computed/ or exp tomography/ or exp tomography, x-ray/
48. computer tomograph$.mp.
49. computer tomogram$.mp.
50. computer assisted tomograph$.mp.
51. computer assisted tomogram$.mp.
52. ct.mp.
53. mr scan$.mp.
54. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
55. or 47 or 48 or 49 or 50 or 51 or 52 or 53
56. 26 and 54

EMBASE (Ovid Gateway) (May 2010)

Two thousand, six hundred and eighty-nine records were retrieved in EMBASE.

1. exp uterine cervix tumor/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp recurrent disease/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp metastasis/
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. exp diagnostic imaging/
27. exp three dimensional imaging/
28. exp nuclear magnetic resonance imaging/
29. exp diffusion weighted imaging/
30. exp nuclear magnetic resonance imaging/

31. exp nuclear magnetic resonance spectroscopy/
32. magnetic resonance imaging.mp.
33. magnetic resonance.mp.
34. mri.mp.
35. mr imaging.mp.
36. mri scan$.mp
37. mr scan$.mp.
38. exp emission tomography/ or exp tomography/ or exp positron emission tomography/
39. (emission adj2 comput$ adj2 tomograph$).mp.
40. (radionuclide adj2 cat scan$).mp.
41. (radionuclide adj2 ct scan$).mp.
42. (scintigraph$ adj2 comput$ adj2 tomograph$).mp.
43. (positron adj2 emission adj2 tomograph$).mp.
44. (positron adj2 tomograph$).mp.
45. (pet or petct).mp.
46. fdg-pet.mp.
47. exp computer assisted tomography/
48. tomography, x-ray.mp. or exp tomography/
49. computer tomograph$.mp.
50. computer tomogram$.mp.
51. computer assisted tomograph$.mp.
52. computer assisted tomogram$.mp.
53. ct.mp.
54. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. 12 and 25
56. 54 and 55

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and Health Technology Assessment database (May 2010)

Eighty-six records were retrieved in CDSR, CENTRAL, DARE and HTA.

1. MeSH descriptor Uterine Cervical Neoplasms explode all trees
2. (cervi* near/5 neoplas*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
3. (cervi* near/5 carcinom*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
4. (cervi* near/5 malignan*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
5. (cervi* near/5 tumor*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
6. (cervi* near/5 tumour*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
7. (cervi* near/5 cancer*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
8. (cervi* near/5 adenocarcinom*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
9. (cervi* near/5 carcinogen*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
10. (cervi* near/5 metasta*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
11. (cervi* near/5 cyst*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments

12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. (recur*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
14. (relaps*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
15. (repeat*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
16. (reappearance*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
17. (reoccurence*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
18. (return) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
19. MeSH descriptor Neoplasm Metastasis explode all trees
20. (restag*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
21. (re-stag) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
22. (metasta*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
23. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24. #12 AND #23
25. (diagnostic imaging) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
26. MeSH descriptor Imaging, Three-Dimensional explode all trees
27. MeSH descriptor Magnetic Resonance Imaging explode all trees
28. MeSH descriptor Diffusion Magnetic Resonance Imaging explode all trees
29. MeSH descriptor Magnetic Resonance Imaging, Cine explode all trees
30. (magnetic resonance) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
31. (mri) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
32. (mr imaging) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
33. (mri scan*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
34. (mr scan*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
35. MeSH descriptor Tomography, Emission-Computed explode all trees
36. MeSH descriptor Tomography explode all trees
37. MeSH descriptor Positron-Emission Tomography explode all trees
38. (emission near/2 comput* near/2 tomograph*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
39. (radionuclide near/2 cat scan*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
40. (radionuclide near/2 ct scan*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
41. (scintigraph* near/2 comput* near/2 tomograph*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
42. (positron near/2 emission near/2 tomograph) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
43. (positron near/2 tomograph*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
44. (pet or petct) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
45. (fdg-pet) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
46. MeSH descriptor Tomography, X-Ray explode all trees
47. MeSH descriptor Tomography, X-Ray Computed explode all trees
48. (computer tomograph*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
49. (computer tomogram*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
50. (computer assisted tomograph*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
51. (computer assisted tomogram*) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments
52. (ct) in Cochrane Reviews, Other Reviews, Clinical Trials and Technology Assessments

53. #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
54. #24 AND #53

Appendix 7 Subjective elicitation questionnaire

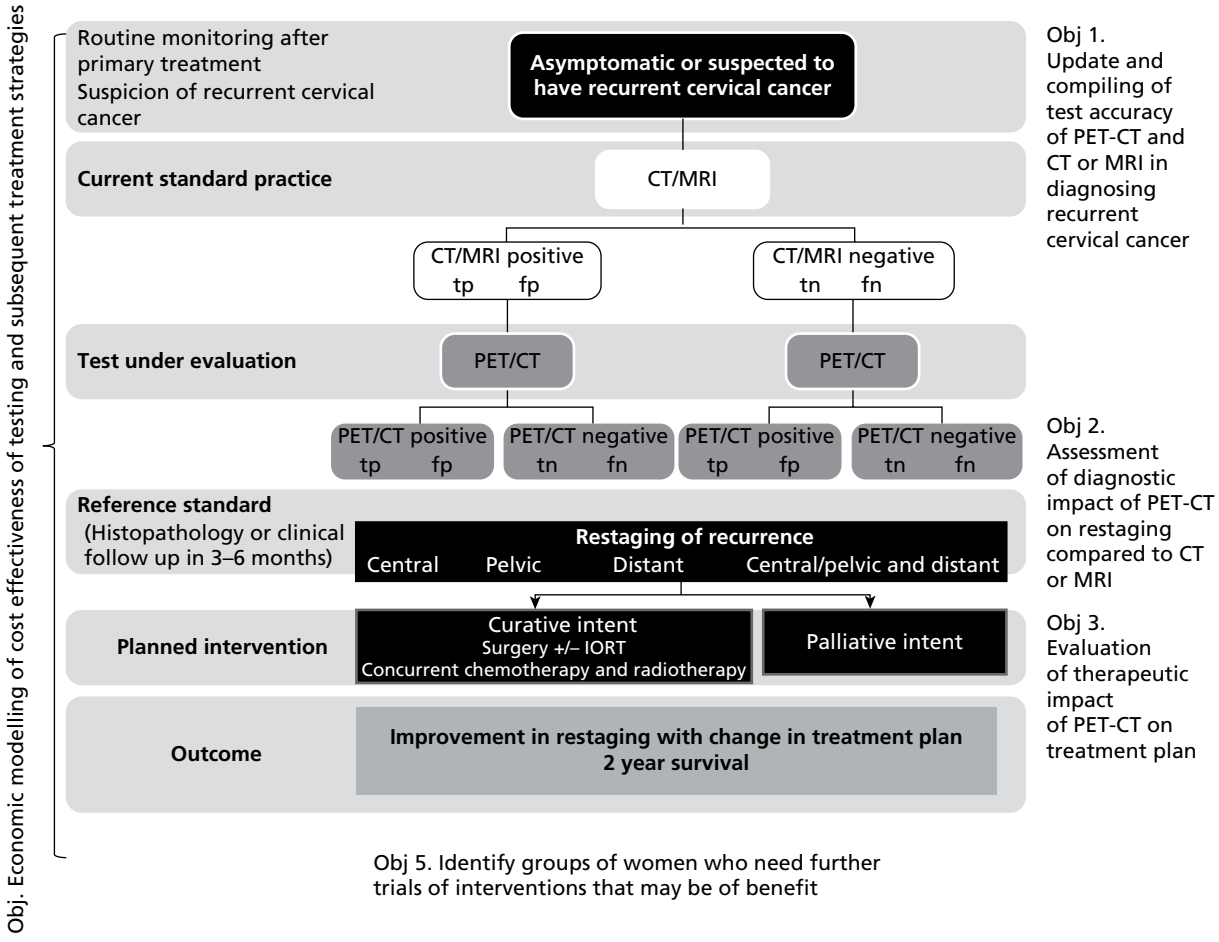
THE USE OF PETCT IN THE INVESTIGATION OF RECURRENT CERVICAL CANCER

Currently in the United Kingdom, patients with suspected cervical cancer recurrence will undergo

- clinical examination (rectovaginal and speculum examination, assessment of inguinal/ supraclavicular lymph nodes)
- cross sectional imaging by MRI (Magnetic Resonance Imaging) or CT (Computed Tomography) of chest, abdomen and pelvis
- examination under anaesthesia, histological confirmation of any vaginal vault mass by biopsies.

The HTA project is evaluating the added value of PET/CT to current imaging practice for restaging women with recurrent cervical cancer. Information from the elicitation exercise will be used to complement the findings of a systematic review in order to achieve objective 1 in figure 1 below:

Fig 1: Imaging modalities and treatment strategies in women with recurrent cervical cancer



The accuracy of PETCT in addition to CT/MRI will be examined for women with initial stage I-IV disease presenting with symptoms and for surveillance of asymptomatic women with initial stage 1B2-IV.

BACKGROUND INFORMATION

The following information is to assist with interpretation of the information we are about to elicit. For example, your estimates of accuracy may vary according to your speciality or to your experience of using PETCT.

1) Speciality

2) Years working in your current speciality

3) In any one single follow up consultation for patients under surveillance following an initial diagnosis of cervical cancer, in what % of patients do you estimate using MRI alone; CT alone; a combination of CT and MRI?

Indicate the % of patients who you estimate receive (CT); (MRI);(CT and MRI)ensuring the total % of patients sums to 100%

Imaging	% of patients receiving tests in any one follow up consultation
CT alone	
MRI alone	
CT + MRI	
TOTAL	**100%**

4) Do you currently use PETCT as part of the investigation of recurrent cervical cancer?

Yes / No

4 a) If you answered 'Yes' to Q.4, please state how long you have been using PETCT as part of the investigation of recurrent cervical cancer

4 b) If you answered 'Yes' to Q.4, please briefly describe in which patients or circumstances you use PETCT

WHAT IS THE PREVALENCE OF RECURRENT DISEASE?

The first piece of information we would like to elicit from you is your estimate of the prevalence of recurrent cancer in symptomatic and asymptomatic women 3 months post completion of primary treatment.

4) Of women with a mix of initial stage I-IV cervical cancer presenting with *symptoms suspicious for recurrence* a minimum of 3 months post completion of treatment, what % would you estimate to have recurrent disease?

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

% of symptomatic women with recurrence confirmed	**<50%**	**51-60%**	**61-70%**	**71–80%**	**81 –90%**	**90-100%**	
Points out of 100							**Total =100**

5) Of *asymptomatic* women with a mix of initial stage IB2-IV cervical cancer a minimum of 3 months post completion of treatment, what % would you estimate to have recurrent disease?

% of asymptomatic women with recurrence confirmed	**0-10%**	**11–20%**	**21-30%**	**31-40%**	**41-50%**	**>50%**	
Points out of 100							**Total =100**

ACCURACY OF IMAGING IN SYMPTOMATIC INITIAL STAGE 1-IV CERVICAL CANCER

The use of MRI and/or CT alone compared to the use of MRI and/or CT + PETCT in the diagnosis of recurrence in patients with an initial diagnosis of stage I to IV cervical cancer.

SYMPTOMATIC PATIENTS

-All patients are assumed to be a minimum of 3 months post completion of initial treatment (surgery+ chemotherapy or chemotherapy only).

-All patients are assumed to be *symptomatic* and have had a clinical examination which may be unde anaesthesia (histological confirmation of any vaginal vault mass by biopsies) or not under general anaesthesia (rectovaginal and speculum examination, assessment of inguinal/ supraclavicular lymph nodes).

-Patients subsequently receive either:
-CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination. In other words clinical examination is not used to triage patients for further imaging with CT and/or MRI; CT and/or MRI are used as an add on to clinical examination.

OR

- CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination ***and* PETCT**. In other words CT and/or MRI are not used to triage patients for further imaging with PETCT ; PETCT is used as an add on to CT and/or MRI.

ACCURACY OF CT and/or MRI

-Of the ***patients who test positive following investigation with CT and/or MRI***, what percentage consider ***will subsequently be diagnosed as negative for recurrence*** following histology and / or follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who t positive with CT and/or MRI who receive a false positive diagnosis*** (are actually disease negativ

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False positives (disease –ve) Test positives on CT and/or MRI	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

-Of the ***patients who test negative following investigation with CT and/or MRI***, what percentage consider ***will subsequently be diagnosed as positive for recurrence*** following histology and / or c follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who t negative with CT and/or MRI who receive a false negative diagnosis*** (are actually disease positiv

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False negatives (disease +ve) Test negatives on CT and/or MRI	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

The use of MRI and/or CT alone compared to the use of MRI and/or CT + PETCT in the diagnosis of recurrence in patients with an initial diagnosis of stage I-IV cervical cancer.

SYMPTOMATIC PATIENTS

-All patients are assumed to be a minimum of 3 months post completion of initial treatment (surgery+/- chemotherapy or chemotherapy only).

-All patients are assumed to be *symptomatic* and have had a clinical examination which may be under anaesthesia (histological confirmation of any vaginal vault mass by biopsies) or not under general anaesthesia (rectovaginal and speculum examination, assessment of inguinal/ supraclavicular lymph nodes).

-Patients subsequently receive either:

- CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination. In other words clinical examination is not used to triage patients for further imaging with CT and/or MRI; CT and/or MRI are used as an add on to clinical examination.

OR

- CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination ***and*** **PETCT**. In other words CT and/or MRI are not used to triage patients for further imaging with PETCT ; PETCT is used as an add on to CT and/or MRI.

ACCURACY OF CT and/or MRI +PETCT

-Of the ***patients who test positive following investigation with CT and/or MRI + PETCT***, what percentage do you consider ***will subsequently be diagnosed as negative for recurrence*** following histology and / or clinical follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who test positive with CT and/or MRI + PETCT who are false positives*** (are actually disease negative).

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False positives (disease –ve) Test positives on CT and/or MRI +PETCT	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

-Of the ***patients who test negative following investigation with CT and/or MRI + PETCT***, what percentage do you consider ***will subsequently be diagnosed as positive for recurrence*** following histology and / or clinical follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who test negative with CT and/or MRI + PETCT who are false negatives*** (are actually disease positive).

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False negatives (disease +ve) Test negatives on CT and/or MRI + PETCT	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

The use of MRI and/or CT alone compared to the use of PETCT as an adjunct to MRI and/or CT in the diagnosis of recurrence in patients with an initial diagnosis of stage I-IV cervical cancer.

SYMPTOMATIC PATIENTS

What do you consider the minimum important clinical reduction in the number of false positives (the difference in the percentage of those who test positive who are false positives (are actually disease negative) before introducing PETCT as an adjunct to CT and/or MRI?

False positives (disease –ve) Test positives **on CT and/or MRI +PETCT**	**0 - 2%**	**3 - 5%**	**6-8%**	**9 - 11%**	**>12% (please specify)**

What do you consider the minimum important clinical reduction in the number of false positives (the difference in the percentage of those who test negative who are false negatives (are actually disease positive) before introducing PETCT as an adjunct to CT and/or MRI?

False negatives (disease +ve**)** Test negatives **on CT and/or MRI + PETCT**	**0 - 2%**	**3 - 5%**	**6-8%**	**9 - 11%**	**>12% (please specify)**

ACCURACY OF IMAGING IN ASYMPTOMATIC INITIAL STAGE 1B2-IV CERVICAL CANCER

The use of MRI and/or CT alone compared to the use of MRI and/or CT + PETCT in the diagnosis of recurrence in patients with an initial diagnosis of stage IB2-IV cervical cancer.

ASYMPTOMATIC PATIENTS

-All patients are assumed to be a minimum of 3 months post completion of initial treatment (surgery+/- chemotherapy or chemotherapy only).

-All patients are assumed to be *asymptomatic* and have had a clinical examination which may be under anaesthesia (histological confirmation of any vaginal vault mass by biopsies) or not under general anaesthesia (rectovaginal and speculum examination, assessment of inguinal/ supraclavicular lymph nodes).
-Patients subsequently receive either:
- CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination. In other words clinical examination is not used to triage patients for further imaging with CT and/or MRI; CT and/or MRI are used as an add on to clinical examination.

OR

- CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination ***and*** **PETCT**. In other words CT and/or MRI are not used to triage patients for further imaging with PETCT ; PETCT is used as an add on to CT and/or MRI.

ACCURACY OF CT and/or MRI

-Of the ***patients who test positive following investigation with CT and/or MRI***, what percentage do you consider ***will subsequently be diagnosed as negative for recurrence*** following histology and / or clinical follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who test positive with CT and/or MRI who receive a false positive diagnosis*** (are actually disease negative).

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False positives (disease –ve) Test positives on CT and/or MRI	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

-Of the ***patients who test negative following investigation with CT and/or MRI***, what percentage do you consider ***will subsequently be diagnosed as positive for recurrence*** following histology and / or clinical follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who test negative with CT and/or MRI who receive a false negative diagnosis*** (are actually disease positive).

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False negatives (disease +ve) Test negatives on CT and/or MRI	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

The use of MRI and/or CT alone compared to the use of MRI and/or CT + PETCT in the diagnosis of recurrence in patients with an initial diagnosis of stage IB2-IV cervical cancer.

ASYMPTOMATIC PATIENTS

-All patients are assumed to be a minimum of 3 months post completion of initial treatment (surgery+/- chemotherapy or chemotherapy only).

-All patients are assumed to be *asymptomatic* and have had a clinical examination which may be under anaesthesia (histological confirmation of any vaginal vault mass by biopsies) or not under general anaesthesia (rectovaginal and speculum examination, assessment of inguinal/ supraclavicular lymph nodes).
-Patients subsequently receive either:
- CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination. In other words clinical examination is not used to triage patients for further imaging with CT and/or MRI; CT and/or MRI are used as an add on to clinical examination.

OR

- CT and/or MRI at the discretion of their physician and irrespective of the results of clinical examination ***and*** PETCT. In other words CT and/or MRI are not used to triage patients for further imaging with PETCT ; PETCT is used as an add on to CT and/or MRI.

ACCURACY OF CT and/or MRI + PETCT

-Of the ***patients who test positive following investigation with CT and/or MRI + PETCT***, what percentage do you consider ***will subsequently be diagnosed as negative for recurrence*** following histology and / or clinical follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who test positive with CT and/or MRI + PETCT who are false positives*** (are actually disease negative).

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False positives (disease –ve) Test positives on CT and/or MRI +PETCT	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

-Of the ***patients who test negative following investigation with CT and/or MRI + PETCT***, what percentage do you consider ***will subsequently be diagnosed as positive for recurrence*** following histology and / or clinical follow up as the gold standard tests. We are asking you to estimate ***the percentage of those who test negative with CT and/or MRI + PETCT who are false negatives*** (are actually disease positive).

Indicate the likelihood of each option by allocating a total of 100 points across the 5 options.

False negatives (disease +ve) Test negatives on CT and/or MRI + PETCT	**0 - 9%**	**10 - 19%**	**20-29%**	**30 - 39%**	**40 - 49%**	
Points out of 100						**Total =100**

The use of MRI and/or CT alone compared to the use of PETCT as an adjunct to MRI and/or CT in the diagnosis of recurrence in patients with an initial diagnosis of stage IB2-IV cervical cancer.

ASYMPTOMATIC PATIENTS

Before introducing PETCT as an adjunct to CT and/or MRI, what % *reduction* in false positives (the percentage of those who test positive who are actually disease free) would you consider necessary?

False positives (disease –ve) Test positives **on CT and/or MRI +PETCT**	**0 - 2%**	**3 - 5%**	**6-8%**	**9 - 11%**	**>12% (please specify)**

Before introducing PETCT as an adjunct to CT and/or MRI, what % *reduction* in false negatives (the percentage of those who test negative who actually have disease) would you consider necessary?

False negatives (disease +ve**)** Test negatives **on CT and/or MRI + PETCT**	**0 - 2%**	**3 - 5%**	**6-8%**	**9 - 11%**	**>12% (please specify)**

Appendix 8 Effectiveness systematic review search strategies

Population: previous chemoradiotherapy or radiotherapy only

MEDLINE (Ovid Gateway) (August 2010)

Four thousand, nine hundred and forty-one records were retrieved in MEDLINE.

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Recurrence/ or exp Neoplasm Recurrence, Local/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp Neoplasm Metastasis/
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
26. 12 and 25
27. exp Radiotherapy/
28. Radiotherapy.mp.
29. irradiation.mp.
30. radiation.mp.
31. brachytherapy.mp.
32. teletherapy.mp.
33. (chemoradiation or chemoradiotherapy).mp.
34. (chemoradiation or chemoradiotherapy).mp.
35. radiochemotherapy.mp.
36. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 26 and 36

EMBASE (Ovid Gateway) (August 2010)

Eight thousand, seven hundred and seventy-nine records were retrieved in EMBASE.

1. (Uterine Cervical Neoplasms
2. cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Recurrence/ or exp Neoplasm Recurrence, Local/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp Neoplasm Metastasis/
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
26. 12 and 25
27. exp Radiotherapy/
28. radiotherapy.mp.
29. irradiation.mp.
30. radiation.mp.
31. brachytherapy.mp.
32. teletherapy.mp.
33. (chemoradiation or chemoradiotherapy).mp.
34. (chemo-radiation or chemo-radiotherapy).mp.
35. radiochemotherapy.mp.
36. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 25 and 36

Population: early palliative treatment

MEDLINE (Ovid Gateway) (August 2010)

One thousand, six hundred and fifty records were retrieved in MEDLINE

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.

5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Neoplasm Recurrence, Local/
14. exp Recurrence/
15. recur$.mp.
16. relaps$.mp.
17. repeat$.mp.
18. repetitive$.mp.
19. reappearance$.mp.
20. reoccurence$.mp.
21. return.mp.
22. exp Neoplasm Metastasis/
23. metasta$.mp.
24. restag$.mp.
25. re-stag.mp. (0)
26. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
27. 12 and 26
28. Randomized Controlled Trials as Topic
29. Randomized Controlled Trial
30. Random Allocation
31. Double-Blind Method
32. Clinical Trial
33. exp Clinical Trials as Topic
34. (clinic$ adj trial$1).tw.
35. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
36. Placebos/
37. Placebo$.tw.
38. Randomly allocated.tw.
39. (allocated adj2 random).tw.
40. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. exp Case-Control Studies/
42. exp Cohort Studies
43. Case control.tw.
44. (cohort adj (study or studies)).tw.
45. Cohort analy$.tw.
46. (Follow up adj (study or studies)).tw.
47. (observational adj (study or studies)).tw.
48. Longitudinal.tw.
49. retrospective.tw.
50. Cross sectional.tw.
51. Cross-Sectional Studies
52. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 40 or 52 27 and 53
54. limit 53 to yr="2004 -Current"

EMBASE (Ovid Gateway) (August 2010)

One thousand, four hundred and eighty-seven records were retrieved in EMBASE

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Recurrence/ or exp Neoplasm Recurrence, Local/
14. recur$.mp.)
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp Neoplasm Metastasis
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
26. 12 and 25
27. Randomized Controlled Trials as Topic
28. Randomized Controlled Trial/
29. Random Allocation
30. Double-Blind Method
31. Clinical Trial
32. exp Clinical Trials as Topic
33. (clinic$ adj trial$1).tw. (145860)
34. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
35. Placebos
36. Placebo$.tw.
37. Randomly allocated.tw.
38. (allocated adj2 random).tw. (731)
39. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. exp Case-Control Studies/
41. exp Cohort Studies/
42. Case control.tw.
43. (cohort adj (study or studies)).tw.
44. Cohort analy$.tw.
45. (Follow up adj (study or studies)).tw.
46. (observational adj (study or studies)).tw.
47. Longitudinal.tw.
48. retrospective.tw.
49. Cross sectional.tw.
50. Cross-Sectional Studies

51. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52. 39 or 51
53. 26 and 52
54. limit 53 to yr="2004 -Current"

Population: previous surgical treatment

MEDLINE (Ovid Gateway) (August 2010)

Two thousand, two hundred and twenty-eight records were retrieved in MEDLINE

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Recurrence/ or exp Neoplasm Recurrence, Local/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp Neoplasm Metastasis/
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 and 25
27. exp Pelvic Exenteration/
28. (pelvi$ adj3 exenteratio$).mp.
29. (pelvi$ adj3 evisceratio$).mp.
30. (pelvi$ adj3 Hysterectom$).mp.
31. (pelvi$ adj3 colpohysterectom$).mp.
32. (pelvi$ adj3 hysterocolpectom$).mp.
33. (pelvi$ adj3 panhysterectom$).mp.
34. (uter$ adj3 extirpatio$).mp.
35. (uter$ adj3 amputatio$).mp.
36. salvage surgery.mp. or Salvage Therapy/
37. leer.mp.
38. hysterectomy.tw.
39. *Hysterectomy/
40. 38 or 39
41. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 40
42. 26 and 41

EMBASE (Ovid Gateway) (August 2010)

Three thousand, one hundred and seventy-nine records were retrieved in EMBASE

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 cancer$).mp.
3. (cervi$ adj5 carcinom$).mp.
4. (cervi$ adj5 adenocarcinom$).mp.
5. (cervi$ adj5 carcinogen$).mp.
6. (cervi$ adj5 sarcoma$).mp.
7. (cervi$ adj5 malignan$).mp.
8. (cervi$ adj5 tumor$).mp.
9. (cervi$ adj5 tumour$).mp.
10. (cervi$ adj5 neoplas$).mp.
11. (cervi$ adj5 metasta$).mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp Recurrence/ or exp Neoplasm Recurrence, Local/
14. recur$.mp.
15. relaps$.mp.
16. repeat$.mp.
17. repetitive$.mp.
18. reappearance$.mp.
19. reoccurence$.mp.
20. return.mp.
21. exp Neoplasm Metastasis/
22. metasta$.mp.
23. restag$.mp.
24. re-stag.mp.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 and 25
27. exp Pelvic Exenteration/
28. (pelvi$ adj3 exenteratio$).mp.
29. (pelvi$ adj3 evisceratio$).mp.
30. (pelvi$ adj3 Hysterectom$).mp.
31. (pelvi$ adj3 colpohysterectom$).mp.
32. (pelvi$ adj3 hysterocolpectom$).mp.
33. (pelvi$ adj3 panhysterectom$).mp.
34. (uter$ adj3 extirpatio$).mp.
35. (uter$ adj3 amputatio$).mp.
36. salvage surgery.mp. or Salvage Therapy/
37. leer.mp.
38. hysterectomy.tw.
39. *HYSTERECTOMY/
40. 38 or 39
41. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 40
42. 26 and 4

Appendix 9 Economic evaluation systematic review search strategies and study categories

The search strategy in this appendix was used to identify economic evaluation studies from the EMBASE database on the use of PET-CT to detect recurrent cervical cancer. Similar search strategies were used for MEDLINE and the ISI Web of Knowledge. NHS EED, DARE and HTA were searched within The Cochrane Library using the 'cervical cancer' search term.

EMBASE (1980 to October 2011)

1. Uterine cervical neoplasms.mp. or Uterine Cervical Neoplasms/
2. cancer.mp. or Neoplasms/
3. Carcinoma/ or carcinoma.mp.
4. Carcinogen$.mp.
5. adenocarcinoma.mp. or Adenocarcinoma/
6. Cervi$.mp.
7. 1 or 2 or 3 or 4 or 5
8. 6 and 7
9. Neoplasm Recurrence, Local/ or Recurrence/ or recur$.mp.
10. 8 and 9
11. "Costs and Cost Analysis"/ or Cost-Benefit Analysis/ or Economic evaluation.mp.
12. cost-effectiveness analysis.mp.
13. "Quality of Life"/ or Quality-Adjusted Life Years/ or cost-utility analysis.mp.
14. 11 or 12 or 13
15. 10 and 14

Study categories

Stage I: selection of the papers.

(a) The study reports an economic evaluation based on primary (i.e. original data collected specifically for the study) or secondary (i.e. unoriginal data collected from already published articles or other sources) research on the costs and use of care and includes formal economic evaluation.
(b) The study discusses the economic aspects of recurrent cervical cancer and contains useful primary or secondary cost or use data but is not an economic evaluation.
(c) The study discusses economic aspects of policies for care but is neither A nor B.
(d) The study has no relevance to recurrent cervical cancer.

Stage II: further categorisation of the relevant studies

Studies that were considered relevant to the systematic review (A, B and C) were read in full and further classified according to the study type as outlined below:

1. economic evaluation studies that reported their results in terms of cost per QALY
2. other economic evaluation studies that did not report their results in terms of cost per QALY (e.g. recurrence detected)
3. studies not categorised as 1 or 2.

All studies categorised as A(1) and A(2) were included in the quality assessment stage. Papers retrieved that were not classified as above were rejected at this stage.

Appendix 10 Diagnostic review list of excluded studies with reasons for exclusion

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion

Reference	Reason for exclusion
Adalsteinsson B, Påhlman L, Hemmingsson A, Glimelius B, Graffman S. Computed tomography in early diagnosis of local recurrence of rectal carcinoma. *Acta Radiol* 1987;**28**:41–7	Lack of full text
Amano M, Kato T, Amano Y, Kumazaki T. Using MR imaging to predict and evaluate the response of invasive cervical carcinoma to systemic chemotherapy. *AJR Am J Roentgenol* 1998;**171:**1335–9	Wrong end points
Babar S, Rockall A, Goode A, Shepherd J, Reznek R. Magnetic resonance imaging appearances of recurrent cervical carcinoma. *Int J Gynecol Cancer* 2007;**17**:637–45	Wrong end points
Batka M, Staudach A, Haidinger M, Doringer E. [Magnetic resonance staging as a decision aid in therapy of cervix cancer.] *Gynakol Rundsch* 1991;**31**(Suppl. 2):239–41	Wrong population
Belhocine T, Thille A, Fridman V, Albert A, Seidel L, Nickers P, *et al*. Contribution of whole-body ^{18}FDG PET imaging in the management of cervical cancer. *Gynecol Oncol* 2002;**87**:90–7	Wrong population
Bellomi M, Bonomo G, Landoni F, Villa G, Leon ME, Bocciolone L, *et al*. Accuracy of computed tomography and magnetic resonance imaging in the detection of lymph node involvement in cervix carcinoma. *Eur Radiol* 2005;**15**:2469–74	Lesion-based analysis
Beyersdorff D, Bahnsen J, Frischbier HJ. Nodal involvement in cancer of the uterine cervix: value of lymphography and MRI. *Eur J Gynaecol Oncol* 1995;**16**:274–7	Wrong population
Bjurberg M, Kjellén E, Ohlsson T, Ridderheim M, Brun E. FDG-PET in cervical cancer: staging, re-staging and follow-up. *Acta Obstet Gynecol Scand* 2007;**86**:1385–91	Wrong intervention
Bjurberg M, Kjellén E, Ohlsson T, Bendahl P-O, Brun E. Prediction of patient outcome with 2-deoxy-2-[18F] fluoro-D-glucose-positron emission tomography early during radiotherapy for locally advanced cervical cancer. *Int J Gynecol Cancer* 2009;**9**:1600–5	Wrong end points
Boss EA, Massuger LF, Pop LA, Verhoef LC, Huisman H-J, Boonstra H, *et al*. Post-radiotherapy contrast enhancement changes in fast dynamic MRI of cervical carcinoma. *J Magn Reson Imaging* 2001;**13**:600–6	Wrong end points
Boughanim M, Leboulkox S, Rey A, Pham CT, Zafrani Y, Haie-Meder C, *et al*. Histologic results of para-aortic lymphadenectomy in patients treated for stage IB2/II cervical cancer with negative [18F] fluorodeoxyglucose positron emission tomography scans in the para-aortic area. *J Clin Oncol* 2008;**26**:2558–61	Wrong population
Brenner DE, Whitley NO, Prempree T, Villasanta U. An evaluation of the computed tomographic scanner for the staging of carcinoma of the cervix. *Cancer* 1982;**50**:2323–8	Wrong population
Brooks RA, Rader JS, Dehdashti F, Mutch DG, Powell MA, Thaker PH, *et al*. Surveillance FDG-PET detection of asymptomatic recurrences in patients with cervical cancer. *Gynecol Oncol* 2009;**112**:104–9	Wrong end points
Brown JJ, Gutierrez ED, Lee JK. MR appearance of the normal and abnormal vagina after hysterectomy. *AJR Am J Roentgenol* 1992;**158**:95–9	No data
Bruneton JN, Merran D, Balu-Maestro C, Rogopoulos A, Giordano P, Chauvel P, *et al*. [Echography and computed tomography in the evaluation and follow-up of uterine cancers]. *Bull Cancer* 1990;**77**:689–94	Lack of full text
Chang TC, Law K-S, Hong J-H, Lai C-H, Ng K-K, Hsueh S, *et al*. Positron emission tomography for unexplained elevation of serum squamous cell carcinoma antigen levels during follow-up for patients with cervical malignancies: a phase II study. *Cancer* 2004;**101**:164–71	Wrong population

continued

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Chang WC, Hung YC, Lin CC, Shen YY, Kao C-H. Usefulness of FDG-PET to detect recurrent cervical cancer based on asymptomatically elevated tumor marker serum levels – a preliminary report. *Cancer Invest* 2004;**22**:180–4	Wrong intervention
Chang YC, Yen T-C, Ng K-K, See L-C, Lai C-H, Chang T-C, *et al*. Does diabetes mellitus influence the efficacy of FDG-PET in the diagnosis of cervical cancer? *Eur J Nucl Med Mol Imaging* 2005;**32**:647–52	Wrong population
Chao A, Ho K-C, Wang C-C, Cheng H-H, Lin G, Yen T-C, *et al*. Positron emission tomography in evaluating the feasibility of curative intent in cervical cancer patients with limited distant lymph node metastases. *Gynecol Oncol* 2008;**110**:172–8	Wrong population
Chen JT, Yamashiro T, Shimizu Y, Nakajama K, Teshima H, Hirai Y, *et al*. [Comparison of ultrasound and computed tomography (CT) for the diagnosis of paraaortic lymphnode metastasis in patients with gynecologic malignancies.] *Acta Obst Gynaecol Jpn* 1989;**41**:55–60	Lack of full text
Choi EK, Kim JK, Choi HJ, Park SH, Park B-W, Kim N, *et al*. Node-by-node correlation between MR and PET/CT in patients with uterine cervical cancer: diffusion-weighted imaging versus size-based criteria on T2WI. *Eur Radiol* 2009;**19**:2024–32	Wrong population
Choi HJ, Roi JW, Seo S-S, Lee S, Kim J-Y, Kim S-K, *et al*. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. *Cancer* 2006;**106**:914–22	Wrong population
Choi SH, Kim S-H, Choi H-J, Park BK, Lee HJ. Preoperative magnetic resonance imaging staging of uterine cervical carcinoma: results of prospective study. *J Comput Assist Tomogr* 2004;**28**:620–7	Wrong population
Chou HH, Chang T-C, Yen T-C, Ng K-K, Hsueh S, Ma SY, *et al*. Low value of [18F]-fluoro-2-deoxy-D-glucose positron emission tomography in primary staging of early-stage cervical cancer before radical hysterectomy. *J Clin Oncol* 2006;**24:**123–8	Wrong population
Chung HH, Lee S, Sim J-S, Kim J-Y, Seo SS, Park S-Y, *et al*. Pretreatment laparoscopic surgical staging in locally advanced cervical cancer: preliminary results in Korea. *Gynecol Oncol* 2005;**97**:468–75	Wrong population
Chung HH, Kim S-K, Kim TH, Lee S, Kang KW, Kim J-Y, *et al*. Clinical impact of FDG-PET imaging in post-therapy surveillance of uterine cervical cancer: from diagnosis to prognosis. *Gynecol Oncol* 2006;**103**:165–70	Wrong intervention
Chung HH, Kang S-B, Cho JY, Kim JW, Park N-H, Song Y-S, *et al*. Can preoperative MRI accurately evaluate nodal and parametrial invasion in early stage cervical cancer? *Jpn J Clin Oncol* 2007;**37**:370–5	Wrong population
Chung HH, Kang WJ, Kim JW, Park N-H, Song Y-S, Chung J-K, *et al*. Characterization of surgically transposed ovaries in integrated PET/CT scan in patients with cervical cancer. *Acta Obstet Gynecol Scand* 2007;**86**:88–93	Wrong population
Chung HH, Park N-H, Kim JW, Song Y-S, Chung J-K, Kang S-B. Role of integrated PET-CT in pelvic lymph node staging of cervical cancer before radical hysterectomy. *Gynecol Obstet Invest* 2009;**67**:61–6	Wrong population
Crawford RA, Richards PJ, Reznek RH, Ngan HY, Shepherd JH. The role of CT in predicting the surgical feasibility of exenteration in recurrent carcinoma of the cervix. *Int J Gynecol Cancer* 1996;**6**:231–4	Wrong study design
Dehdashti F, Grigsby PW, Lewis JS, LaForest R, Siegel BA, Welch MJ. Assessing tumor hypoxia in cervical cancer by PET with 60Cu-labeled diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med* 2008;**49**:201–5	Wrong intervention
Dehong L, Mulan S, Zhengang X, Wu N, Yao D, Hao Y, *et al*. Cervical lymph node metastasis: CT, ultrasound versus physical palpation. *Chin J Oncol* 1998;**20**:48–50	Lack of full text
deSouza NM, Dina R, McIndoe GA, Soutter WP. Cervical cancer: value of an endovaginal coil magnetic resonance imaging technique in detecting small volume disease and assessing parametrial extension. *Gynecol Oncol* 2006;**102**:80–5	Wrong population

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Dolezelova H, Slampa P, Ondrova B, Gombosova J, Sovadinova S, Novotny T, *et al*. The impact of PET with ^{18}FDG in radiotherapy treatment planning and in the prediction in patients with cervix carcinoma: results of pilot study. *Neoplasma* 2008;**55**:437–41	Lack of gold standard
Donaldson SB, Buckley DL, O'Connor JP, Davidson SE, Carrington BM, Jones AP, *et al*. Enhancing fraction measured using dynamic contrast-enhanced MRI predicts disease-free survival in patients with carcinoma of the cervix. *Br J Cancer* 2010;**102**:23–6	Wrong population
Eiber M, Dütsch S, Gaa J, Fauser C, Rummeny EJ, Holzapfel K. [Diffusion-weighted magnetic resonance imaging (DWI-MRI): a new method to differentiate between malignant and benign cervical lymph nodes]. *Laryngorhinootologie* 2008;**87**:850–5	Lack of full text
Esthappan J, Chaudhari S, Santanam L, Mutic S, Olsen J, MacDonald DM, *et al*. Prospective clinical trial of positron emission tomography/computed tomography image-guided intensity-modulated radiation therapy for cervical carcinoma with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2008;**72**:1134–9	Wrong study design
Ferdova E, Finek J, Ferda J. A role of ^{18}F-FDG-PET/CT in the treatment decisions of uterine and ovarian tumors, our clinical practice experience. *Ceska Radiol* 2009;**63**:290–302	Lack of full text
Fluckiger F, Ebner F, Poschauko H, Arian-Schad K, Einspieler E, Hausegger K. [Value of magnetic resonance tomography after primary irradiation of carcinoma of the cervix uteri: evaluation of therapeutic success and follow-up.] *Strahlenther Onkol* 1991;**167**:152–7	No data
Flueckiger F, Ebner F, Poschauko H, Tamussino K, Einspieler R, Ranner G. Cervical cancer: serial MR imaging before and after primary radiation therapy – a 2-year follow-up study. *Radiology* 1992;**184**:89–93	No data
Franchi M, La Fianza A, Babilonti L, Bolis PF, Alerci M, Di Giulio G, *et al*. Clinical value of computerized tomography (CT) in assessment of recurrent uterine cancers. *Gynecol Oncol* 1989;**35**:31–7	No data
Genolet PM, Hanggi W, Dreher E. [Evaluation of tumor extension in invasive cancer of the uterine cervix. Diagnostic evaluation of cervix cancer.] *Gynakol Geburtshilfliche Rundsch* 1993;**33**:180–4	Lack of full text
Ginaldi S, Wallace S, Jing B-S, Bernardino ME. Carcinoma of the cervix: lymphangiography and computed tomography. *AJR Am J Roentgenol* 1981;**136**:1087–91	Lack of gold standard
Gochev G, Totsev N, Vasilev D, Simeonova L, Ianev N, Elenchev L, *et al*. [The potentials of computed axial tomography (CAT) in the diagnosis of carcinoma of the cervix uteri.] *Akush Ginekol* 1994;**33**:25–6	Lack of full text
Goff BA, Muntz HG, Paley PJ, Tamimi HK, Koh W-J, Greer BE. Impact of surgical staging in women with locally advanced cervical cancer. *Gynecol Oncol* 1999;**74**:436–42	Wrong population
Gong QY, Tan LT, Romanuik CS, Jones B, Brunt JN, Roberts N. Determination of tumour regression rates during radiotherapy for cervical carcinoma by serial MRI: comparison of two measurement techniques and examination of intraobserver and interobserver variability. *Br J Radiol* 1999;**72**:62–72	Wrong population
Goudy G, Stoeckle E, Thomas L, Kind M, Guyon F, Brouste V, *et al*. [Prognostic impact of tumour volume and lymph node involvement in intermediate stage T1b1 to T2b cancer of the uterine cervix.] *Bull Cancer* 2009;**96**:685–94	Wrong population
Grigsby PW, Dehdashti F, Siegel BA. FDG-PET evaluation of carcinoma of the cervix. *Clin Positron Imaging* 1999;**2**:105–9	Small sample size
Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol* 2001;**19**:3745–9	No data
Grigsby PW, Singh AK, Siegel BA, Dehdashti F, Rader J, Zoberi I. Lymph node control in cervical cancer. *Int J Radiat Oncol Biol Phys* 2004;**59**:706–12	No data
Grigsby PW, Siegel BA, Dehdashti F, Rader J, Zoberi I. Posttherapy [18F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. *J Clin Oncol* 2004;**22**:2167–71	Wrong population

continued

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Grigsby PW. The role of FDG-PET/CT imaging after radiation therapy. *Gynecol Oncol* 2007;**107**:S27–9	Wrong study design
Hancke K, Heilmann V, Straka P, Kreienberg R, Kurzeder C. Pretreatment staging of cervical cancer: is imaging better than palpation?: role of CT and MRI in preoperative staging of cervical cancer: single institution results for 255 patients. *Ann Surg Oncol* 2008;**15**:2856–61	Wrong population
Hauth EA, Kuhl H, Kimmig R, Forsting M. Evaluation of MR imaging of the pelvis for the staging, follow-up and recurrence diagnosis of cervical cancer. *Geburtshilfe Frauenheilkd* 2006;**66**:1177–85	No data
Havrilesky LJ, Wong TZ, Secord AA, Berchuck A, Clarke-Pearson DL, Jones EL. The role of PET scanning in the detection of recurrent cervical cancer. *Gynecol Oncol* 2003;**90**:186–90	Wrong intervention
Hawighorst H, Knapstein PG, Schaeffer U, Brix G, Weikel P, Essig M, *et al*. [Diagnosis of recurrence of cervix carcinoma using dynamic MRI: correlation of pharmacokinetic analysis and histopathology.] *Radiologe* 1995;**35**:945–51	Lesion-based analysis
Hawighorst H, Knapstein PG, Schaeffer U, Knopp MV, Brix G, Hoffman U, *et al*. Pelvic lesions in patients with treated cervical carcinoma: efficacy of pharmacokinetic analysis of dynamic MR images in distinguishing recurrent tumors from benign conditions. *AJR Am J Roentgenol* 1996;**166**:401–8	Lesion-based analysis
Hawighorst H, Knapstein PG, Weikel P, Knopp MV, Schaeffer U, Essig M, *et al*. [Invasive cervix carcinoma (pT2b-pT4a). Value of conventional and pharmacokinetic magnetic resonance tomography (MRI) in comparison with extensive cross sections and histopathologic findings.] *Radiologe* 1997;**37**:130–8	Wrong population
Hawighorst H, Schoenberg SO, Knapstein PG. Staging of invasive cervical carcinoma and of pelvic lymph nodes by high resolution MRI with a phased-array coil in comparison with pathological findings. *J Comput Assist Tomogr* 1998;**22**:75–81	Wrong population
Hawighorst H, Knapstein PG, Knopp MV, Weikel P, Schaeffer U, Zuna I, *et al*. [Angiogenesis of cervix carcinoma. Contrast enhanced dynamic MRI, histologic quantification of capillary density and lymphatic system infiltration.] *Radiologe* 1998;**38**:50–7	Wrong population
Hawighorst H, Weikel P, Knapstein PG, Knopp MV, Zuna I, Schonberg SO, *et al*. Angiogenic activity of cervical carcinoma: assessment by functional magnetic resonance imaging-based parameters and a histomorphological approach in correlation with disease outcome. *Clin Cancer Res* 1998;**4**:2305–12	Wrong end points
Hawnaur JM, Johnson RJ, Hunter RD, Jenkins PR, Isherwood I. The value of magnetic resonance imaging in assessment of carcinoma of the cervix and its response to radiotherapy. *Clin Oncol* 1992:**4**:11–17	Wrong end points
Hawnaur JM, Johnson RJ, Buckley CH, Tindall V, Isherwood I. Staging, volume estimation and assessment of nodal status in carcinoma of the cervix: comparison of magnetic resonance imaging with surgical findings. *Clin Radiol* 1994;**49**:443–52	Wrong population
Heller PB, Malfetano JH, Bundy BN, Barnhill DR, Okagaki T. Clinical-pathologic study of stage IIB, III, and IVA carcinoma of the cervix: extended diagnostic evaluation for paraaortic node metastasis – a Gynecologic Oncology Group study. *Gynecol Oncol* 1990;**38**:425–30	Lack of full text
Heuck A, Scheidler J, Rimmig R, Muller-Lisse U, Steinborn M, Helmberger T, Reiser M. [Lymph node staging in cervix carcinomas: the results of high-resolution magnetic resonance tomography (MRT) with a phased-array body coil.] *Rofo* 1997;**166**:210–4	Wrong population
Heung-Tat NG, Shen-Li C, Jen-Chung W, Ming-Huei S. Preoperative examination with CT, MRI and comparison of both to histopathologic findings in cervical carcinoma. *CME J Gynecol Oncol* 1998;**3**:256–7	Lack of full text
Ho CM, Chien TY, Jeng CM, Tsang YM, Shih BY, Chang SC. Staging of cervical cancer: comparison between magnetic resonance imaging, computed tomography and pelvic examination under anesthesia. *J Formos Med Assoc* 1992;**91**:982–90	Lack of full text
Hope AJ, Saha P, Grigsby PW. FDG-PET in carcinoma of the uterine cervix with endometrial extension. *Cancer* 2001;**106**:196–200.	Wrong population

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Hori M, Kim T, Murakami T, Imaoka I, Onishi H, Tomoda K, *et al*. Uterine cervical carcinoma: preoperative staging with 3.0-T MR imaging – comparison with 1.5-T MR imaging. *Radiology* 2009;**251**:96–104	Wrong population
Houvenaeghel G, Delpero JR, Rosello R, Resbeut M, Viens P, Jacquemier J, *et al*. Results of a prospective study with comparison of clinical, endosonographic, computed tomography, magnetic resonance imaging and pathologic staging of advanced gynecologic carcinoma and recurrence. *Surg Gynecol Obstet* 1993;**177**:231–6	No data
Hricak H. Cancer of the uterus: the value of MRI pre- and post-irradiation. *Int J Radiat Oncol Biol Phys* 1991;**21**:1089–94	Lack of full text
Hricak H, Swift PS, Campos Z, Quivey JM, Gildengorin V, Goranson H, *et al*. Irradiation of the cervix uteri: value of unenhanced and contrast-enhanced MR imaging. *Radiology* 1993;**189**:381–8	Lesion-based analysis
Hricak H, Quivey JM, Campos Z, Gildengorin V, Hindmarsh T, Bis KG, *et al*. Carcinoma of the cervix: predictive value of clinical and magnetic resonance (MR) imaging assessment of prognostic factors. *Int J Radiat Oncol Biol Phys* 1993;**27**:791–801	No data
Hricak H, Mendelson E, Bohm-Velez M, Bree R, Finberg H, Fishman EK, *et al*. Role of imaging in cancer of the cervix. American College of Radiology. ACR Appropriateness Criteria. *Radiology* 2000;**215**:925–30	Lack of full text
Husain A, Akhurst T, Larson S, Alektiar K, Barakat RR, Chi DS. A prospective study of the accuracy of 18Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) in identifying sites of metastasis prior to pelvic exenteration. *Gynecol Oncol* 2007;**106**:177–80	Wrong intervention
Iizuka Y. [Clinical significance of magnetic resonance imaging (MRI) in evaluation of radiotherapeutic effect on uterine cervical cancer.] *Acta Obstet Gynaecol Jpn* 1996;**48**:37–44	Lack of full text
Ishii C, Tada S, Tsukioka M, Tanaka H. [CT diagnosis of uterine cancer.] *Gan to Kagaku Ryoho* 1982;**9**:204–8	Lack of full text
Ishii C, Tada S, Kato Y, Tanaka H. Computed tomographic evaluation of hydronephrosis in uterine carcinoma. *Radiat Med* 1983;**1**:42–5	Lack of full text
Ito H, *et al*. [Computed tomographic diagnosis in patients with recurrent cervical cancer invaded to the iliac bone (authors' translation).] *Rinsho Hoshasen* 1981;**26**:469–73	Lack of full text
Kajiwara TH, Kataoka M, Hamamoto Y, Ikura M, Hosakawa A, Inoue T, *et al*. [Prediction of pelvic control using MRI for patients with cervical carcinoma treated with radiotherapy.] *Nihon Igaku Hoshasen Gakkai Zasshi* 2005;**65**:438–43	Lack of full text
Kanehira C, Arai T, Suda Y, Suzuki M. [CT diagnosis and treatment of lymph node metastases from carcinoma of the cervix.] *Rinsho Hoshasen* 1983;**28**:285–92	Lack of full text
Kecmanovic DM, Pavlov MJ, Kovacevic PA, Sepetkovski AV, Ceranic MS, Stamenkovic AB, *et al*. Management of advanced pelvic cancer by exenteration. *Eur J Surg Oncol* 2003;**29**:743–6	Wrong end points
Keller TM, Michel SC, Frohlich J, Fink D, Caduff R, Marincek B, *et al*. USPIO-enhanced MRI for preoperative staging of gynecological pelvic tumors: preliminary results. *Eur Radiol* 2004;**14**:937–44	Wrong population
Kerr IG, Manji MF, Powe J, Bakheet S, Al Suhaibani H, Subhi J. Positron emission tomography for the evaluation of metastases in patients with carcinoma of the cervix: a retrospective review. *Gynecol Oncol* 2001;**81**:477–80	Lack of gold standard
Kidd EA, Grigsby PW. Intratumoral metabolic heterogeneity of cervical cancer. *Clin Cancer Res* 2008;**14**:5236–41	Wrong end points
Kidd EA, Siegel BA, Dhdashti F, Rader J, Mutch DG, Powell MA, *et al*. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. *J Clin Oncol* 2010;**28**:2108–13	Wrong population

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TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Kilcheski TS, Arger PH, Mulhern CB, Coleman BG, Kressel HY, Mikuta JI. Role of computed tomography in the presurgical evaluation of carcinoma of the cervix. *J Comput Assist Tomogr* 1981;**5**:378–83	No data
Kim H, Kim W, Lee M, Song E, Loh JJ. Tumor volume and uterine body invasion assessed by MRI for prediction of outcome in cervical carcinoma treated with concurrent chemotherapy and radiotherapy. *Jpn J Clin Oncol* 2007;**37**:858–66	Wrong population
Kim MJ, Chung JJ, Lee YH, Lee JT, Yoo HS. Comparison ofthe use of the transrectal surface coil and the pelvic phased-array coil in MR imaging for preoperative evaluation of uterine cervical carcinoma. *AJR Am J Roentgenol* 1997;**168**:1215–21	Wrong population
Kim SH, Choi BI, Han JK, Kim HD, Lee HP, Kang SB, *et al*. Preoperative staging of uterine cervical carcinoma: comparison of CT and MRI in 99 patients. *J Comput Assist Tomogr* 1993;**17**:633–40	Wrong population
Kim SH, Kim SC, Choi BI, Han MC. Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. *Radiology* 1994;**190**:807–11	Wrong population
Kim SK, Choi HJ, Park S-Y, Lee H-Y, Seo S-S, Yoo CW, *et al*. Additional value of MR/PET fusion compared with PET/CT in the detection of lymph node metastases in cervical cancer patients. *Eur J Cancer* 2009;**45**:2103–9	Wrong population
King LA, Talledo OE, Gallup DG, El Gammal TA. Computed tomography in evaluation of gynecologic malignancies: a retrospective analysis. *Am J Obstet Gynecol* 1986;**155**:960–4	Wrong population
Kinkel K, Ariche M, Tardivon AA, Spatz A, Castaigne D, Lhomme C, *et al*. Differentiation between recurrent tumor and benign conditions after treatment of gynecologic pelvic carcinoma: value of dynamic contrast-enhanced subtraction MR imaging. *Radiology* 1997;**204**:55–63	Wrong population
Kitagaki H. [MR imaging-evaluation of therapeutic effect of radiotherapy for uterine cervix cancer.] *Nihon Igaku Hoshasen Gakkai Zasshi* 1995;**55**:215–21	Lack of full text
Kitajima K, Murakami K, Yamasaki E, Kaji Y, Sugimura K. Accuracy of integrated FDG-PET/contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer. *Eur Radiol* 2009;**19**:1529–36	Wrong population
Kitajima K, Murakami K, Yamasaki E, Domeki Y, Kaji Y, Sugimura K. Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent uterine cancer: comparison with PET and enhanced CT. *Eur J Nucl Med Mol Imaging* 2009;**36**:362–72	No data
Klerkx WM, Heintz AP, Mali WP, de Kort GA, Takahara T, van Dorst EB, *et al*. Lymph node detection by MRI before and after a systematic pelvic lymphadenectomy. *Gynecol Oncol* 2009;**114**:315–18	No data
Kodaira T, Fuwa N, Toita T, Nomoto Y, Kazuya K, Tachibana H, *et al*. Comparison of prognostic value of MRI and FIGO stage among patients with cervical carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;**56**:769–77	Wrong end points
Kodaira T, Fuwa N, Toita T, Nomoto Y, Kuzuya K, Tachibana K, *et al*. Clinical evaluation using magnetic resonance imaging for patients with stage III cervical carcinoma treated by radiation alone in multicenter analysis: its usefulness and limitations in clinical practice. *Am J Clin Oncol* 2003;**26**:574–83	Wrong population
Kolesnikova EK. [Computed tomography in the diagnosis of cervical cancer.] *Akush Ginekol* 1986;(11):18–23	Lack of full text
Kühnel G, Horn L-C, Fischer U, Hesse S, Seese A, Georgi P, *et al*. [^{18}F-FDG positron-emission-tomography in cervical carcinoma: preliminary findings.] *Zentralb Gynakol* 2001;**123**:229–35	Wrong population
Kumar R, Dadparvar S. 18F-fluoro-2-deoxy-D-glucose-positron emission tomography (PET)/PET-computed tomography in carcinoma of the cervix. *Cancer* 2007;**110**:1650–3	Wrong study design
La Fianza A, Dore R, Di Giulio G, Alerci M, Di Maggio EM, Franchi M, *et al*. [Lymph node metastasis of carcinoma of the cervix uteri. Role of lymphography and computerized tomography.] *Radiol Med* 1990;**80**:486–91	No data

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
La Fianza A, Campani R, Dore R, Babilonti L, Tateo S, Calliada F. [CT in the diagnosis and treatment of lymphoceles following gynecologic cancer surgery.] *Radiol Med* 1993;**86**:106–15	No data
Lai CH, Huang K-G, See L-C, Yen T-C, Tsai C-S, Chang T-C, *et al*. Restaging of recurrent cervical carcinoma with dual-phase [18F]fluoro-2-deoxy-D-glucose positron emission tomography. *Cancer* 2001;**100**:544–52	No data
Lai PH, Yang CF, Pan HB, Wu MT, Chu ST, Ger LP, *et al*. Recurrent inverted papilloma: diagnosis with pharmacokinetic dynamic gadolinium-enhanced MR imaging. *AJNR Am J Neuroradiol* 1999;**20**:1445–51	Lesion-based analysis
Lien HH, Blomlie V, Kjørstad K, Abeler V, Kaalhus O. Clinical stage I carcinoma of the cervix: value of MR imaging in determining degree of invasiveness. *AJR Am J Roentgenol* 1991;**156**:1191–4	Wrong study design
Lin CT, Yen T-C, Chang T-C, Ng K-K, Tsai C-S, Ho K-C, *et al*. Role of [18F]fluoro-2-deoxy-D-glucose positron emission tomography in re-recurrent cervical cancer. *Int J Gynecol Cancer* 2006;**16**:1994–2003	Wrong intervention
Lin G, Ho K-C, Wang J-J, Ng K-K, Wai Y-Y, Chen Y-T, *et al*. Detection of lymph node metastasis in cervical and uterine cancers by diffusion-weighted magnetic resonance imaging at 3T. *J Magn Reson Imaging* 2008;**28**:128–35	Wrong population
Lin WC, Hung YC, Yeh LS, Kao CH, Yen RF, Shen YY. Usefulness of (18)F-fluorodeoxyglucose positron emission tomography to detect para-aortic lymph nodal metastasis in advanced cervical cancer with negative computed tomography findings. *Gynecol Oncol* 2003;**89**:73–6	Wrong intervention
Liu FY, Yen T-C, Chen M-Y, Lai C-H, Chang T-C, Chou H-H, *et al*. Detection of hematogenous bone metastasis in cervical cancer: 18F-fluorodeoxyglucose-positron emission tomography versus computed tomography and magnetic resonance imaging. *Cancer* 2009;**115**:5470–80	Lack of gold standard
Liu Y, Bai R, Sun H, Liu H, Zhao X, Li Y. Diffusion-weighted imaging in predicting and monitoring the response of uterine cervical cancer to combined chemoradiation. *Clin Radiol* 2009;**64**:1067–74	Wrong end points
Loft A, Berthelsen AK, Roed H, Ottosen C, Lundvall L, Knudsen J, *et al*. The diagnostic value of PET/CT scanning in patients with cervical cancer: a prospective study. *Gynecol Oncol* 2007;**106**:29–34	Wrong population
Lorenzen M, Nicolas V, Kopp A. [MRT diagnosis of recurrence of gynecologic tumors]. *Rofo* 1994;**161**:526–30	Wrong population
Lorenzen M, Braun J, Gehrckens A, Nicolas V. [Value of MRI, CT and findings in staging of gynecologic malignancies.] *Aktuelle Radiol* 1998;**8**:266–72	Lack of full text
Luo D, Shi M, Xu Z. [Cervical lymph node metastasis: CT, ultrasound versus physical palpation.] *Chung-Hua Chung Liu Tsa Chih – Chin J Oncol* 1998;**20**:48–50	Lack of full text
Ma SY, See L-C, Lai C-H, Chou H-H, Tsai C-S, Ng K-K, *et al*. Delayed (18)F-FDG PET for detection of paraaortic lymph node metastases in cervical cancer patients. *J Nucl Med* 2003;**44**:1775–83	Wrong population
Manfredi R, Maresca G, Smaniotto D, Greggi S, Andrulli D, Rabitti C, *et al*. Cervical cancer response to neoadjuvant therapy: MR imaging assessment. *Radiology* 1998;**209**:819–24	Wrong population
Manfredi R, Baltieri S, Tognolini A, Graziani R, Smaniotto D, Cellini N, *et al*. Recurrent uterine cancer after surgery: magnetic resonance imaging patterns and their changes after concomitant chemoradiation. *Radiol Med* 2008;**113**:1143–56	Wrong population
Manfredi R, Gui B, Giovanzana A, Marini S, Di Stefano M, Zannoni G, *et al*. Localized cervical cancer (stage <IIB): accuracy of MR imaging in planning less extensive surgery. *Radiol Med* 2009;**114**:960–75	Wrong population
Marano P, Summaria V, Smaniotto D, Danza FM, Speca S, Valantini AL, *et al*. [Experience with the combined diagnosis and therapy of locally advanced carcinoma of the uterine cervix (stage FIGO IIB–III). Transrectal ultrasonography and CT in the staging and in follow-up after therapy. Preliminary results.] *Radiol Med* 1993;**86**:630–8	Wrong population

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TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Matsubara M. [Clinical significance of magnetic resonance imaging (MRI) in evaluation of the extension of uterine cervical cancer]. *Acta Obstet Gynaecol Jpn* 1993;**45**:1115–22	Lack of full text
Matsukuma K, Tsukamoto N, Matsuyama T, Ono M, Nakano H. Preoperative CT study of lymph nodes in cervical cancer – its correlation with histological findings. *Gynecol Oncol* 1989;**33**:168–71	Wrong population
Matsukuma K, Tsukamoto N, Jo S, Imachi M, Kamura T, Matsuyama T, *et al*. [An evaluation of scalene lymph node metastasis in patients with gynecologic malignancies.] *Gan No Rinsho* 1989;**35**:275–9	Lack of full text
Mayr NA, Yuh WT, Magnotta VA, Erhardt TC, Wheeler JA, Sorosky JI, *et al*. Tumor perfusion studies using fast magnetic resonance imaging technique in advanced cervical cancer: a new noninvasive predictive assay. *Int J Radiat Oncol Biol Phys* 1996;**36**:623–33	Wrong population
Mayr NA, Magnotta VA, Erhardt TC, Wheeler JA Sorosky JI, Wen B-C, *et al*. Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1996;**35**:915–24	Wrong population
Mayr NA, Yuh WT, Zheng J, Erhardt TC, Magnotta VA, Sorosky JI, *et al*. Prediction of tumor control in patients with cervical cancer: analysis of combined volume and dynamic enhancement pattern by MR imaging. *AJR Am J Roentgenol* 1998;**170**:177–82	Wrong end points
Mayr NA, Taoka T, Yuh WT, Denning LM, Zhen WK, Paulino AC, *et al*. Method and timing of tumor volume measurement for outcome prediction in cervical cancer using magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2001;**52**:14–22	Wrong population
Mayr NA, Yu WT, Jajoura D, Wang JZ, Lo SS, Montebello JF, *et al*. Ultra-early predictive assay for treatment failure using functional magnetic resonance imaging and clinical prognostic parameters in cervical cancer. *Cancer* 2010;**116**:903–12	Wrong end points
Meanwell CA, Rolfe EB, Blackledge G, Docker MF, Lawton FG, Mould JJ. Recurrent female pelvic cancer: assessment with transrectal ultrasonography. *Radiology* 1987;**162**:278–81	Wrong population
Miller TR, Grigsby PW. Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;**53**:353–9	Wrong population
Miller TR, Pinkus E, Dehdashti F, Grigsby PW. Improved prognostic value of ^{18}F-FDG PET using a simple visual analysis of tumor characteristics in patients with cervical cancer. *J Nucl Med* 2003;**44**:192–7	Wrong population
Mitchell DG, Snyder B, Coakley F, Reinhold C, Thomas G, Amendola MA, *et al*. Early invasive cervical cancer: MRI and CT predictors of lymphatic metastases in the ACRIN 6651/GOG 183 intergroup study. *Gynecol Oncol* 2009;**112**:95–103	Wrong population
Monzen Y, Mori H, Matsumoto A, Yoshida S, Wakisaka M, Komatsu E, *et al*. [Uterine cervical cancer: usefulness of MR imaging after the initial radiation therapy.] *Nihon Igaku Hoshasen Gakkai Zasshi* 1995;**55**:745–50	Lack of full text
Moore DH, Dotters DJ, Fowler WCJ. Computed tomography: does it really improve the treatment of cervical carcinoma? *Am J Obstet Gynecol* 1992;**167**:768–21	Wrong population
Mortier DG, Stroobants S, Amant F, Neven P, Van Limbergen E, Vergote I. Laparoscopic para-aortic lymphadenectomy and positron emission tomography scan as staging procedures in patients with cervical carcinoma stage IB2–IIIB. *Int J Gynecol Cancer* 2008;**18**:723–9	Wrong population
Nakai G, Matsuki M, Inada Y, Tatsugami F, Tanikake M, Narabayashi I, *et al*. Detection and evaluation of pelvic lymph nodes in patients with gynecologic malignancies using body diffusion-weighted magnetic resonance imaging. *J Comput Assist Tomogr* 2008;**32**:764–8	Wrong population
Nakamoto Y, Eisbruch A, Achtyes ED, Sugawara Y, Reynolds KR, Johnston CM, *et al*. Prognostic value of positron emission tomography using F-18-fluorodeoxyglucose in patients with cervical cancer undergoing radiotherapy. *Gynecol Oncol* 2002;**84**:289–95	Wrong intervention
Namimoto T, Awai K, Nakaura T, Yanaga Y, Hirai T, Yamashita Y. Role of diffusion-weighted imaging in the diagnosis of gynecological diseases. *Eur Radiol* 2009;**19**:745–60	Wrong study design

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Narayan K, Hicks RJ, Jobling T, Bernshaw D, McKenzie AF. A comparison of MRI and PET scanning in surgically staged loco-regionally advanced cervical cancer: potential impact on treatment. *Int J Gynecol Cancer* 2001;**11**:263–71	Wrong population
Narayan K, McKenzie AF, Hicks RJ, Fisher R, Bernshaw D, Bau S. Relation between FIGO stage, primary tumor volume, and presence of lymph node metastases in cervical cancer patients referred for radiotherapy. *Int J Gynecol Cancer* 2003;**13**:657–63	Wrong population
Narayan K, Fisher RJ, Bernshaw D. Patterns of failure and prognostic factor analyses in locally advanced cervical cancer patients staged by positron emission tomography and treated with curative intent. *Int J Gynecol Cancer* 2009:**19**:912–18	Wrong study design
Newton WA, Roberts WS, Marsden DE, Cavanagh D. Value of computerized axial tomography in cervical cancer. *Oncology* 1987;**44**:124–7	Wrong population
Oberoi R, Vohra S, Jain P, Jena A. Staging of carcinoma cervix with MRI and histopathological correlation in 105 cases. *Asian Oceanian J Radiol* 2002;**7**:88–94	Lack of full text
Odunsi KO, Lele S, Ghamande S, Seago P, Driscoll DL. The impact of pre-therapy extraperitoneal surgical staging on the evaluation and treatment of patients with locally advanced cervical cancer. *Eur J Gynaecol Oncol* 2001;**22**:325–30	Lack of full text
Oellinger JJ, Blohmer JU, Michniewicz K, Siewert C, Wust P, Guthberlet M, *et al*. Pre-operative staging of cervical cancer: comparison of magnetic resonance imaging (MRI) and computed tomography (CT) with histologic results. *Zentralbl Gynakol* 2000;**122**:82–91	Wrong population
Ogino I, Okamoto N, Andoh K, Kitamura T, Okajima H, Matsubara S. Analysis of prognostic factors in stage IIB–IVA cervical carcinoma treated with radiation therapy: value of computed tomography. *Int J Radiat Oncol Biol Phys* 1997;**37**:1071–7	Wrong end points
Ohara K, Tanaka YO, Tsunoda H, Nishida M, Sugahara S, Itai Y. Assessment of cervical cancer radioresponse by serum squamous cell carcinoma antigen and magnetic resonance imaging. *Obstet Gynecol* 2002;**100**:781–7	Wrong end points
Page JE, Constant O, Parsons C. The role of abdominal computed tomography in the assessment of patients with malignant tumours of the cervix and body of the uterus. *Clin Radiol* 1988;**39**:273–7	Lack of gold standard
Pakkal MV, Rudralingam V, McCluggage WG, Kelly BE. MR staging in carcinoma of the endometrium and carcinoma of the cervix. *Ulster Med J* 2004;**73**:20–4	Wrong population
Park W, Park YJ, Huh SJ, Kim BG, Bae DS, Lee J, *et al*. The usefulness of MRI and PET imaging for the detection of parametrial involvement and lymph node metastasis in patients with cervical cancer. *Jpn J Clin Oncol* 2005;**35**:260–4	Wrong population
Parker LA, McPhail AH, Yankanskas BC, Mauro MA. Computed tomography in the evaluation of clinical stage IB carcinoma of the cervix. *Gynecol Oncol* 1990;**37**:332–4	Wrong population
Pellegrino A, Cormio G, Maneo A, Vanzulli A, Villa G, Lissoni A, *et al*. [Nuclear magnetic resonance imaging in the staging of adenocarcinoma of the uterine cervix.] *Minerva Ginecol* 1995;**47**:523–6	Wrong population
Potter R, Dimopoulos J, Georg P, Lang S, Waldha C, Wachter-Gerstner N, *et al*. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007;**83**:148–55	Wrong end points
Qiu JT, Ho KC, Lai CH, Yen TC, Huang YT, Chao A, *et al*. Supraclavicular lymph node metastases in cervical cancer. *Eur J Gynaecoll Oncol* 2007;**28**:33–8	Wrong intervention
Reinhardt MJ, Eritt-Braun C, Vogelgesang D, Ihling C, Hogerle S, Mix M, *et al*. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology* 2001;**218**:776–82	Wrong population
Reinhardt MJ, Technau-Ihling K, Altehoefer C, Vogelgesang D, Krause TM. Lymphangiography causes false-positive findings on 18F-FDG PET imaging. *Anticancer Res* 2003;**23**:2941–4	Lack of full text

continued

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Rockall AG, Sohaib SA, Harisinghani MG, Babar SA, Singh N, Jeyarajah AR, *et al*. Diagnostic performance of nanoparticle-enhanced magnetic resonance imaging in the diagnosis of lymph node metastases in patients with endometrial and cervical cancer. *J Clin Oncol* 2005;**23**:2813–21. [Erratum published in *J Clin Oncol* 2005;**23**:4808]	Wrong population
Roh JW, Seo SS, Lee S, Kang KW, Kim S-K, Sim JS, *et al*. Role of positron emission tomography in pretreatment lymph node staging of uterine cervical cancer: a prospective surgicopathologic correlation study. *Eur J Cancer* 2005;**41**:2086–92	Wrong population
Rose PG, Adler LP, Rodriguez PF, Abdul-Karim FW, Miraldi F. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol* 1999;**17**:41–5	Wrong population
Roy C, le Bras Y, Mangold L, Saussinej C, Tuchmann C, Pfleger D, *et al*. Small pelvic lymph node metastases: evaluation with MR imaging. *Clin Radiol* 1997;**52**:437–40	Wrong population
Rubens D, Thornbury JR, Angel C, Stoler MH, Weiss SL, Lerner RM, *et al*. Stage IB cervical carcinoma: comparison of clinical, MR, and pathologic staging. *AJR Am J Roentgenol* 1988;**150**:135–8	Wrong study design
Russell AH, Walter JP, Anderson MW, Zukowski CL. Sagittal magnetic resonance imaging in the design of lateral radiation treatment portals for patients with locally advanced squamous cancer of the cervix. *Int J Radiat Oncol Biol Phys* 1992;**23**:449–55	Wrong population
Ryu SY, Kim M-H, Choi C-S, Choi C-W, Lee K-H. Detection of early recurrence with ^{18}F-FDG PET in patients with cervical cancer. *J Nucl Med* 2003;**44**:347–52	Wrong population
Sahdev A, Sohaib SA, Wenaden AE, Shepherd JH, Reznek RH. The performance of magnetic resonance imaging in early cervical carcinoma: a long-term experience. *Int J Gynecol Cancer* 2007;**17**:629–36	Wrong population
Sakurai H, Suzuki Y, Nonaka T, Ishikawa H, Shioya M, Kiyohara H, *et al*. FDG-PET in the detection of recurrence of uterine cervical carcinoma following radiation therapy – tumor volume and FDG uptake value. *Gynecol Oncol* 2006;**100**:601–7	Wrong intervention
Schaffer U, Hawighorst H, Pilch H, Welkel W, Zuna I, Knapstein PG. [Value of clinically established MRI procedures concerning the pretherapeutic evaluation of maximal tumor diameter in primary or recurrent cervix cancer in relation to palpation findings and histopathologic whole mount specimens.] *Zentralbl Gynakol* 1999;**121**:131–6	No data
Schwarz JK, Seigel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA* 2007;**298**:2289–95	Wrong end points
Schwarz JK, Grigsby PW, Dehdashti F, Delbeke D. The role of 18F-FDG PET in assessing therapy response in cancer of the cervix and ovaries. *J Nucl Med* 2009;**50**:64S–73S	Wrong study design
Semple SIK, Harry VN, Parkin DE, Gilbert FJ. A combined pharmacokinetic and radiologic assessment of dynamic contrast-enhanced magnetic resonance imaging predicts response to chemoradiation in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2009;**75**:611–17	Wrong population
Shatov AV. [Potentialities of low-field magnetic resonance tomography in the diagnosis and treatment of invasive cancer of cervix uteri.] *Vestn Rentgenol Radiol* 2003;**3**:48–53	Wrong population
Sheu M, Chang C-Y, Wang J-H, Yen M-S. MR staging of clinical stage I and IIa cervical carcinoma: a reappraisal of efficacy and pitfalls. *Eur J Radiol* 2001;**38**:225–31	Wrong population
Sheu MH, Chang CY, Wang JH, Yen MS. Cervical carcinoma: assessment of parametrial invasion and lymph node metastasis with magnetic resonance imaging. *Chung Hua i Hsueh Tsa Chih – Chin Med J* 2000;**63**:634–40	Lack of full text
Shiraiwa M, Joja I, Asakawa T, Okuno K, Shibutani O, Akamatsu N, *et al*. Cervical carcinoma: efficacy of thin-section oblique axial T2-weighted images for evaluating parametrial invasion. *Abdom Imaging* 1999;**24**:514–19	Wrong population
Silberer H, Wölber L, Fuchs L, Schwarz J. Pre-therapeutic determination of tumor stage in patients with cervical carcinoma – a comparison of clinical evaluation, NMR and CT. *Geburtshilfe Frauenheilkd* 2007;**67**:837–42	Wrong population

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Singh AK, Grigsby PW, Dehdashti F, Herzog TJ, Siegel BA. FDG-PET lymph node staging and survival of patients with FIGO stage IIIb cervical carcinoma. *Int J Radiat Oncol Biol Phys* 2001;**56**:489–93	Wrong population
Sironi S, Belloni C, Taccagni GL, DelMaschio A. Carcinoma of the cervix: value of MR imaging in detecting parametrial involvement. *AJR Am J Roentgenol* 1991;**156**:753–6	Wrong population
Sironi S, Buda A, Picchio M, Perego P, Moreni R, Pellegrino A, *et al*. Lymph node metastasis in patients with clinical early-stage cervical cancer: detection with integrated FDG PET/CT. *Radiology* 2006;**238**:272–9	Wrong population
Smaniotto D, Smaniotto D, Andrulli AD, Tortoreto F, Niespolo RM, Valentini V. Organ preservation in locally advanced carcinoma of the uterine cervix. *Rays* 1997;**22**:472–7	Lack of full text
Soeters RP, Beningfield SJ, Dehaeck K, Levin W, Bloch B. The value of magnetic resonance imaging in patients with carcinoma of the cervix (a pilot study). *Eur J Surg Oncol* 1991;**17**:119–24	Wrong population
Soutter WP, Hanoch J, D'Arcy T, Dina R, McIndoe GA, deSouza NM. Pretreatment tumour volume measurement on high-resolution magnetic resonance imaging as a predictor of survival in cervical cancer. *BJOG* 2004;**111**:741–7	Wrong population
Steinbrich W, Rohde U, Friedmann G. [Importance of computed tomography for the diagnosis of tumors of the uterus and recurrent lesions.] *Radiologe* 1982;**22**:154–61	Lack of full text
Steinkamp HJ, Heim T, Schubeus P, Schorner W, Felix R. [The magnetic resonance tomographic differential diagnosis between reactively enlarged lymph nodes and cervical lymph node metastases.] *Rofo* 1992;**157**:406–13	Wrong population
Steinkamp HJ, Zwicker C, Langer M, Mathe M, Ehritt C, Neumann K, *et al*. [Reactive enlargement of cervical lymph nodes and cervical lymph node metastases: sonography (M/Q quotient) and computed tomography.] *Aktuelle Radiol* 1992;**2**:188–95	Lack of full text
Stryker JA, Mortel R. Survival following extended field irradiation in carcinoma of cervix metastatic to para-aortic lymph nodes. *Gynecol Oncol* 2000;**79**:399–405	Wrong end points
Stummvoll W, Holbock E, Schoissengeier A. [Diagnostic value of abdominal computerized tomography. After-care of gynecologic malignancies.] *Gynakol Geburtshilfliche Rundsch* 1994;**34**:55–7	Lack of full text
Subak LL, Hricak H, Powell B, Azizi L, Stern JL. Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging. *Obstet Gynecol* 1995;**86**:43–50	Wrong population
Sugawara Y, Eisbruch A, Kosuda S, Recker BE, Kison PV, Wahl RL. Evaluation of FDG PET in patients with cervical cancer. *J Nucl Med* 1999;**40**:1125–31	Wrong intervention
Sugimura K, Carrington BM, Quivey JM, Hricak H. Postirradiation changes in the pelvis: assessment with MR imaging. *Radiology* 1990;**175**:805–13	Wrong end points
Sun SS, Chen T-Z, Yen R-F, Shen Y-Y, Changlai S-P, Kao A. Value of whole body 18F-fluoro-2-deoxyglucose positron emission tomography in the evaluation of recurrent cervical cancer. *Anticancer Res* 2001;**21**:2957–61	Wrong intervention
Tardivon AA, Kinkel K, Lartigau E, Masselot J, Gerbaulet AP, Vanel D. MR imaging during intracavitary brachytherapy of vaginal and cervical cancer: preliminary results. *Radiographics* 1996;**16**:1363–70	Wrong population
Tatsumi M, Cohade C, Bristow RE, Wahl RL. Imaging uterine cervical cancer with FDG-PET/CT: direct comparison with PET. *Mol Imaging Biol* 2009;**11**:229–35	Lesion-based analysis
Taylor MB, Carrington BM, Davidson SE, Swindell R, Lawrance JA. Staging of advanced cervical carcinoma using MRI-predictors of outcome after radical radiotherapy. *Clin Radiol* 2003;**58**:532–41	Wrong population
Testa AC, Ludovisi M, Manfredi R, Zanoni G, Gui B, Basso D, *et al*. Transvaginal ultrasonography and magnetic resonance imaging for assessment of presence, size and extent of invasive cervical cancer. *Ultrasound Obstet Gynecol* 2009;**34**:335–44	Wrong population

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TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Thomas L, Chacon B, Kind M, Lasbareilles O, Muyldermans P, Chemin A, *et al*. Magnetic resonance imaging in the treatment planning of radiation therapy in carcinoma of the cervix treated with the four-field pelvic technique. *Int J Radiat Oncol Biol Phys* 1997;**37**:827–32	Wrong end points
Thorvinger B. Diagnostic and interventional radiology in gynecologic neoplasms. *Acta Radiol Suppl* 1992;**378**:93–108	Wrong study design
Togashi K, Nishimura K, Itoh K, Fujisawa I, Asato R, Nakano Y, *et al*. Uterine cervical cancer: assessment with high-field MR imaging. *Radiology* 1986;**160**:431–5	Lack of full text
Thurnher S, McPhillips M, von Schulthess GK, Maricek B. [Cervical carcinoma staging with magnetic resonance tomography: the use of gadolinium-DOTA with 31 patients.] *Rofo* 1991;**154**:643–9	Wrong population
Toita T, Nakano M, Higashi M, Sakumto K, Kanazawa K. Prognostic value of cervical size and pelvic lymph node status assessed by computed tomography for patients with uterine cervical cancer treated by radical radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;**33**:843–9	Wrong end points
Tran BN, Grigsby PW, Dehdashti F, Herzog TJ, Siegel BA. Occult supraclavicular lymph node metastasis identified by FDG-PET in patients with carcinoma of the uterine cervix. *Gynecol Oncol* 2003;**90**:572–6	Wrong population
Trinci M, Raffeto N, Petrozza V, Melis M, Biagini C. Pretreatment scalene node biopsy in cervical carcinoma. *Eur J Gynaecol Oncol* 1988;**9**:308–12	Wrong population
Tsai CS, Chang T-C, Lai C-H, Tsai C-C, Ng K-K, Hsueh S, *et al*. Preliminary report of using FDG-PET to detect extrapelvic lesions in cervical cancer patients with enlarged pelvic lymph nodes on MRI/CT. *Int J Radiat Oncol Biol Phys* 2004;**58**:1506–12	Wrong population
Tsai CS, Lai C-H, Chang C-C, Yen T-C, Ng K-K, Hsueh S, *et al*. A prospective randomized trial to study the impact of pretreatment FDG-PET for cervical cancer patients with MRI-detected positive pelvic but negative para-aortic lymphadenopathy. *Int J Radiat Oncol Biol Phys* 2010;**76**:477–84	Wrong population
Umesaki N, Tanaka T, Miyama M, Kawabe J, Okamura T, Koyama K, *et al*. The role of 18F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG-PET) in the diagnosis of recurrence and lymph node metastasis of cervical cancer. *Oncol Rep* 2000;**7**:1261–4	Lack of full text
Unger JB, Ivy JJ, Connor P, Charrier A, Ramaswamy MR, Ampil FL, *et al*. Detection of recurrent cervical cancer by whole-body FDG PET scan in asymptomatic and symptomatic women. *Gynecol Oncol* 2004;**94**:212–16	Differential verification of reference standard
Unger JB, Ivy JJ, Ramaswamy MR, Charrier A, Connor P. Whole-body [^{18}F]fluoro-2-deoxyglucose positron emission tomography scan staging prior to planned radical hysterectomy and pelvic lymphadenectomy. *Int J Gynecol Cancer* 2005;**15**:1060–4	Wrong intervention
Unger JB, Lilien DL, Caldito G, Ivy JJ, Charrier A, Bellaire B. The prognostic value of pretreatment 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography scan in women with cervical cancer. *Int J Gynecol Cancer* 2007;**17**:1062–7	Wrong population
van der Veldt AA, Hooft L, van Diest PJ, Berkhof J, Buist MR, Comans EF, *et al*. Microvessel density and p53 in detecting cervical cancer by FDG PET in cases of suspected recurrence. *Eur J Nucl Med Mol Imaging* 2006;**33**:1408–16	Wrong intervention
van der Veldt AA, Buist MR, van Baal MW, Comans EF, Hoekstra OS, Molthoff CF. Clarifying the diagnosis of clinically suspected recurrence of cervical cancer: impact of ^{18}F-FDG PET. *J Nucl Med* 2008;**49**:1936–43	Wrong intervention
Van Engelshoven J, Versteege CWM, Ruys JHJ. Computed tomography in staging untreated patients with cervical cancer. *Gynecol Obstet Invest* 1984;**18**:289–95	Wrong population
Vergote I, Tsolakidis D, Mortier D, Neven P, Amant F. Value of positron emission tomography of the para-aortic lymph nodes in cervical carcinoma stage IB2–IIIB. *J Clin Oncol* 2008;**26**:5654–5	Wrong study design
Villasanta U, Whitley NO, Haney PJ, Brenner D. Computed tomography in invasive carcinoma of the cervix: an appraisal. *Obstet Gynecol* 1983;**62**:218–24	Wrong population

TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Voss AC, Hubener KH, Metzger H. [The value of radiometry in the treatment planning of inoperable carcinomas of the cervix (authors' translation).] *Rofo* 1981;**135**:225–9	Wrong end points
Wagenaar HC, Trimbos JB, Postema S, Anastasopoulou A, van der Geest RJ, Reiber JH, *et al*. Tumor diameter and volume assessed by magnetic resonance imaging in the prediction of outcome for invasive cervical cancer. *Gynecol Oncol* 2001;**82**:474–82	Wrong population
Walsh JW, Amendola MA, Konerding KF, Tisnado J, Hazra TA. Computed tomographic detection of pelvic and inguinal lymph-node metastases from primary and recurrent pelvic malignant disease. *Radiology* 1980;**137**:157–66	Small sample size
Walton LA, McCartney WH, Vesterinen E. The use of computerized tomography to obviate celiotomy in recurrent carcinoma of the cervix. *Gynecol Oncol* 1981;**12**:166–76	Wrong study design
Wang LJ, Wong Y-C, Chen C-J, Huang K-G, Hsueh S. Cervical carcinoma: MR imaging with integrated endorectal/phased-array coils: a pilot study. *Eur Radiol* 2001;**11**:1822–7	Wrong population
Weiss E, Eberlein K, Pradier O, Schmidberger H, Hess CF. The impact of patient positioning on the adequate coverage of the uterus in the primary irradiation of cervical carcinoma: a prospective analysis using magnetic resonance imaging. *Radiother Oncol* 2002;**63**:83–7	Wrong end points
Whitley NO, Brenner DE, Francis A, Villasanta V, Aisner J, Wiernik PH. Computed tomographic evaluation of carcinoma of the cervix. *Radiology* 1982;**142**:439–46	Wrong population
Wong TZ, Jones EL, Coleman RE. Positron emission tomography with 2-deoxy-2-[(18)F]fluoro-D-glucose for evaluating local and distant disease in patients with cervical cancer. *Mol Imaging Biol* 2004;**6**:55–62	Wrong intervention
Wright JD, Dehdashti F, Herzog TJ, Mutch DG, Huettner PC, Rader JS. Preoperative lymph node staging of early-stage cervical carcinoma by [18F]-fluoro-2-deoxy-D-glucose-positron emission tomography. *Cancer* 2005;**104**:2484–91	Wrong population
Xue F, Lin LL, Dehdashti F, Miller TR, Siegel BA, Grigsby PW. F-18 fluorodeoxyglucose uptake in primary cervical cancer as an indicator of prognosis after radiation therapy. *Gynecol Oncol* 2006;**101**:147–51	Wrong end points
Xue HD, Li SL, Sun F, Sun H-Y, Jin Z-Y, Yang J-X, *et al*. Clinical application of body diffusion weighted MR imaging in the diagnosis and preoperative N staging of cervical cancer. *Chin Med Sci J* 2008;**23**:133–7	Wrong population
Yamashita Y, Harada M, Torashima M, Takahashi M, Miyazaki K, Tanaka N, *et al*. Dynamic MR imaging of recurrent postoperative cervical cancer. *J Magn Reson Imaging* 1996;**6**:167–71	No data
Yang WT, Lam WW, Yu MY, Cheung TH, Metreweli C. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. *AJR Am J Roentgenol* 2000;**175**:759–66	Wrong population
Yeh LS, Hung Y-C, Shen Y-Y, Kao C-H, Lin C-C, Lee C-C. Detecting para-aortic lymph nodal metastasis by positron emission tomography of 18F-fluorodeoxyglucose in advanced cervical cancer with negative magnetic resonance imaging findings. *Oncol Rep* 2002;**9**:1289–92	Wrong intervention
Yen TC, Ng K-K, Ma S-Y, Chou H-H, Tsai C-S, Hsueh S, *et al*. Value of dual-phase 2-fluoro-2-deoxy-D-glucose positron emission tomography in cervical cancer. *J Clin Oncol* 2003;**21**:3651–8	Wrong intervention
Yen TC, See L-C, Chang T-C, Huang K-G, Ng K-K, Tang SG, *et al*. Defining the priority of using ^{18}F-FDG PET for recurrent cervical cancer. *J Nucl Med* 2004;**45**:1632–9	Wrong intervention
Yen TC, Lai CH. Positron emission tomography in gynecologic cancer. *Semin Nucl Med* 2006;**36**:93–104	Wrong study design
Yen TC, Lai C-H, Ma S-Y, Huang K-G, Huang H-J, Hong J-H, *et al*. Comparative benefits and limitations of ^{18}F-FDG PET and CT-MRI in documented or suspected recurrent cervical cancer. *Eur J Nucl Med Mol Imaging* 2006;**33**:1399–407	Wrong intervention

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TABLE 79 Diagnostic review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Yildirim Y, Sehirali S, Avci ME, Yilmaz C, Ertopcu K, Tinar S, *et al*. Integrated PET/CT for the evaluation of para-aortic nodal metastasis in locally advanced cervical cancer patients with negative conventional CT findings. *Gynecol Oncol* 2008;**108**:154–9	Wrong population
Yokoyama T, Hiura M, Myoga H, Yorishima M, Tanaka M, Chiba T. [Computed tomography for the assessment of pelvic lymph node metastasis in cases of uterine cervical carcinoma.] *Gan No Rinsho* 1990;**36**:495–8	Lack of full text
Yoo SC, Kim WY, Yoon JH, Kim HY, Lee EJ, Chang SJ, *et al*. Accuracy of preoperative magnetic resonance imaging in assessing lymph node metastasis and myometrial invasion in patients with uterine cancer. *Eur J Gynaecol Oncol* 2009;**30**:167–70	Wrong population
Yousem DM, Sorn PM, Hackney DB, Schwaibold F, Hendrix RA. Central nodal necrosis and extracapsular neoplastic spread in cervical lymph nodes: MR imaging versus CT. *Radiology* 1992;**182**:753–9	Wrong population
Yu KK, Hricak H, Subak LL, Zaloudek CJ, Powell CB. Preoperative staging of cervical carcinoma: phased array coil fast spin-echo versus body coil spin-echo T2-weighted MR imaging. *AJR Am J Roentgenol* 1998;**171**:707–11	Wrong population
Zanetta G, Pellegrino A, Vanzulli A, Di Lelio A, Milani R, Mangioni C. Magnetic resonance imaging of cervical cancer in pregnancy. *Int J Gynecol Cancer* 1998;**8**:265–9	Wrong population
Zapf S, Halbsguth A, Schweden F, Klose K, Lochner B, Beck T, *et al*. [Problem of pretherapeutic staging of cervical carcinoma. Studies of the diagnostic value of computerized tomography and magnetic resonance tomography in comparison with gynecologic palpation findings and pathologic-anatomic diagnosis.] *Geburtshilfe Frauenheilkd* 1987;**47**:838–42	Wrong population
Zeisler H, Joura EA, Moeschl P, Maier U, Koebl H. Preoperative evaluation of tumor extension in patients with recurrent cervical cancer. *Acta Obstet Gynecol Scand* 1997;**76**:474–7	Small sample size

Appendix 11 Diagnostic meta-analysis logistic regression results

TABLE 80 Results of univariate random-effects logistic regression models of all PET-CT studies

Summary	Estimate	SE	95% lower limit	95% upper limit
Sensitivity	0.9215686	0.02662	0.850943	0.9602922
Specificity	0.880597	0.0396149	0.7789671	0.9391483

SE, standard error.

TABLE 81 Results of univariate random-effects logistic regression models of PET-CT studies: sensitivity analysis omitting Amit *et al.*[48]

Summary	Estimate	SE	95% lower limit	95% upper limit
Sensitivity	0.9263158	0.0268043	0.8534262	0.9644673
Specificity	0.8730159	0.0419484	0.7660703	0.9352045

SE, standard error.

Appendix 12 Subjective elicitation results

TABLE 82 Elicitation: prevalence of recurrent disease in symptomatic patients a minimum of 3 months post completion of primary treatment

	Percentage of symptomatic women with recurrence						Mean prevalence (%)
	≤50	51–60	61–70	71–80	81–90	91–100	
Midpoint (%)	25.5	55.5	65.5	75.5	85.5	95.5	
Likelihood – clinician 1	50	50	0	0	0	0	40.5
Likelihood – clinician 2	44	22	22	11	0	0	46.6
Likelihood – clinician 3	57	14	10	8	7	5	44.7
Likelihood – clinician 4	10	80	10	0	0	0	53.5
Likelihood – clinician 5	0	10	10	70	10	0	73.5
Likelihood – clinician 6	10	10	50	30	0	0	63.5
Likelihood – clinician 7	0	100	0	0	0	0	55.5
Likelihood – clinician 8	100	0	0	0	0	0	25.5
Likelihood – clinician 9							
Likelihood – clinician 10	80	20	0	0	0	0	31.5
Likelihood – clinician 11	90	10	0	0	0	0	28.5
Likelihood – clinician 12	95	0	0	0	0	5	29.0
Likelihood – clinician 13	100	0	0	0	0	0	25.5
Likelihood – clinician 14	0	0	50	50	0	0	70.5
Likelihood – clinician 15	0	20	60	20	0	0	65.5
Likelihood – clinician 16	0	10	20	40	20	10	75.5
Likelihood – clinician 17	70	20	10	0	0	0	35.5
Likelihood – clinician 18	0	0	100	0	0	0	65.5
Likelihood – clinician 19	20	80	0	0	0	0	49.5
Likelihood – clinician 20	40	25	15	10	5	5	50.5
Likelihood – clinician 21	100	0	0	0	0	0	25.5
Mean prevalence symptomatic	43.3	23.6	17.8	11.9	2.1	1.2	47.8
SD prevalence							20.8

TABLE 83 Elicitation: prevalence of recurrent disease in asymptomatic patients a minimum of 3 months post completion of primary treatment

	Percentage of asymptomatic women with recurrence						Mean prevalence (%)
	0–10	11–20	21–30	31–40	41–50	>50	
Midpoint (%)	5.5	15.5	25.5	35.5	45.5	75.5	
Likelihood – clinician 1	30	30	40	0	0	0	16.5
Likelihood – clinician 2	100	0	0	0	0	0	5.5
Likelihood – clinician 3	10	5	50	30	5	0	27.0
Likelihood – clinician 4	90	10	0	0	0	0	6.5
Likelihood – clinician 5	90	10	0	0	0	0	6.5
Likelihood – clinician 6	20	20	20	20	15	5	27.0
Likelihood – clinician 7	0	100	0	0	0	0	15.5
Likelihood – clinician 8	10	80	10	0	0	0	15.5
Likelihood – clinician 9							
Likelihood – clinician 10	100	0	0	0	0	0	5.5
Likelihood – clinician 11	0	10	90	0	0	0	24.5
Likelihood – clinician 12	95	0	0	0	0	5	9.0
Likelihood – clinician 13	100	0	0	0	0	0	5.5
Likelihood – clinician 14	0	0	50	50	0	0	30.5
Likelihood – clinician 15	10	60	30	0	0	0	17.5
Likelihood – clinician 16	10	20	40	20	10	0	25.5
Likelihood – clinician 17	100	0	0	0	0	0	5.5
Likelihood – clinician 18	100	0	0	0	0	0	5.5
Likelihood – clinician 19	10	80	10	0	0	0	15.5
Likelihood – clinician 20	5	5	40	30	10	10	34.0
Likelihood – clinician 21	0	6	22	56	11	6	35.5
Mean prevalence asymptomatic	44	21.8	20.1	10.3	2.6	1.3	16.7
SD prevalence							13.1

TABLE 84 Elicitation: accuracy (PPV) – symptomatic women investigated using CT and/or MRI

	Mid-point PPV (%)					
	95.5	85.5	75.5	65.5	55.5	Mean PPV (%)
Likelihood – clinician 1	0	0	80	20	0	73.5
Likelihood – clinician 2	50	50	0	0	0	90.5
Likelihood – clinician 3	40	40	10	10	0	86.5
Likelihood – clinician 4	90	10	0	0	0	94.5
Likelihood – clinician 5	70	30	0	0	0	92.5
Likelihood – clinician 6	95	5	0	0	0	95
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	100	0	0	0	0	95.5
Likelihood – clinician 11	50	50	0	0	0	90.5
Likelihood – clinician 12	100	0	0	0	0	95.5
Likelihood – clinician 13	0	0	50	50	0	70.5
Likelihood – clinician 14	50	50	0	0	0	90.5
Likelihood – clinician 15	15	70	15	0	0	85.5
Likelihood – clinician 16	10	80	10	0	0	85.5
Likelihood – clinician 17	90	10	0	0	0	94.5
Likelihood – clinician 18	10	80	10	0	0	85.5
Likelihood – clinician 19	90	10	0	0	0	94.5
Likelihood – clinician 20	10	20	40	20	10	75.5
Likelihood – clinician 21	90	10	0	0	0	94.5
Mean PPV	53.3	28.6	11.9	5.6	0.6	88.4
SD PPV						9.2

TABLE 85 Elicitation: accuracy (NPV) – symptomatic women investigated using CT and/or MRI

	Mid-point NPV (%)					
	95.5	85.5	75.5	65.5	55.5	Mean NPV (%)
Likelihood – clinician 1	0	80	20	0	0	83.5
Likelihood – clinician 2	70	30	0	0	0	92.5
Likelihood – clinician 3	30	40	20	10	0	84.5
Likelihood – clinician 4	5	90	5	0	0	85.5
Likelihood – clinician 5	80	20	0	0	0	93.5
Likelihood – clinician 6	95	5	0	0	0	95
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	80	20	0	0	0	93.5
Likelihood – clinician 11						
Likelihood – clinician 12	10	0	90	0	0	77.5
Likelihood – clinician 13	0	0	100	0	0	75.5
Likelihood – clinician 14	0	50	50	0	0	80.5
Likelihood – clinician 15	80	10	10	0	0	92.5
Likelihood – clinician 16	10	80	10	0	0	85.5
Likelihood – clinician 17	90	10	0	0	0	94.5
Likelihood – clinician 18	0	10	80	10	0	75.5
Likelihood – clinician 19	20	80	0	0	0	87.5
Likelihood – clinician 20	40	30	10	10	10	83.5
Likelihood – clinician 21	90	10	0	0	0	94.5
Mean NPV	41.2	33.2	23.2	1.8	0.6	87.1
SD NPV						8.7

TABLE 86 Elicitation: accuracy (PPV) – symptomatic women investigated using CT and/or MRI and PET-CT

	Mid-point PPV (%)					
	95.5	85.5	75.5	65.5	55.5	Mean PPV (%)
Likelihood – clinician 1	0	0	50	50	0	70.5
Likelihood – clinician 2	20	50	30	0	0	84.5
Likelihood – clinician 3	50	40	5	5	0	89.0
Likelihood – clinician 4	100	0	0	0	0	95.5
Likelihood – clinician 5	90	10	0	0	0	94.5
Likelihood – clinician 6	10	90	0	0	0	86.5
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	100	0	0	0	0	95.5
Likelihood – clinician 11	5	90	5	0	0	85.5
Likelihood – clinician 12	95	0	0	0	5	93.5
Likelihood – clinician 13	0	100	0	0	0	85.5
Likelihood – clinician 14	0	50	50	0	0	80.5
Likelihood – clinician 15	11.1	22.2	33.3	22.2	11.1	75.5
Likelihood – clinician 16	0	10	80	10	0	75.5
Likelihood – clinician 17	90	10	0	0	0	94.5
Likelihood – clinician 18	100	0	0	0	0	95.5
Likelihood – clinician 19	20	80	0	0	0	87.5
Likelihood – clinician 20	5	30	40	20	5	76.5
Likelihood – clinician 21	0	5	90	5	0	75.5
Mean PPV	38.7	32.6	21.3	6.2	1.2	85.6
SD PPV						9.8

TABLE 87 Elicitation: accuracy (NPV) – symptomatic women investigated using CT and/or MRI and PET-CT

	Mid-point NPV (%)					
	95.5	85.5	75.5	65.5	55.5	Mean NPV (%)
Likelihood – clinician 1	80	20	0	0	0	93.5
Likelihood – clinician 2	40	40	20	0	0	87.5
Likelihood – clinician 3	90	10	0	0	0	94.5
Likelihood – clinician 4	90	10	0	0	0	94.5
Likelihood – clinician 5	95	5	0	0	0	95.0
Likelihood – clinician 6	100	0	0	0	0	95.5
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	90	10	0	0	0	94.5
Likelihood – clinician 11	0	50	50	0	0	80.5
Likelihood – clinician 12	90	0	0	0	10	91.5
Likelihood – clinician 13	0	100	0	0	0	85.5
Likelihood – clinician 14	0	50	50	0	0	80.5
Likelihood – clinician 15	80	20	0	0	0	93.5
Likelihood – clinician 16	10	80	10	0	0	85.5
Likelihood – clinician 17	90	10	0	0	0	94.5
Likelihood – clinician 18	90	10	0	0	0	94.5
Likelihood – clinician 19	0	80	20	0	0	83.5
Likelihood – clinician 20	80	10	5	3	2	91.8
Likelihood – clinician 21	100	0	0	0	0	95.5
Mean NPV	62.5	28.1	8.6	0.2	0.7	90.7
SD NPV						7.2

TABLE 88 Elicitation: accuracy (PPV) – asymptomatic women investigated using CT and/or MRI

	Mid-point PPV (%)					Mean PPV (%)
	95.5	85.5	75.5	65.5	55.5	
Likelihood – clinician 1	0	0	50	50	0	70.5
Likelihood – clinician 2	20	50	30	0	0	84.5
Likelihood – clinician 3	50	40	5	5	0	89.0
Likelihood – clinician 4	100	0	0	0	0	95.5
Likelihood – clinician 5	90	10	0	0	0	94.5
Likelihood – clinician 6	10	90	0	0	0	86.5
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	100	0	0	0	0	95.5
Likelihood – clinician 11	5	90	5	0	0	85.5
Likelihood – clinician 12	95	0	0	0	5	93.5
Likelihood – clinician 13	0	100	0	0	0	85.5
Likelihood – clinician 14	0	50	50	0	0	80.5
Likelihood – clinician 15	11.1	22.2	33.3	22.2	11.1	75.5
Likelihood – clinician 16	0	10	80	10	0	75.5
Likelihood – clinician 17	90	10	0	0	0	94.5
Likelihood – clinician 18	100	0	0	0	0	95.5
Likelihood – clinician 19	20	80	0	0	0	87.5
Likelihood – clinician 20	5	30	40	20	5	76.5
Likelihood – clinician 21	0	5	90	5	0	75.5
Mean PPV	38.7	32.6	21.3	6.2	1.2	38.7
SD PPV						9.8

TABLE 89 Elicitation: accuracy (NPV) – asymptomatic women investigated using CT and/or MRI

	Mid-point NPV (%)					Mean NPV (%)
	95.5	85.5	75.5	65.5	55.5	
Likelihood – clinician 1	100	0	0	0	0	95.5
Likelihood – clinician 2	40	40	20	0	0	87.5
Likelihood – clinician 3	80	15	5	0	0	93
Likelihood – clinician 4	100	0	0	0	0	95.5
Likelihood – clinician 5	90	10	0	0	0	94.5
Likelihood – clinician 6	10	90	0	0	0	86.5
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	80	20	0	0	0	93.5
Likelihood – clinician 11	5	90	5	0	0	85.5
Likelihood – clinician 12	5	0	95	0	0	76.5
Likelihood – clinician 13	0	100	0	0	0	85.5
Likelihood – clinician 14	100	0	0	0	0	95.5
Likelihood – clinician 15	80	10	10	0	0	92.5
Likelihood – clinician 16	0	10	80	10	0	75.5
Likelihood – clinician 17	90	10	0	0	0	94.5
Likelihood – clinician 18	90	10	0	0	0	94.5
Likelihood – clinician 19	80	20	0	0	0	93.5
Likelihood – clinician 20	40	30	20	5	5	85
Likelihood – clinician 21	100	0	0	0	0	95.5
Mean NPV	60.6	25.3	13.1	0.81	0.28	90
SD NPV						7.7

TABLE 90 Elicitation: accuracy (PPV) – asymptomatic women investigated using CT and/or MRI and PET-CT

	Mid-point PPV (%)					Mean PPV (%)
	95.5	85.5	75.5	65.5	55.5	
Likelihood – clinician 1	80	20	0	0	0	93.5
Likelihood – clinician 2	10	40	40	10	0	80.5
Likelihood – clinician 3	80	20	0	0	0	93.5
Likelihood – clinician 4	100	0	0	0	0	95.5
Likelihood – clinician 5	95	5	0	0	0	95.0
Likelihood – clinician 6	20	80	0	0	0	87.5
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	100	0	0	0	0	95.5
Likelihood – clinician 11	90	10	0	0	0	94.5
Likelihood – clinician 12	0	95	0	0	5	84.0
Likelihood – clinician 13	0	100	0	0	0	85.5
Likelihood – clinician 14	50	50	0	0	0	90.5
Likelihood – clinician 15	20	30	20	20	10	78.5
Likelihood – clinician 16	10	80	10	0	0	85.5
Likelihood – clinician 17	100	0	0	0	0	95.5
Likelihood – clinician 18	100	0	0	0	0	95.5
Likelihood – clinician 19	80	20	0	0	0	93.5
Likelihood – clinician 20	40	30	20	5	5	85.0
Likelihood – clinician 21	90	10	0	0	0	94.5
Mean PPV	59.2	32.8	5.0	1.9	1.1	90.2
SD PPV						7.7

TABLE 91 Elicitation: accuracy (NPV) – asymptomatic women investigated using CT and/or MRI and PET-CT

	Mid-point NPV (%)					Mean NPV (%)
	95.5	85.5	75.5	65.5	55.5	
Likelihood – clinician 1	100	0	0	0	0	95.5
Likelihood – clinician 2	50	30	20	0	0	88.5
Likelihood – clinician 3	90	10	0	0	0	94.5
Likelihood – clinician 4	100	0	0	0	0	95.5
Likelihood – clinician 5	95	5	0	0	0	95
Likelihood – clinician 6	90	10	0	0	0	94.5
Likelihood – clinician 7						
Likelihood – clinician 8						
Likelihood – clinician 9						
Likelihood – clinician 10	90	10	0	0	0	94.5
Likelihood – clinician 11	90	10	0	0	0	94.5
Likelihood – clinician 12	95	0	0	0	5	93.5
Likelihood – clinician 13	100	0	0	0	0	95.5
Likelihood – clinician 14	100	0	0	0	0	95.5
Likelihood – clinician 15	90	7	3	0	0	94.2
Likelihood – clinician 16	90	10	0	0	0	94.5
Likelihood – clinician 17	100	0	0	0	0	95.5
Likelihood – clinician 18	100	0	0	0	0	95.5
Likelihood – clinician 19	10	80	10	0	0	85.5
Likelihood – clinician 20	30	40	20	5	5	84
Likelihood – clinician 21	100	0	0	0	0	95.5
Mean NPV	84.4	11.8	2.9	0.3	0.6	93.4
SD NPV						5.5

TABLE 92 Minimum increase in accuracy required before PET-CT is introduced as a routine investigation in symptomatic women with initial stage IB–IVA cervical cancer

Clinician	Minimum decrease in FP (%)	Mid-point decrease in FP (%)	Minimum decrease in FN (%)	Mid-point decrease in FN (%)
1	9–11	10	9–11	10
2	20	20	9–11	10
3	9–11	10	6–8	7
4	3–5	4	3–5	4
5	3–5	4	3–5	4
6	9–11	10	3–5	4
7	NS	NA	NS	NA
8	NS	NA	NS	NA
9	9–11	10	9–11	10
10	0–2	1	0–2	1
11	9–11	10	9–11	10
12	0–2	1	0–2	1
13	6–8	7	6–8	7
14	3–5	4	3–5	4
15	6–8	7	6–8	7
16	9–11	10	9–11	10
17	6–8	7	6–8	7
18	6–8	7	6–8	7
19	6–8	7	9–11	10
20	6–8	7	6–8	7
21	9–11	10	0–2	1
Average		7.7		6.4

FN, false-negative; FP, false-positive; NA, not applicable; NS, not stated.

TABLE 93 Minimum increase in accuracy required before PET-CT is introduced as a routine investigation in asymptomatic women with initial stage IB–IVA cervical cancer

Clinician	Minimum decrease in FP (%)	Mid-point decrease in FP (%)	Minimum decrease in FN (%)	Mid-point decrease in FN (%)
1	9–11	10	9–11	10
2	30	30	2–6	4
3	9–11	10	3–5	4
4	0–2	1	0–2	1
5	3–5	4	3–5	4
6	20	20	20	20
7	NS	NA	NS	NA
8	NS	NA	NS	NA
9	30	30	6–8	7
10	0–2	1	0–2	1
11	3–5	4	9–11	10
12	0–2	1	0–2	1
13	3–5	4	3–5	4
14	9–11	10	9–11	10
15	6–8	7	6–8	7
16	9–11	10	9–11	10
17	3–5	4	6–8	7
18	3–5	4	3–5	4
19	3–5	4	3–5	4
20	9–11	10	9–11	10
21	0–2	1	0–2	1
Average		8.7		6.3

FN, false-negative; FP, false-positive; NA, not applicable; NS, not stated.

Appendix 13 Effectiveness review list of excluded studies with reasons for exclusion

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion

Reference	Reason for exclusion
Chemotherapy	
Atahan IL, Yildiz F, Ozyar E, Pehlivan B, Genc M, Kose MF, *et al*. Radiotherapy in the adjuvant setting of cervical carcinoma: treatment, results, and prognostic factors. *Int J Gynecol Cancer* 2007;**17**:813–20	Wrong intervention – adjuvant radiotherapy
Benjapibal M, Thirapakawong C, Leelaphatanadit C, Therasakvichya S, Inthasorn P. A pilot phase II study of capecitabine plus cisplatin in the treatment of recurrent carcinoma of the uterine cervix. *Oncology* 2007;**72**:33–8	Wrong study design – not a RCT
Bigler LR, Tate Thigpen J, Blessing JA, Fiorica J, Monk BJ; Gynecologic Oncology Group. Evaluation of tamoxifen in persistent or recurrent nonsquamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Int J Gynecol Cancer* 2004;**14**:871–4	Wrong study design – not a RCT
Brave M, Dagher R, Farrell A, Abraham S, Ramchandani R, Gobburu J. Topotecan in combination with cisplatin for the treatment of stage IVB, recurrent, or persistent cervical cancer. *Oncology* 2006;**20**:1401–11	Wrong study design – not a RCT
Brewer CA, Blessing JA, Nagourney RA, McMeekin DS, Lele S, Zweizig SL. Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol* 2006;**100**:385–8	Wrong study design – not a RCT
Brooks RA, Rader JS, Dehdashti F, Mutch DG, Powell MA, Thaker PH. Surveillance FDG-PET detection of asymptomatic recurrences in patients with cervical cancer. *Gynecol Oncol* 2009;**112**:104–9	Wrong study design – diagnostic study
Candelaria M, Arias-Bonfill D, Chávez-Blanco A, Chanona J, Cantú D, Pérez C, *et al*. Lack in efficacy for imatinib mesylate as second-line treatment of recurrent or metastatic cervical cancer expressing platelet-derived growth factor receptor alpha. *Int J Gynecol Cancer* 2009;**19**:1632–7	Wrong study design – not a RCT
Chen SW, Liang JA, Hung YC, Yeh LS, Chang WC, Lin WC, *et al*. Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications. *Int J Radiat Oncol Biol Phys* 2006;**66**:1370–7	Waiting to be received
Dobrowsky W, Huigol NG, Jayatilake RS, Kizilbash NI, Okkan S, Kagiya VT, *et al*. AK-2123 (Sanazol) as a radiation sensitizer in the treatment of stage III cervical cancer: results of an IAEA multicentre randomised trial. *Radiother Oncol* 2007;**82**:24–9	Wrong population – primary treatment
Duenas-Gonzalez A, Cetina-Perez L, Lopez-Graniel C, Gonzalez-Enciso A, Gómez-Gonzalez E, Rivera-Rubi L, *et al*. Pathologic response and toxicity assessment of chemoradiotherapy with cisplatin versus cisplatin plus gemcitabine in cervical cancer: a randomised Phase II study. *Int J Radiat Oncol Biol Phys* 2005;**61**:817–23	Wrong population – primary treatment
Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, *et al*. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2001;**22**:872–80	Wrong population – primary treatment
Elst P, Ahankour F, Tjalma WAA. Management of recurrent cervical cancer. Review of the literature and case report. *Eur J Gynaecol Oncol* 2007;**28**:435–41	Wrong study design – not a RCT

continued

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group study. *Cancer* 1954;**112**:1954–63	Wrong study design – not a RCT
Long H III, Nelimark RA, Podratz KC, Suman V, Keeney GL, Nikcevich DA, *et al*. Phase III comparison of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) vs. doxorubicin and cisplatin (AC) in women with advanced primary or recurrent metastatic carcinoma of the uterine endometrium. *Gynecol Oncol* 2006;**100**:501–5	Wrong population – endometrial cancer
Mabuchi S, Morishige K, Isohashi F, Yoshioka Y, Takeda T, Yamamoto T, *et al*. Postoperative concurrent nedaplatin-based chemoradiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors. *Gynecol Oncol* 2000;**115**:482–7	Wrong study design – not a RCT
Mabuchi S, Morishige K, Fujita M, Tsutsui T, Sakata M, Enomoto T, *et al*. The activity of carboplatin and paclitaxel for recurrent cervical cancer after definitive radiotherapy. *Gynecol Oncol* 2009;**113**:200–4	Wrong study design – not a RCT
Maluf FC, Leiser AL, Aghajanian C, Sabbatini P, Pezzulli S, Chi DS, *et al*. Phase II study of tirapazamine plus cisplatin in patients with advanced or recurrent cervical cancer. *Int J Gynecol Cancer* 2006;**16**:1165–71	Wrong study design – not a RCT
Martinez-Monge R, Jurado M, Cambeiro M, Valero J, Villafranca E, Alcázar JL. Perioperative high-dose-rate brachytherapy in locally advanced and recurrent gynecologic cancer: initial results of a phase II trial. *Brachytherapy* 2003;**5**:203–10	Waiting to be received
Matulonis UA, Campos S, Duska L, Krasner CN, Atkinson T, Penson RT, *et al*. Phase I/II dose finding study of combination cisplatin and gemcitabine in patients with recurrent cervix cancer. *Gynecol Oncol* 2006;**103**:160–4	Wrong study design – not a RCT
Micha JP, Goldstein BH, Rettenmaier MA, Brown JV 3rd, John CR, Markman M. Surgery alone or surgery with a combination radiation or chemoradiation for management of patients with bulky-stage IB2 cervical carcinoma. *Int J Gynecol Cancer* 2006;**16**:1147–51	Wrong study design – not a RCT
Miglietta L, Franzone P, Centurioni MG, Boni L, Tacchini L, Cosso M, *et al*. A phase II trial with cisplatin-paclitaxel cytotoxic treatment and concurrent external and endocavitary radiation therapy in locally advanced or recurrent cervical cancer. *Oncology* 2006;**70**:19–24	Wrong study design – not a RCT
Motton S, Houvenaeghel G, Delannes M, Querleu D, Soulé-Tholy M, Hoff J, *et al*. Results of surgery after concurrent chemoradiotherapy in advanced cervical cancer: comparison of extended hysterectomy and extrafascial hysterectomy. *Int J Gynecol Cancer* 2010;**20**:268–75	Waiting to be received
Nagy V, Coza O, Ordeanu C, Traila A, Rancea A, Todor N, *et al*. Radiotherapy versus concurrent 5-day cisplatin and radiotherapy in locally advanced cervical carcinoma: long-term results of a phase III randomised trial. *Strahlenther Onkol* 2009;**185**:177–83	Wrong population – primary treatment
Noda K, Ohashi Y, Sugimori H, Ozaki M, Niibe H, Ogita S, *et al*. Phase III double-blind randomised trial of radiation therapy for stage IIIB cervical cancer in combination with low- or high-dose Z-100: treatment with immunomodulator, more is not better. *Gynecol Oncol* 2006;**101**:455–63	Wrong population – primary treatment
Piura B, Rabinovich A, Friger M. Recurrent cervical carcinoma after radical hysterectomy and pelvic lymph node dissection: a study of 32 cases. *Eur J Gynaecol Oncol* 2008;**29**:31–6	Waiting to be received
Poolkerd S, Leelahakorn S, Manusirivithaya S, Tangjitgamol S, Thavaramara T, Sukwattana P, *et al*. Survival rate of recurrent cervical cancer patients. *J Med Assoc Thail* 2006;**89**:275–82	Wrong study design – not a RCT

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Saito I, Kitagawa R, Fukuda H, Shibata T, Katsumata N, Konishi I, *et al*. A phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent cervical cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group Study (JCOG0505). *Jpn J Clin Oncol* 2010;**40**:90–3	Ongoing study – description of methodology
Smaniotto D, D'Agostino G, Luzi S, Valentini V, Macchia G, Mantini G, *et al*. Concurrent 5-fluorouracil, mitomycin C and radiation with or without brachytherapy in recurrent cervical cancer: a scoring system to predict clinical response and outcome. *Tumori* 2005;**91**:295–301	Waiting to be received
Tacev T, Vacek A, Ptácková B, Strnad V. Hypoxic versus normoxic external-beam irradiation of cervical carcinoma combined with californium-252 neutron brachytherapy. Comparative treatment results of a 5-year randomised study. *Strahlenther Onkol* 2005;**181**:273–84	Wrong population – primary treatment
Tan LT, Zahra M. Long-term survival and late toxicity after chemoradiotherapy for cervical cancer – the Addenbrooke's experience. *Clin Oncol* 2008;**20**:358–64	Wrong study design – not a RCT
Tewari KS, Monk BJ. Recent achievements and future developments in advanced and recurrent cervical cancer: trials of the Gynecologic Oncology Group. *Semin Oncol* 2009;**36**:170–80	Wrong study design – not a RCT
Tran PT, Su Z, Hara W, Husain A, Teng N, Kapp DS. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2007;**69**:504–11	Wrong population – population with gynecological malignancies
Vasishta S, Varghese A, Ragheb A. Patterns of failure in cervical carcinoma and outcome of salvage therapy: a retrospective study. *Gulf J Oncol* 2007;**1**:43–9	Wrong study design – not a RCT
Vieira SC, Costa DR, Meneses AD, Borges e Silva J, Oliveira AK, Sousa RB. [Post-radiotherapy pelvic exenteration in relapsed cervical cancer: experience of a tertiary health service in the northeast of Brazil.] *Rev Bras Ginecol Obstet* 2009;**31**:22–7	Wrong study design – not a RCT
Vorgias G, Profitis E, Sarris G, Strigou S, Kosmas C, Katsoulis M, *et al*. Evaluation of the possible benefits of post-radiotherapy surgery after concomitant chemoradiotherapy with a new radio-sensitizing regimen (irinotecan/CPT-11, interferon A2b and amifostine) for advanced-stage cervical carcinoma. Preliminary results of a pilot phase-II study. *J BUON* 2007;**14**:197–202	Wrong population – primary treatment
Radiotherapy/chemoradiotherapy	
Badakh DK, Grover AH. Reirradiation with high-dose-rate remote afterloading brachytherapy implant in patients with locally recurrent or residual cervical carcinoma. *J Cancer Res Ther* 2009;**5**:24–30	Wrong population – re-irradiation
Bellotti JE, Kagan AR, Wollin M, Olch A. Application of the ICRU Report 38 reference volume concept to the radiotherapeutic management of recurrent endometrial and cervical carcinoma. *Radiother Oncol* 1993;**26**:254–9	Irrelevant or inadequate presented outcomes – results presented separately for each patient
Bignardi M, Bardelli D, Bertoni F, Tordiglione M. Treatment by radiotherapy alone of uterine cervix carcinoma recurrent in the pelvis. *Radiol Med* 1988;**75**:540–4	Irrelevant or inadequate presented outcomes – results presented altogether for patients with different types of primary treatment (radiotherapy and/or chemoradiotherapy with surgery)
Blake PR, Branson AN, Lambert HE. Combined radiotherapy and chemotherapy for advanced carcinoma of the cervix. *Clin Radiol* 1986;**37**:465–9	Wrong population – primary treatment
Boyce J, Fruchter RG, Nicastri AD, Ambiavagar PC, Reinis MS, Nelson JH Jr. Prognostic factors in stage I carcinoma of the cervix. *Gynecol Oncol* 1981;**12**:154–65	Wrong population – primary treatment

continued

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Chung CK, Nahhas WA, Stryker JA, Mortel R. Treatment outcome of recurrent cervical cancer. *J Surg Oncol* 1983;**24**:5–10	Irrelevant or inadequate presented outcomes – results presented altogether for patients with or without previous irradiation
Eifel PJ, Jhingran A, Brown J, Levenback C, Thames H. Time course and outcome of central recurrence after radiation therapy for carcinoma of the cervix. *Int J Gynecol Cancer* 2006;**16**:1106–11	Wrong population – primary treatment
Evans RA. Radical hysterectomy for recurrent carcinoma of the uterine cervix following radiotherapy. *Gynecol Oncol* 1995;**59**:162–3	Wrong study design – letter
Evans SR Jr, Hilaris BS, Barber HRK. External vs. interstitial irradiation in unresectable recurrent cancer of the cervix. *Cancer* 1971;**28**:1284–8	Irrelevant or inadequate presented outcomes – results presented altogether for different types of primary treatment [radiation (60% of patients) and/or surgery]
Fang FM, Yeh CY, Lai YL, Chiou JF, Chang KH. Radiotherapy following simple hysterectomy in patients with invasive carcinoma of the uterine cervix. *J Formos Med Assoc* 1993;**92**:420–5	Waiting to be received
Friedman M, Pearlman AW. Carcinoma of the cervix: radiation salvage of surgical failures. *Radiology* 1965;**84**:801–11	Irrelevant or inadequate presented outcomes – not all patients were analysed, results separate for each patient
Grigsby PW. Radiotherapy for pelvic recurrence after radical hysterectomy for cervical cancer. *Radiat Med* 2005;**23**:327–30	Waiting to be received
Guttmann R. Significance of postoperative irradiation in carcinoma of the cervix: a ten year survey. *Am J Roentgenol Radium Ther Nucl Med* 1970;**108**:102–8	Wrong intervention – adjuvant radiotherapy
Heaton D, Yordan E, Reddy S, Bonomi P, Lee MS, Lincoln S, *et al*. Treatment of 29 patients with bulky squamous cell carcinoma of the cervix with simultaneous cisplatin, 5-fluorouracil, and split-course hyperfractionated radiation therapy. *Gynecol Oncol* 1990;**38**:323–7	Wrong population – primary treatment
Hogan WM, Littman P, Griner L, Miller CL, Mikuta JJ. Results of radiation therapy given after radical hysterectomy. *Cancer* 1982;**49**:1278–85	Irrelevant or inadequate presented outcomes – results presented altogether for patients with and without previous irradiation
Hong JH, Tsai CS, Lai CH, Chang TC, Wang CC, Chou HH, *et al*. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;**60**:249–57	Wrong population – primary radiotherapy
Ito H, Kumagaya H, Shigematsu N, Nishiguchi I, Nakayama T, Hashimoto S. High dose rate intracavitary brachytherapy for recurrent cervical cancer of the vaginal stump following hysterectomy. *Int J Radiat Oncol Biol Phys* 1991;**20**:927–32	Wrong study design – letter
Kaneyasu Y, Okawa MK, Kokubo N, Takemoto M, Karasawa K, Fukuhara N, *et al*. [Clinical evaluation of intra-arterial infusion chemotherapy for advanced or recurrent pelvic tumors with or without radiotherapy.] *Gan to Kagaku Ryoho* 1996;**23**:1486–93	Waiting to be received
Karlan BY, Chamorro T, Fowler JM, Muderspach LI, Greenberg S, Lagasse LD. Concurrent interstitial radiotherapy and infusional chemotherapy for recurrent gynecologic malignancies. *Int J Gynecol Cancer* 1993;**3**:304–10	Waiting to be received
Kucera H, Riss P, Weghaupt K. [Irradiation therapy of recurrent cervical carcinoma (authors' translation).] *Geburtshilfe Frauenheilkd* 1980;**40**:1000–5	Irrelevant or inadequate presented outcomes – results presented together for patients with and without previous irradiation

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Kumagaya H, Ito H, Hashimoto S. [High-dose intracavitary brachytherapy of a recurrent cervical cancer following surgery.] *Gan No Rinsho* 1990;**36**:51–6	Waiting to be received
Lanciano R. Radiotherapy for the treatment of locally recurrent cervical cancer. *J Natl Cancer Inst Monogr* 1996;**96**:113–15	Waiting to be received
Larson DM, Copeland LJ, Stringer CA, Gershenson DM, Malone JM Jr, Edwards CL. Recurrent cervical carcinoma after radical hysterectomy. *Gynecol Oncol* 1988;**30**:381–7	Wrong population – 26% of patients received adjuvant radiotherapy – lack of separate results
Macia M, Novo A, Ces J, Gonzalez M, Huidobro C, Yuste J, *et al*. Neoadjuvant and salvage chemotherapy with cisplatin (CDDP) and 5-fluorouracil (5-FU) in cervical carcinoma. *Eur J Gynaecol Oncol* 1993;**14**:192–6	Wrong intervention – neoadjuvant chemotherapy, or salvage therapy after radiotherapy
Mahe MA, Gerard JP, Dubois JB, Roussel A, Bussieres E, Delannes M, *et al*. Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: report of the French intraoperative group on 70 patients. *Int J Radiat Oncol Biol Phys* 1996;**34**:21–6	Wrong intervention – radiotherapy plus surgery
Malfetano J, Keys H, Kredentser D, Cunningham M, Kotlove D, Weiss L. Weekly cisplatin and radical radiation therapy for advanced, recurrent, and poor prognosis cervical carcinoma. *Cancer* 1993;**71**:3703–6	Wrong population – mixed primary and recurrence – results presented together
Martinez Monge R, Jurado M, Azinovic I, Aristu JJ, Tangco E, Viera JC, *et al*. Intraoperative radiotherapy in recurrent gynecological cancer. *Radiother Oncol* 1993;**28**:127–33	Irrelevant or inadequate presented outcomes – results presented together for different types of primary cancer site
Martinez-Monge R, Jurado M, Aristu JJ, Moreno M, Cambeiro M, Perez-Ochoa A, *et al*. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. *Gynecol Oncol* 2001;**82**:538–43	Wrong intervention – surgery
Martino M, Houvenaeghel G, Hardwigsen J, Moutardier V, Resbeut M, Delpero JR. Pelvic recurrence of cancers of the uterine cervix. A study of a series of 49 cases. *Ann Chir* 1997;**51**:36–45	Wrong intervention – surgery plus radiotherapy
Miglietta L, Franzone P, Centurioni MG, Boni L, Tacchini L, Cosso M, *et al*. A phase II trial with cisplatin-paclitaxel cytotoxic treatment and concurrent external and endocavitary radiation therapy in locally advanced or recurrent cervical cancer. *Oncology* 2006;**70**:19–24	Irrelevant or inadequate presented outcomes – results presented together for different populations
Monk BJ, Walker JL, Tewari K, Ramsinghani NS, Nisar Syed AM, DiSaia PJ. Open interstitial brachytherapy for the treatment of local-regional recurrences of uterine corpus and cervix cancer after primary surgery. *Gynecol Oncol* 1994;**52**:222–8	Irrelevant or inadequate presented outcomes – results presented together for different types of primary cancer site
Nakano T, Gomi H, Morita S, Arai T. Interstitial radiotherapy for recurrent cancer of the uterine cervix. *Jpn J Cancer Clin* 1986;**32**:481–4	Waiting to be received
Niibe Y, Kenjo M, Kazumoto T, Michimoto K, Takayama M, Yamauchi C, *et al*. Multi-institutional study of radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma: 84 subjects of a population of more than 5,000. *Int J Radiat Oncol Biol Phys* 2006;**66**:1366–9	Not adequate population – results presented together for patients with and without previous irradiation
Nori D, Hilaris BS. Interstitial irradiation in recurrent cervical cancer. *Indian J Cancer* 1980;**17**:253–7	Wrong population, results presented together for patients with and without previous irradiaition
Poolkerd S, Leelahakorn S, Manusirivithaya S, Tangjitgamol S, Thavaramara T, Sukwattana P, *et al*. Survival rate of recurrent cervical cancer patients. *J Med Assoc Thail* 2006;**89**:275–82	Irrelevant or inadequate presented outcomes – results presented together for different types of intervention

continued

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Prempree T, Amornmarn R, Villasanta U. Retreatment of very late recurrent invasive squamous cell carcinoma of the cervix with irradiation. II. Criteria for patients' selection to achieve the success. *Cancer* 1984;**54**:1950–5	Wrong population – re-irradiation
Roth TM, Secord AA, Havrilesky LJ, Jones E, Clarke-Pearson DL. High dose rate intraoperative radiotherapy for recurrent cervical cancer and nodal disease. *Gynecol Oncol* 2003;**91**:258–60	Wrong study design – case study, one patient
Sakurai H, Mitsuhashi N, Takahashi M, Akimoto T, Muramatsu H, Ishikawa H, *et al*. Analysis of recurrence of squamous cell carcinoma of the uterine cervix after definitive radiation therapy alone: patterns of recurrence, latent periods, and prognosis. *Int J Radiat Oncol Biol Phys* 2001;**50**:1136–44	Wrong population – primary radiotherapy
Schulz-Wendtland R, Kramer S, Sabel M, Heller F, Keilholz L, Jager W, *et al*. [Pelvic wall recurrence of cervix carcinomas. Combined surgical-radio-chemotherapeutic procedure (CORCT).] *Strahlenther Onkol* 1998;**174**:279–83	Wrong intervention – surgical-radio-chemotherapeutic procedure
Singh AK, Grigsby PW, Rader JS, Mutch DG, Powell MA. Cervix carcinoma, concurrent chemoradiotherapy, and salvage of isolated paraaortic lymph node recurrence. *Int J Radiat Oncol Biol Phys* 2001;**61**:450–5	Wrong population – primary radiotherapy
Sommers GM, Grigsby PW, Perez CA, Camel HM, Kao MS, Galakatos AE, *et al*. Outcome of recurrent cervical carcinoma following definitive irradiation. *Gynecol Oncol* 1989;**35**:150–5	Wrong population – primary radiotherapy
Stelzer KJ, Koh WJ, Greer BE, Cain JM, Tamimi HK, Figge DC, *et al*. The use of intraoperative radiation therapy in radical salvage for recurrent cervical cancer: outcome and toxicity. *Am J Obstet Gynecol* 1995;**172**:1881–8	Wrong intervention – radiotherapy plus surgery
Tan D, Wan H, Peng X. Treatment of recurrent carcinoma of the uterine cervix. *Chin J Oncol* 1995;**17**:47–9	Waiting to be received
Tan LT, Zahra M. Long-term survival and late toxicity after chemoradiotherapy for cervical cancer – the Addenbrooke's experience. *Clin Oncol* 2008;**20**:358–64	Wrong population – primary and recurrent together
Thomas G, Dembo A, Beale F. Concurrent radiation, mitomycin C and 5-fluorouracil in poor prognosis carcinoma of cervix: preliminary results of a phase I–II study. *Int J Radiat Oncol Biol Phys* 1984;**10**:1785–90	Irrelevant or inadequate presented outcomes – results presented together for different types of primary treatment (radiotherapy and/or chemoradiotherapy, surgery)
Thomas G, Dembo A, Fyles A, Gadalla T, Beale F, Bean H, *et al*. Concurrent chemoradiation in advanced cervical cancer. *Gynecol Oncol* 1990;**38**:446–51	Wrong population – primary treatment
Thomas GM, Dembo AJ, Myhr T, Black B, Pringle JF, Rawlings G. Long-term results of concurrent radiation and chemotherapy for carcinoma of the cervix recurrent after surgery. *Int J Gynecol Cancer* 2003;**3**:193–8	Waiting to be received
Vasishta S, Varghese A, Ragheb A. Patterns of failure in cervical carcinoma and outcome of salvage therapy: a retrospective study. *Gulf J Oncol* 2007;**1**:43–9	Irrelevant or inadequate presented outcomes – results presented together for different types of salvage therapy
Wang CJ, Lai CH, Huang HJ, Hong JH, Chou HH, Huang KG, *et al*. Recurrent cervical carcinoma after primary radical surgery. *Am J Obstet Gynecol* 1999;**181**:518–24	Wrong population – patients received adjuvant radiotherapy
Windschall A, Ott OJ, Sauer R, Strnad V. Radiation therapy and simultaneous chemotherapy for recurrent cervical carcinoma. *Strahlenther Onkol* 2005;**181**:545–50	Irrelevant or inadequate presented outcomes – results presented together for different types of primary treatment (radiotherapy and/or chemotherapy with surgery)
Xiang E, Shu-mo C, Ya-qin D, Ke W. Treatment of late recurrent vaginal malignancy after initial radiotherapy for carcinoma of the cervix: an analysis of 73 cases. *Gynecol Oncol* 1998;**69**:125–9	Wrong population – primary radiotherapy
Yang MG. Radiotherapy for locoregional recurrent cervix cancer after surgery. *J Korean Soc Ther Radiol* 1994;**12**:377–86.	Waiting to be received

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Salvage surgery	
Allum WH, Ambrose NS, Fielding JW, Chan KK. Selective salvage surgery in gastrointestinal and gynaecological cancer. *Ann R Coll Surg Engl* 1990;**72**:2–5	Small number of patients
Ayhan A, Otegen U, Guven S, Kucukali T. Radical reoperation for invasive cervical cancer found in simple hysterectomy. *J Surg Oncol* 2006;**94**:28–34	Wrong intervention – radical reoperation
Azria E, Morice P, Haie-Meder C, Thoury A, Pautier P, Lhomme C, *et al*. Results of hysterectomy in patients with bulky residual disease at the end of chemoradiotherapy for stage IB2/II cervical carcinoma. *Ann Surg Oncol* 2005;**12**:332–7	Wrong study design – case report
Bader AA, Petru E, Winter R. Long-term follow-up after neoadjuvant chemotherapy for high-risk cervical cancer during pregnancy. Gynecol *Oncol* 2007;**105**:269–72	Wrong study design – case report
Barber HR. Pelvic exenteration. *Cancer Invest* 1987;**5**:331–8	Wrong study design – literature review
Barber HRK, Roberts S, Brunschwig A. Prognostic significance of preoperative nonvisualized kidney in patients receiving pelvic exenteration. *Cancer* 1963;**16**:614–15	Wrong study design – inadequate aim of study, advanced cervical cancer
Barber HRK, Brunschwig A. Pelvic exenteration for extensive visceral necrosis following radiation therapy for gynecologic cancer. *Obstet Gynecol* 1965;**25**:575–8	Wrong population – patients with visceral necrosis
Barber HRK, Graber EA. Treatment of advanced cancer of the cervix by pelvic exenteration. *Bull N Y Acad Med* 1973;**49**:870–86	Wrong study design – literature review
Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. *Gynecol Oncol* 2005;**99**:153–9	Wrong population – different types of cancer
Bjornstahl H, Johnsson JE, Lindberg LG. Hysterectomy in central recurrence of carcinoma of the uterine cervix. *Acta Obstet Gynecol Scand* 1977;**56**:227–31	Waiting to be received
Bobin JY, Romestaing P, Gerard JP. [Treatment of loco-regional recurrences of cervix cancers.] *Ann Chir* 1999;**53**:904	Waiting to be received
Bochner BH, McCreath WA, Aubey JJ, Levine DA, Barakat RR, Abu-Rustum N, *et al*. Use of an ureteroileocecal appendicostomy urinary reservoir in patients with recurrent pelvic malignancies treated with radiation. *Gynecol Oncol* 2004;**94**:140–6	Wrong study design – surgical techniques
Bolla M, Berland E, Salvat J, Artignan X, de Cornulier J, Colonna M. Fast growing cervical carcinomas. A retrospective analysis of 20 IB–IIB FIGO. *Eur J Obstet Gynecol Reprod Biol* 2000;**90**:81–5	Wrong study design – inadequate aim of study, fast-growing cervical cancer
Bompiani A, Benedetti Panici P, Greggi S, Margariti PA, Di Roberto P. Pelvic exenteration in gynaecologic oncology: analysis of 44 cases. *Eur J Gynaecol Oncol* 1985;**6**:165–9	Waiting to be received
Brand E. Cecal rupture after continent ileocecal urinary diversion during total pelvic exenteration. *Obstet Gynecol* 1991;**78**:570–2	Wrong study design – case report
Bricker EM. Radical evisceration of the pelvis for advanced and recurring carcinoma. *Arch Gynakol* 1967;**2**:1–19	Wrong study design – literature review
Brodsky JT, Sloane BB, Khanna OP. Total pelvic exenteration with preservation of fecal continence. *J Surg Oncol* 1993;**53**:261–4	Wrong study design – case report
Brunschwig A. The possibilities of radical surgery, in cancer of the cervix uteri recurrent after radiation therapy. *Am J Roentgenol* 1951;**65**:720–5	Waiting to be received
Brunschwig A. The surgical treatment of cancer of the cervix. *Cancer* 1953;**6**:980–6	Wrong population – unclear primary treatment, not directly recurrent or persistent
Brunschwig A. Surgical treatment of stage I cancer of the cervix. *Cancer* 1960;**13**:34–6	Wrong population – primary treatment

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TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Brunschwig A, Daniel WW. The surgery of pelvic lymph node metastases from carcinoma of the cervix. *Am J Obstet Gynecol* 1962;**83**:389–92	No relevant outcomes reported
Brunschwig A. Surgical treatment of carcinoma of the cervix, recurrent after irradiation or combination of irradiation and surgery. *Am J Roentgenol Radium Ther Nucl Med* 1967;**99**:365–70	Waiting to be received
Brunschwig A. The surgical treatment of cancer of the cervix stages I and II. *Minerva Ginecol* 1968;**102**:147–51	Wrong population – primary treatment
Brunschwig A, Daniel WW. Surgical treatment of cancer of the cervix recurrent after previous radiation therapy. *Surg Gynecol Obstet* 1957;**105**:186–90	Waiting to be received
Brunschwig A, Barber HR. Extended pelvic exenteration for advanced cancer of the cervix. Long survivals following added resection of involved small bowel. *Cancer* 1964;**17**:1267–70	Wrong study design – case report
Brunschwig A, Barber HRK. Surgical treatment of carcinoma of the cervix. *Obstet Gynecol* 1966;**27**:21–9	Wrong intervention – palliative treatment
Caceres A, Mourton SM, Bochner BH, Gerst SR, Liu L, Alektiar KM, *et al*. Extended pelvic resections for recurrent uterine and cervical cancer: out-of-the-box surgery. *Int J Gynecol Cancer* 2008;**18**:1139–44	Wrong intervention – extended surgical treatment
Cantrell LA, Mendivil A, Gehrig PA, Boggess JF. Survival outcomes for women undergoing type III robotic radical hysterectomy for cervical cancer: a 3-year experience. *Gynecol Oncol* 2010;**117**:260–5	Wrong population – patients after surgical procedure
Carter J, Chi DS, Abu-Rustum N, Brown CL, McCreath W, Barakat RR. Brief report: total pelvic exenteration – a retrospective clinical needs assessment. *Psychooncology* 2004;**13**:125–31	Wrong population – gynecological cancers, unclear primary therapy
Cetina L, Garcia-Arias A, Candelaria M, Cantú D, Rivera L, Coronel J, et *al*. Brachytherapy versus radical hysterectomy after external beam chemoradiation: a non-randomised matched comparison in IB2–IIB cervical cancer patients. *World J Surg Oncol* 2009;**7**:19	Wrong intervention – external-beam chemoradiotherapy plus radical hysterectomy vs external-beam chemoradiotherapy plus brachytherapy
Chang HK, Lo KY, Chiang HS. Complications of urinary diversion after pelvic exenteration for gynecological malignancy. *Int Urogynecol J* 2000;**11**:358–60	Wrong population – patients with different gynecological cancers, radiotherapy and surgery as primary treatment
Cheewakriangkrai C, Srisomboon J, Chitapanarux I, Suprasert P, Phongnarisorn C, Siriaree S, et *al*. Concurrent cisplatin-based chemoradiation and adjuvant hysterectomy for bulky stage IB–IIA cervical cancer. *J Med Assoc Thai* 2005;**88**:1331–7	Wrong population – previously untreated, chemoradiotherapy plus adjuvant hysterectomy
Chiva LM, Lapuente F, González-Cortijo L, González-Martín A, Rojo A, García JF, *et al*. Surgical treatment of recurrent cervical cancer: state of the art and new achievements. *Gynecol Oncol* 2008;**110**:S60–6	Wrong study design – literature review
Chou HH, Wang CC, Lai CH, Hong JH, Ng KK, Chang TC, *et al*. Isolated paraaortic lymph node recurrence after definitive irradiation for cervical carcinoma. *Int J Radiat Oncol Biol Phys* 2001;**51**:442–8	Wrong population – para-aortic recurrence
Colombo PE, Bertrand MM, Gutowski M, Mourregot A, Fabbro M, Saint-Aubert B, *et al*. Total laparoscopic radical hysterectomy for locally advanced cervical carcinoma (stages IIB, IIA and bulky stages IB) after concurrent chemoradiation therapy: surgical morbidity and oncological results. *Gynecol Oncol* 2009;**114**:404–9	Wrong population – neoadjuvant chemoradiotherapy plus radical hysterectomy
Cox EF, Ketchum AS, Villasanta U, Munford RS. Patient evaluation for pelvic exenteration. *Am Surg* 1964;**30**:574–7	No relevant outcomes reported – lack of adequate clinical data
Creasman WT, Rutledge F. Preoperative evaluation of patients with recurrent carcinoma of the cervix. *Gynecol Oncol* 1972;**1**:11–18	Wrong study design – literature review
Crozier M, Morris M, Levenback C, Lucas KR, Atkinson EN, Wharton JT. Pelvic exenteration for adenocarcinoma of the uterine cervix. *Gynecol Oncol* 1995;**58**:74–8	Wrong population – primary radiotherapy or radiotherapy plus surgery

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Curry SL, Nahhas WA, Jahshan AE. Pelvic exenteration: a 7-year experience. *Gynecol Oncol* 1981;**11**:119–23	Wrong population – unclear primary treatment
Deckers PJ, Olsson C, Williams LA, Mozden PJ. Pelvic exenteration as palliation of malignant disease. *Am J Surg* 1976;**131**:509–15	Wrong population – patients with different gynecological malignancies
Delmore JE, Turner DA, Gershenson DM, Horbelt DV. Perineal hernia repair using human dura. *Obstet Gynecol* 1987;**70**:507–8	Wrong study design – case report
Dem A. [Evaluation of surgical resection in the locally advanced cervical carcinomas after neoadjuvant external beam radiation therapy.] *Bull Cancer* 2008;**95**:235–40	Wrong population – patients after neoadjuvant radiotherapy plus surgery
DePasquale SE, Mylonas I, Falkenberry SS. Fatal recurrent ureteroarterial fistulas after exenteration for cervical cancer. *Gynecol Oncol* 2001;**82**:192–6	Wrong study design – case report
deSouza NM, Soutter WP, Rustin G, Mahon MM, Jones B, Dina R, *et al*. Use of neoadjuvant chemotherapy prior to radical hysterectomy in cervical cancer: monitoring tumour shrinkage and molecular profile on magnetic resonance and assessment of 3-year outcome. *Br J Cancer* 2004;**90**:2326–31	Wrong intervention – neoadjuvant chemotherapy plus radical hysterectomy plus partial radiotherapy
Di Saia PJ, Morrow CP. Pelvic exenteration. *Calif Med* 1973;**118**:13–17	Wrong study design – literature review
Distefano M, Ferrandina G, Smaniotto D, Margariti AP, Zannoni G, Macchia G, *et al*. Concomitant radiochemotherapy plus surgery in locally advanced cervical cancer: update of clinical outcome and cyclooxygenase-2 as predictor of treatment susceptibility. Oncology 2004;**67**:103–11	Wrong population – patients with locally advanced cervical cancer, chemoradiotherapy plus hysterectomy
Dottino PR, Segna RA, Jennings TS, Mandeli JP, Konsker K, Cohen CJ. Pelvic exenteration in gynecologic oncology: experience at the Mount Sinai Center, 1975–1992. *Mt Sinai J Med* 1995;**62**:431–5	Waiting to be received
Durrance FY, Fletcher GH, Rutledge FN. Analysis of central recurrent disease in stages I and II squamous cell carcinomas of the cervix on intact uterus. *Am J Roentgenol* 1969;**106**:831–8	No relevant outcomes reported
El-Lamie IK. Preliminary experience with Mainz type II pouch in gynecologic oncology patients. *Eur J Gynaecol Oncol* 2001;**22**:77–80	Wrong population – gynecological cancers
Elst P, Ahankour F, Tjalma W. Management of recurrent cervical cancer. Review of the literature and case report. *Eur J Gynaecol Oncol* 2007;**28**:435–41	Wrong study design – literature review
Ferenschild FT, Vermaas M, Verhoef C, Ansink AC, Kirkels WJ, Eggermont AM, *et al*. Total pelvic exenteration for primary and recurrent malignancies. *World J Surg* 2009;**33**:1502–8	Wrong population – different primary treatment
Ferron G, Querleu D, Martel P, Letourneur B, Soulié M. Laparoscopy-assisted vaginal pelvic exenteration. *Gynecol Oncol* 2006;**100**:551–5	Wrong population – different primary treatment
Fleisch MC, Pantke P, Beckmann MW, Schnuerch HG, Ackermann R, Grimm MO, *et al*. Predictors for long-term survival after interdisciplinary salvage surgery for advanced or recurrent gynecologic cancers. *J Surg Oncol* 2007;**95**:476–84	Wrong population – diffrent types of cancer
Fotopoulou C, Neumann U, Kraetschell R, Schefold JC, Weidemann H, Lichtenegger W, *et al*. Long-term clinical outcome of pelvic exenteration in patients with advanced gynecological malignancies. *J Surg Oncol* 2010;**101**:507–12	Wrong population – diffrent types of cancer
Friedberg V. Results of 108 exenteration operations in advanced gynaecological carcinomas. *Geburtshilfe Frauenheilkd* 1989;**49**:423–7	Wrong population – diffrent types of cancer
Füller J, Guderian D, Köhler C, Schneider A, Wendt TG. Lymph edema of the lower extremities after lymphadenectomy and radiotherapy for cervical cancer. *Strahlenther Onkol* 2008;**184**:206–11	Wrong intervention – patients after surgery and adjuvant radiotherapy or chemoradiotherapy

continued

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Galante M, Hill EC. Pelvic exenteration: a critical analysis of a ten-year experience with the use of the team approach. *Trans Pac Coast Obstet Gynecol Soc* 1970;**38**:59–68	Waiting to be received
Gemignani ML, Alektiar KM, Leitao M, Mychalczak B, Chi D, Venkatraman E, *et al*. Radical surgical resection and high-dose intraoperative radiation therapy (HDR-IORT) in patients with recurrent gynecologic cancers. *Int J Radiat Oncol Biol Phys* 2001;**50**:687–94	Wrong population – inadequte primary treatment (surgery +/– radiotherapy)
Gillitzer R, Hampel C, Thuroff JW. Pelvic exenteration for gynecologic malignancies. Urological reconstructive armamentarium. *Gynakologe* 2007;**40**:883–90	Wrong study design – literature review
Goldberg GL, Sukumvanich P, Einstein MH, Smith HO, Anderson PS, Fields AL. Total pelvic exenteration: the Albert Einstein College of Medicine/Montefiore Medical Center Experience (1987 to 2003). *Gynecol Oncol* 2006;**101**:261–8	Wrong population – different types of cancer
Green AE, Escobar PF, Neubaurer N, Michener CM, Vongruenigen VE. The Martius flap neovagina revisited. *Int J Gynecol Cancer* 2005;**15**:964–6	Wrong study design – case report
Guimarães GC, Baiocchi G, Rossi BM, Ferreira FO, Aguiar S, Nakagawa WT, *et al*. The use of silicone expander and cecal transposition after pelvic exenteration. *Eur J Surg Oncol* 2007;**33**:586–9	Wrong population – women and men, reconstruction procedures
Hatch KD, Shingleton HM, Potter ME, Baker VV. Low rectal resection and anastomosis at the time of pelvic exenteration. *Gynecol Oncol* 1988;**31**:262–7	Wrong study design – case reports
Hatch KD, Shingleton HM, Soong SJ, Baker VV, Gelder MS. Anterior pelvic exenteration. *Gynecol Oncol* 1988;**31**:205–16	Waiting to be received
Hawighorst-Knapstein S, Fusshoeller C, Franz C, Trautmann K, Schmidt M, Pilch H, *et al*. The impact of treatment for genital cancer on quality of life and body image – results of a prospective longitudinal 10-year study. *Gynecol Oncol* 2004;**94**:398–403	Wrong intervention – surgery +/– adjuvant radiotherapy/ chemotherapy
Hays DM, Raney RB Jr, Lawrence W Jr, Gehan EA, Soule EH, Tefft M, *et al*. Rhabdomyosarcoma of the female urogenital tract. *J Pediatr Surg* 1981;**16**:828–34	Wrong population – different types of cancer
Hill EC, Galante M. Radical surgery in the management of clear cell adenocarcinoma of the cervix and vagina in young women. *Am J Obstet Gynecol* 1981;**140**:221–6	Wrong population – inadequate primary treatment (surgery)
Ho YH, Cheng C, Tay SK. Total pelvic exenteration: results from a multispecialty team approach to complex cancer surgery. *Int Surg* 2001;**86**:107–11	Waiting to be received
Höckel M. Laterally extended endopelvic resection: surgical treatment of infrailiac pelvic wall recurrences of gynecologic malignancies. *Am J Obstet Gynecol* 1999;**180**:306–12	Wrong population – inadequate primary treatment (radiotherapy, radiotherapy/surgery), adjuvant postoperative radiotherapy
Höckel M. Laterally extended endopelvic resection (LEER) for surgical treatment of pelvic wall recurrences of cervical carcinoma. *Onkologe* 2001;**7**:875–9	Wrong population – inadequate previous treatment, LEER
Höckel M. Laterally extended endopelvic resection: novel surgical treatment of locally recurrent cervical carcinoma involving the pelvic side wall. *Gynecol Oncol* 2003;**91**:369–77	Wrong population – some patients had inadequate primary treatment or received adjuvant radiotherapy
Höckel M. Laterally extended endopelvic resection for surgical treatment of gynecological malignancies with infiltration of the pelvic wall. *Gynakol Praxis* 2003;**27**:369–77	Waiting to be received
Höckel M. New developments in the surgical therapy of cervical carcinoma. *J Turkish German Gynecol Assoc* 2005;**6**:2–11	Wrong study design – literature review
Höckel M. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. *Lancet Oncol* 2006;**7**:837–47	Wrong study design – literature review
Höckel M, Dornhofer N. How to manage locally advanced primary and recurrent cancer of the uterine cervix: the surgeon's view. *Rev Gynaecol Pract* 2005;**5**:212–20	Wrong study design – literature review

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Hoffman MS, Fiorica JV, Roberts WS, Hewitt S, Shepherd JH, Owens S, *et al*. Williams' vulvovaginoplasty after supralevator total pelvic exenteration. *South Med J* 1991;**84**:43–5	No relevant outcomes reported
Hong JH, Tsai CS, Lai CH, Chang TC, Wang CC, *et al*. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;**60**:249–57	Wrong intervention – salvage surgery included total hysterectomy, radical hysterectomy, anterior pelvic exenteration, posterior pelvic exenteration, TPE and other
Houvenaeghel G, Moutardier V, Karsenty G, Bladou F, Lelong B, Buttarelli M, *et al*. Major complications of urinary diversion after pelvic exenteration for gynecologic malignancies: a 23-year mono-institutional experience in 124 patients. *Gynecol Oncol* 2004;**92**:680–3	Wrong population – different types of cancer
Houvenaeghel G, Lelievre L, Gonzague-Casabianca L, Buttarelli M, Moutardier V, Goncalves A, *et al*. Long-term survival after concomitant chemoradiotherapy prior to surgery in advanced cervical carcinoma. *Gynecol Oncol* 2006;**100**:338–43	Wrong population – patients with locally advanced cervical cancer
Houvenaeghel G, Lelievre L, Buttarelli M, Jacquemier J, Carcopino X, Viens P, *et al*. Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma. *Eur J Surg Oncol* 2007;**33**:498–503	Wrong population – patients with locally advanced cervical cancer
Huang WY, Huang CY, Chen CA, Hsieh CY, Cheng WF. Ruptured pseudoaneurysm of the external iliac artery in an advanced cervical cancer patient treated by endovascular covered stent placement. *J Formos Med Assoc* 2008;**107**:348–51	Wrong study design – case report
Huguet F, Cojocariu OM, Levy P, Lefranc JP, Darai E, Jannet D, *et al*. Preoperative concurrent radiation therapy and chemotherapy for bulky stage IB2, IIA, and IIB carcinoma of the uterine cervix with proximal parameterial invasion. *Int J Radiat Oncol Biol Phys* 2008;**72**:1508–15	Wrong intervention – some patients underwent adjuvant radiotherapy after surgery
Husain A, Curtin J, Brown C, Chi D, Hoskins W, Poynor E, *et al*. Continent urinary diversion and low-rectal anastomosis in patients undergoing exenterative procedures for recurrent gynecologic malignancies. *Gynecol Oncol* 2000;**78**:208–11	Wrong population – different primary treatment
Ingersoll FM, Ulfelder H. Pelvic exenteration for carcinoma of the cervix. *N Engl J Med* 1966;**274**:648–51	No relevant outcomes reported
Ingiulla W, de Laurentiis G. [Considerations on 241 pelvic eviscerations.] *Riv Ostet Ginecol* 1967;**22**:85–92	Waiting to be received
Jakowatz JG, Porudominsky D, Riihimaki DU, Kemeny M, Kokal WA, Braly PS, *et al*. Complications of pelvic exenteration. *Arch Surg* 1985;**120**:1261–5	Waiting to be received
Janser JC, Rodier JF, Rodier D, Vergnes Y. Current place of pelvis exenteration in treatment of recurrent cervix carcinoma. A 41 case report. *Chirurgie* 1995;**120**:409–15	Waiting to be received
Jaspers KD, Reck G. [Unusual course of metastatic cancer of the uterine cervix.] *Geburtshilfe Frauenheilkd* 1989;**49**:64–6	Wrong study design – case report
Jurado Chacon M, Berian JM, Zudaire JJ. Role of pelvic exenteration in the treatment of some advanced or recurrent gynecological cancers. *Prog Obstet Ginecol* 1995;**38**:121–8	Waiting to be received
Jurado M, Alcazar JL, Martinez-Monge R. Resectability rates of previously irradiated recurrent cervical cancer (PIRCC) treated with pelvic exenteration: is still the clinical involvement of the pelvis wall a real contraindication? A twenty-year experience. *Gynecol Oncol* 2010;**116**:38–43	Wrong population – primary treatment (radiotherapy or surgery/radiotherapy)
Karlen JR, Piver MS. Reduction of mortality and morbidity associated with pelvic exenteration. *Gynecol Oncol* 1975;**3**:164–7	Wrong population – primary treatment (radiotherapy or surgery/radiotherapy)

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TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Kasamatsu T, Onda T, Yamada T, Tsunematsu R. Clinical aspects and prognosis of pelvic recurrence of cervical carcinoma. *Int J Gynaecol Obstet* 2005;**89**:39–44	Wrong population – primary treatment (radiotherapy or surgery/radiotherapy)
Kecmanovic DM, Pavlov MJ, Kovacevic PA, Sepetkovski AV, Ceranic MS, Stamenkovic AB. Management of advanced pelvic cancer by exenteration. *Eur J Surg Oncol* 2003;**29**:743–6	Wrong population – unclear primary treatment
Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL III, *et al*. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999;**340**:1154–61. [Erratum published in *N Engl J Med* 1999;**341**:708.]	Wrong population – primary teratment
Khoury GG, Bulman AS, Joslin CA. Long term results of Cathetron high dose rate intracavitary radiotherapy in the treatment of carcinoma of the cervix. *Br J Radiol* 1991;**64**:1036–43	Wrong study design – literature review
Kinney WK, Egorshin EV, Ballard DJ, Podratz KC. Long-term survival and sequelae after surgical management of invasive cervical carcinoma diagnosed at the time of simple hysterectomy. *Gynecol Oncol* 1992;**44**:24–7	Wrong population – inadequate primary treatment (surgery)
Kirova YM, Bourhaleb Z, Alran S, Campitelli M, Plancher C, Fourchotte V, *et al*. [Preoperative concomitant radiochemotherapy in bulky carcinoma of the cervix: Institut Curie experience.] *Cancer Radiother* 2009;**13**:291–7	Wrong population – neoadjuvant chemoradiotherapy plus extended radical hysterectomy
Kiselow M Butcher HR Jr, Bricker EM. Results of the radical surgical treatment of advanced pelvic cancer: a fifteen-year study. *Ann Surg* 1967;**166**:428–36	Wrong population – different types of cancer
Kneale B, Anderson B. T-tube suction drainage and radical pelvic surgery. *Aust N Z J Obstet Gynaecol* 1963;**24**:178–81	No relevant outcomes reported
Kohler C, Klemm P, Schau A, Possover M, Krause N, Tozzi R, *et al*. Introduction of transperitoneal lymphadenectomy in a gynecologic oncology center: analysis of 650 laparoscopic pelvic and/or paraaortic transperitoneal lymphadenectomies. *Gynecol Oncol* 2004;**95**:52–61	Wrong study design – description of investigation protocols, laparoscopy as method of diagnosis
Kunkler IH, Kerr GR, Ludgate SM. The value of follow-up in stage II carcinoma of the cervix. *Clin Oncol* 1991:**3**:28–31	No relevant outcomes reported
Lambaudie E, Narducci F, Leblanc E, Bannier M, Houvenaeghel G. Robotically-assisted laparoscopic anterior pelvic exenteration for recurrent cervical cancer: report of three first cases. *Gynecol Oncol* 2010;**116**:582–3	Wrong study design – case report
Larciprete G, Casalino B, Segatore MF, Jarvis S, Catarinella V, Cirese E. Pelvic lymphadenectomy for cervical cancer: extraperitoneal versus laparoscopic approach. *Eur J Obstet Gynecol Rep Biol* 2006;**126**:259–63	Wrong population – patients with advanced cervical cancer
Lawhead RA Jr, Clark DG, Smith DH, Pierce VK, Lewis JL Jr. Pelvic exenteration for recurrent or persistent gynecologic malignancies: a 10-year review of the Memorial Sloan-Kettering Cancer Center experience (1972–1981). *Gynecol Oncol* 1989;**33**:279–82	Wrong population – different types of cancer
Lawson JB, Nwosu SSO, Olafimihan KA. Carcinoma of the cervix in Nigeria. A review of 246 cases seen in Ibadan in the ten years 1953-1962. *J Obst Gynaecol Br Commonw* 1964;**71**:701–6	Wrong population – surgery only
Leath CA, Wilder JL, Decherd ME. Panniculectomy concurrent with anterior pelvic exenteration for recurrent cervical cancer. *Gynecol Oncol* 2008;**110**:268–9	Wrong study design – letter
Lim PC. Robotic assisted total pelvic exenteration: a case report. *Gynecol Oncol* 2009;**115**:310–11	Wrong study design – case report
Lim SW, Lim SB, Park JY, Park SY, Choi HS, Jeong SY. Outcomes of colorectal anastomoses during pelvic exenteration for gynaecological malignancy. *Br J Surg* 2008;**95**:770–3	No relevant outcomes reported

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Lin MY, Fan EW, Chiu AW, Tian YF, Wu MP, Liao AC. Laparoscopy-assisted transvaginal total exenteration for locally advanced cervical cancer with bladder invasion after radiotherapy. *J Endourol* 2004;**18**:867–70	Wrong study design – case report
Lindsey WF, Wood DK, Briele HA, Greager JA, Walker MJ, Bork J, *et al*. Pelvic exenteration. *J Surg Oncol* 1985;**30**:231–4	Wrong population – different types of cancer
Lobaton AT, Garcia MC, Mandujano M, Díaz Rodríguez LR. [Histerectomia radical en al tratamiento de1 cancer cervicouterino recurrente a radiacion.] *Ginecol Obstet Mex* 1983;**51**:7–12	Waiting to be received
Lopez MJ, Luna-Perez P. Composite pelvic exenteration: is it worthwhile? *Ann Surg Oncol* 2004;**11**:27–33	Wrong population – different types of cancer
Lopez-Graniel C, Dolores R, Cetina L, Gonzalez A, Cantu D, Chanona J, *et al*. Pre-exenterative chemotherapy, a novel therapeutic approach for patients with persistent or recurrent cervical cancer. *BMC Cancer* 2005;**5**:118	Wrong intervention – pre-exenterative chemoradiotherapy
Maenpaa JU, Kangasniemi K, Luukkaala T. Pelvic exenteration for gynecological malignancies: an analysis of 15 cases operated on at a single institution. *Acta Obstet Gynecol Scand* 2010;**89**:279–83	Wrong population – different types of cancer
Magrina JF, Stanhope CR, Weaver AL. Pelvic exenterations: supralevator, infralevator, and with vulvectomy. *Gynecol Oncol* 1997;**64**:130–5	Wrong population – different types of cancer
Marie G, Barjot P, Crouet H, De Ranieri J. [Place of pelvic exenteration in the treatment of recurrence of cancer of the uterine cervix.] *J Chir* 1993;**130**:165–9	Wrong intervention – total pelvectomy, palliative treatment
Marnitz S, Köhler C, Müller M, Behrens K, Hasenbein K, Schneider A. Indications for primary and secondary exenterations in patients with cervical cancer. *Gynecol Oncol* 2006;**103**:1023–30	Waiting to be received
Martinez-Monge R, Jurado M, Cambeiro M, Valero J, Villafranca E, Alcázar JL. Perioperative high-dose-rate brachytherapy in locally advanced and recurrent gynecologic cancer: initial results of a phase II trial. *Brachytherapy* 2003;**5**:203–10	Wrong population – different types of cancer, some patients underwent adjuvant CH
Matthews CM, Morris M, Burke TW, Gershenson DM, Wharton JT, Rutledge FN. Pelvic exenteration in the elderly patient. *Obstet Gynecol* 1992;**79**:773–7	Wrong population – different primary treatment
Mayer M, Bobin JY, Colon J, Borg G. [Pelvic exenteration for carcinoma of the uterine cervix (authors' transl.).] *Bull Cancer* 1980;**67**:70–7	Wrong study design – literature review
McGarry RC, Smith C, Seemayer TA. Treatment resistant small cell carcinoma of the cervix. *Oncology* 1999;**57**:293–6	Wrong study design – case report
Méndez L, Bernal A, Escudero P, González G, Fajardo A. [Pelvic exenteration, morbidity and survival.] *Ginecol Obstet Mex* 1994;**62**:161–5	Waiting to be received
Miller B, Morris M, Rutledge F, Mitchell MF, Atkinson EN, Burke TW, *et al*. Aborted exenterative procedures in recurrent cervical cancer. *Gynecol Oncol* 1993;**50**:94–9	Wrong study design – literature review
Mirhashemi R, Averette HE, Estape R, Angioli R, Mahran R, Mendez L, *et al*. Low colorectal anastomosis after radical pelvic surgery: a risk factor analysis. Am *J Obstet Gynecol* 2000;**183**:1375–9	No relevant outcomes reported
Monaghan JM. Surgical management of advanced and recurrent cervical carcinoma: the place of pelvic exenteration. *Clin Obstet Gynaecol* 1985;**12**:169–82	Wrong study design – literature review
Monk BJ, Solh S, Johnson MT, Montz FJ. Radical hysterectomy after pelvic irradiation in patients with high risk cervical cancer or uterine sarcoma: morbidity and outcome. *Eur J Gynaecol Oncol* 1993;**14**:506–11	Wrong population – primary radiotherapy plus radical hysterectomy
Morgan DJ, Hunter DC, McCracken G, McClelland HR, Price JH, Dobbs SP. Is laparoscopically assisted radical vaginal hysterectomy for cervical carcinoma safe? A case control study with follow up. *BJOG* 2007;**114**:537–42. [Erratum published in BJOG 2007;**114**:914.]	Wrong population – open radical hysterectomy with other surgery

continued

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Morley GW. Pelvic exenterative therapy and the treatment of recurrent carcinoma of the cervix. *Semin Oncol* 1982;**9**:331–40	Waiting to be received
Morley GW, Lindenauer SM. Pelvic exenterative therapy in recurrent pelvic carcinoma. *Am J Obstet Gynecol* 1971;**109**:1175–86	No relevant outcomes reported
Morley GW, Lindenauer SM. Pelvic exenterative therapy for gynecologic malignancy: an analysis of 70 cases. *Cancer* 1976;**38**:581–6	Wrong population – different types of cancer
Morley GW, Hopkins MP, Lindenauer SM, Roberts JA. Pelvic exenteration, University of Michigan: 100 patients at 5 years. *Obstet Gynecol* 1989;**74**:934–43	Wrong population – unclear primary treatment
Mourton SM, Chi DS, Sonoda Y, Alektiar KM, Venkatraman ES, Barakat RR, *et al*. Mesorectal lymph node involvement and prognostic implications at total pelvic exenteration for gynecologic malignancies. *Gynecol Oncol* 2006;**100**:533–6	Wrong population – different types of cancer
Mourton SM, Sonoda Y, Abu-Rustum NR, Bochner BH, Barakat RR, Chi DS. Resection of recurrent cervical cancer after total pelvic exenteration. *Int J Gynecol Cancer* 2007;**17**:137–40	Wrong population – different types of cancer
Moutardier V, Houvenaeghel G, Lelong B, Mokart D, Delpero JR. Colorectal function preservation in posterior and total supralevator exenteration for gynecologic malignancies: an 89-patient series. *Gynecol Oncol* 2003;**89**:155–9	Wrong population – different types of cancer
Moutardier V, Houvenaeghel G, Martino M, Lelong B, Bardou VJ, Resbeut M, *et al*. Surgical resection of locally recurrent cervical cancer: a single institutional 70 patient series. *Int J Gynecol Cancer* 2004;**14**:846–51	Wrong population – different primary treatment
Narayansingh GV, Cumming GP, Dighe S, Parkin DE, Millar I. Invasive adenocarcinoma of the vagina fallowing surgery for adenocarcinoma in situ of the cervix – recurrence or implantation? *Int J Gynecol Cancer* 2001;**11**:493–5	Wrong study design – case report
Norton JA, Javadpour N. Jejunal loop interposition in patients with ileal conduit failure after pelvic exenteration. *Am J Surg* 1977;**134**:404–7	Wrong study design – case report
Oliveira Poletto AH, Lopes A, Lopes Carvalho A, Ribeiro EA, Aloísio da Costa Vieira R, Mauro Rossi B, *et al*. Pelvic exenteration and sphincter preservation: an analysis of 96 cases. *J Surg Oncol* 2004;**86**:122–7	Wrong population – different types of cancer
Orr JW Jr, Shingleton HM, Hatch KD, Taylor PT, Partridge EE, Soong SJ. Gastrointestinal complications associated with pelvic exenteration. *Am J Obstet Gynecol* 1983;**145**:325–32	Wrong population – different primary treatment
Osorio Gullón A, de Oca J, Lopéz Costea MA, Virgili J, Ramos E, del Rio C, *et al*. Double-barreled wet colostomy: a safe and simple method after pelvic exenteration. *Int J Colorectal Dis* 1997;**12**:37–41	No relevant outcomes reported
Ota T, Takeshima N, Tabata T, Hasumi K, Takizawa K. Adjuvant hysterectomy for treatment of residual disease in patients with cervical cancer treated with radiation therapy. *Br J Cancer* 2008;**99**:1216–20	Wrong population – radiotherapy plus adjuvant hysterectomy
Palfalvi L, Ungar L. Extended Wertheim procedure: the laterally extended parameterectomy (LER), a new radical technique for pelvic side wall dissection. *CME J Gynecol Oncol* 2004;**9**:45–8	Wrong study design – description of the procedure
Papp Z, Csapó Z, Hupuczi P, Mayer A. Nerve-sparing radical hysterectomy for stage IA2–IIB cervical cancer: 5-year survival of 501 consecutive cases. *Eur J Gynaecol Oncol* 2006;**27**:553–60	Wrong population – unclear primary treatment
Park JY, Choi HJ, Jeong SY, Chung J, Park JK, Park SY. The role of pelvic exenteration and reconstruction for treatment of advanced or recurrent gynecologic malignancies: analysis of risk factors predicting recurrence and survival. *J Surg Oncol* 2007;**96**:560–8	Wrong population – different primary treatment
Pawlik TM, Skibber JM, Rodriguez-Bigas MA. Pelvic exenteration for advanced pelvic malignancies. *Ann Surg Oncol* 2006;**13**:612–23	Wrong study design – literature review

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Perches RD, Lobaton AT, Garcia MC. Radiotherapy combined with surgery as treatment for advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 1983;**9**:1785–8	Wrong population – patients with advanced cervical cancer and radiotherapy plus pelvic exenteration or radical hysterectomy
Perez-Mesa C. Persistent postirradiatioim carcinoma of cervix uteri: a pathologic study of 83 pelvic exenteration specimens. *Arch Pathol* 1963;**75**:462–74	Wrong population – different primary treatment
Pikaart DP, Holloway RW, Ahmad S, Finkler NJ, Bigsby GE IV, Ortiz BH, *et al*. Clinical-pathologic and morbidity analyses of types 2 and 3 abdominal radical hysterectomy for cervical cancer. *Gynecol Oncol* 2007;**107**:205–10	Wrong population – primary treatment
Plante M, Roy M. The use of operative laparoscopy in determining eligibility for pelvic exenteration in patients with recurrent cervical cancer. *Gynecol Oncol* 1995;**59**:401–4	Wrong intervention – laparoscopy
Plante M, Roy M. Operative laparoscopy prior to a pelvic exenteration in patients with recurrent cervical cancer. *Gynecol Oncol* 1998;**69**:94–9	No relevant outcomes reported
Plukker JT, Aalders JG, Mensink HJ, Oldhoff J. Total pelvic exenteration: a justified procedure. *Br J Surg* 1993;**80**:1615–17	Wrong population – different types of cancer
Pomel C, Rouzier R, Pocard M, Thoury A, Sideris L, Morice P, *et al*. Laparoscopic total pelvic exenteration for cervical cancer relapse. *Gynecol Oncol* 2003;**91**:616–18	Wrong study design – case report
Pras E, Willemse PH, Boonstra H, Hollema H, Heesters MA, Szabó BG, *et al*. Concurrent chemo- and radiotherapy in patients with locally advanced carcinoma of the cervix. *Ann Oncol* 1996;**7**:511–16	Wrong population – advanced cervical cancer, primary cancer
Printz C. CancerScope: cervical cancer patients may benefit from new surgical technique. *Cancer* 2009;**115**:5131	Wrong study design – literature review
Puntambekar S, Kudchadkar RJ, Gurjar AM, Sathe RM, Chaudhari YC, Agarwal GA, *et al*. Laparoscopic pelvic exenteration for advanced pelvic cancers: a review of 16 cases. *Gynecol Oncol* 2006;**102**:513–16	Wrong population – patients with locally advanced primary pelvic cancers
Puntambekar SP, Palep RJ, Puntambekar SS, Wagh GN, Patil AM, Rayate NV, *et al*. Laparoscopic total radical hysterectomy by the Pune technique: our experience of 248 cases. *J Minim Invasive Gynecol* 2007;**14**:682–9	Wrong population – patients with primary cancers
Quigley MM, Knab DR, McMahon EB. Carcinoma of the cervix: a third treatment. *Obstet Gynecol* 1975;**45**:650–5	Wrong intervention – extraperitoneal lymphadenectomy
Reid GC, Morley GW, Schmidt RW, Hopkins MP. The role of pelvic exenteration for sarcomatous malignancies. *Obstet Gynecol* 1989;**74**:80–4	Wrong population – different types of cancer
Richardson DL, Seamon LG, Gong MC, Chapman DM, Cohn DE. Panniculectomy concurrent with anterior pelvic exenteration for recurrent cervical cancer. *Gynecol Oncol* 2008;**108**:449–51	Wrong study design – case report
Rietbroek RC, Schilthuis MS, Bakker PJ, van Dijk JD, Postma AJ, González González D, *et al*. Phase II trial of weekly locoregional hyperthermia and cisplatin in patients with a previously irradiated recurrent carcinoma of the uterine cervix. *Cancer* 1997;**79**:935–43	Wrong intervention – radiotherapy plus chemotherapy or hyperthermia
Roberts WS, Cavanagh D, Bryson SC, Lyman GH, Hewitt S. Major morbidity after pelvic exenteration: a seven-year experience. *Obstet Gynecol* 1987;**69**:617–21	Wrong population – different primary treatment
Rochard F, Michel G, Castaigne D, Lacour J. [Surgical treatment of carcinomas of the cervix stage III (authors' transl.).] *Bull Cancer* 1980;**67**:63–9	No relevant outcomes reported
Rodriguez C, Torres A, De L, Hernandez D, Herrera L. Pelvic exenteration for carcinoma of the cervix: analysis of 252 cases. *J Surg Oncol* 1988;**38**:121–5	Wrong population – different types of cancer

continued

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Rose PG. Type II radical hysterectomy: evaluating its role in cervical cancer. *Gynecol Oncol* 2001;**80**:1–2	Wrong study design – literature review
Rouzier R, Morice P, De Crevoisier R, Pomel C, Rey A, Bonnet K, et al. Survival in cervix cancer patients treated with radiotherapy fallowed by radical surgery. *Eur J Surg Oncol* 2005;**31**:424–33	Wrong intervention – radiotherapy or chemoradiotherapy plus adjuvant extrafacial hysterectomy and pelvic and para-aortic lymphadenectomy
Rutledge FN, McGuffee VB. Pelvic exenteration: prognostic significance of regional lymph node metastasis. *Gynecol Oncol* 1987;**26**:374–80	Wrong study design – literature review
Sahu L, Bupathy A, Badhe BA. Leiomyosarcoma of the uterine cervix in a young woman. *J Obstet Gynaecol Res* 2008;**34**:717–20	Wrong study design – case report
Saunders N. Pelvic exenteration: by whom and for whom? *Lancet* 1995;**345**:5–6	Wrong study design – literature review
Schmitz HE, Smith CJ, Foley DV, Schack CB. Evaluation of surgical procedures employed fallowing the failure of irradiation therapy in cancer of the cervix. *Am J Obstet Gynecol* 1957;**74**:1165–73	Waiting to be received
Schmitz RL, Schmitz HE, Smith CJ, Molitor JJ. Details of pelvic exenteration evolved during an experience with 75 cases. *Am J Obstet Gynecol* 1960;**80**:43–52	Waiting to be received
Schwarz H. Total pelvic exenteration in the treatment of recurrent carcinoma of the cervix. *West J Surg Obst Gynecol* 1958;**66**:40–3	Waiting to be received
Shah K, Olson MH, Dillard EH. Carcinoma of the cervix: surgical staging and radiotherapy with 32 MeV betatron. *Int J Radiat Oncol Biol Phys* 1982;**8**:1601–6	No relevant outcomes reported
Sharma DN, Chawla S, Chander S, Gairola M, Thulkar S, Singh MK. Cervical carcinoma recurring in an abdominal wall incision. *Clin Oncol* 2000;**12**:354–6	Wrong study design – case report
Sharma S, Odunsi K, Driscoll D, Lele S. Pelvic exenterations for gynecological malignancies: twenty-year experience at Roswell Park Cancer Institute. *Int J Gynecol Cancer* 2005;**15**:475–82	Wrong population – primary SR
Shepherd JH, Ngan HY, Neven P, Fryatt I, Woodhouse CR, Hendry WF. Multivariate analysis of factors affecting survival in pelvic exenteration. *Int J Gynecol Cancer* 1994;**4**:361–70	Wrong population – different types of cancer
Shepherd JH, Crawford RA, Christmas TJ, Hendry WF. Total pelvic reconstruction after exenteration for recurrent cervical cancer. *Br J Urol* 1997;**80**:79–81	Wrong population – primary radiotherapy plus radical hysterectomy
Shiromizu K, Ogawa M, Kotake K, Koyama Y, Nakazono M, Hirao K. Reconstruction of sigmoid vagina and conduit in total pelvic exenteration for recurrent cervical carcinoma. *Jpn J Clin Oncol* 1989;**19**:170–2	Wrong study design – case report
Sloukgi JC, Guillemin F. [Repair surgery in the treatment of cancer of the cervical remnant.] *Rev Fr Gynecol Obst* 1991;**86**:336–40	Wrong study design – case reports
Smith RR, Ketcham AS, Thomas LB. Carcinoma of the uterine cervix. Experience with radical surgery. *Cancer* 1963;**16**:1105–12	Wrong population – different primary treatment
Soeiro Fidalgo de Matos C, Nogaret JM, Philippson C, Veys I, Van Velthoven R. The place for surgery in central recurrences of invasive cancer of cervix uteri. *Acta Chir Belg* 1995;**95**:38–43	Wrong intervention – different types of SR
Stallworthy J. Radical surgery fallowing radiation treatment for cervical carcinoma. *Ann R Coll Surg Engl* 1964;**34**:161–78	Wrong study design – literature review
Stanhope CR, Symmonds RE. Palliative exenteration – what, when, and why? *Am J Obst Gynecol* 1985;**152**:12–16	Waiting to be received

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Stelzer KJ, Koh WJ, Greer BE, Cain JM, Tamimi HK, Figge DC, *et al*. The use of intraoperative radiation therapy in radical salvage for recurrent cervical cancer: outcome and toxicity. *Am J Obstet Gynecol* 1995;**172**:1881–6	Wrong population – different primary treatment
Symmonds RE. [The current role of exenteration for the treatment of malignant pelvic tumors.] *Gynakologe* 1981;**14**:170–6	Wrong population – different types of cancer
Talledo OE. Pelvic exenteration. Medical callege of Georgia experience. *Gynecol Oncol* 1985;**22**:181–8	Wrong population – different types of cancer
Terai Y, Kanemura M, Sasaki H, Tsunetoh S, Tanaka Y, Yamashita Y, *et al*. Long-term fallow-up of neoadjuvant intraarterial chemotherapy using an original four-lumen double-balloon (4L-DB) catheter for locally advanced uterine cervical cancer. *Int J Clin Oncol* 2009;**14**:56–62	Wrong population – patients with locally advanced primary cervical cancer, neoadjuvant CH
Thompson LJ. Cancer of the cervix. *Semin Oncol Nurs* 1990;**6**:190–7	Wrong study design – literature review
Torres Lobatón A, Rodríguez Cuevas H, Velázquez Venegas GJ, Díaz Rodríguez LR. [Pelvic exenteration in cancer of the cervix uteri. Analysis of 252 cases.] *Ginecol Obstet Mex* 1985;**53**:297–302	Waiting to be received
Torres-Lobatón A, González-Mendoza RL, Román-Bassaure E, Hernández-Aten D, Rojo-Herrera G. [Current status of frequency and complications of pelvic exenterations for recurrent cervico-uterine cancer after radiation.] *Ginecol Obstet Mex* 1996;**64**:538–43	Waiting to be received
Trelford JD, Goodnight J, Schneider P, Wolfe B, Sauder MT. Total exenteration, two or one ostomy. *Surg Gynecol Obstet* 1992;**175**:126–8	No relevant outcomes reported
Trelford-Sauder M, Trelford JD, Matolo NM. Replacement of the peritoneum with amnion fallowing pelvic exenteration. *Surg Gynecol Obstet* 1977;**145**:699–701	No relevant outcomes reported
Turko M, Benedet JL, Boyes DA, Nickerson KG. Pelvic exenteration: 1949–1971. *Gynecol Oncol* 1977;**5**:246–50	Wrong population – different primary treatment
Turrini O, Guiramand J, Moutardier V, Viret F, Mokart D, Madroszyk A, et *al*. Perineal small bowel fistula after pelvic exenteration for cancer: technical guidelines for perineal fistula. *Ann Surg Oncol* 2006;**13**:1622–6	No relevant outcomes reported
Twombly GH. The use of radical surgery in the treatment of cancer of the cervix. *Am J Roentgenol* 1959;**8**:115–19	Wrong population – primary treatment
Ulfelder H. Extended radical surgery for recurrent and advanced cervical cancer. *Clinical Obstet Gynecol* 1967;**10**:940–57	Wrong population – different types of cancer
Ungar L, Pálfalvi L, Siklós P, Csermely G, Szepesi J, Solt G. Orthotopic bladder replacement in irradiated female patients. *Int J Gynecol Cancer* 1998;**8**:307–9	Wrong study design – case reports
Uzan C, Rouzier R, Castaigne D, Pomel C. [Laparoscopic pelvic exenteration for cervical cancer relapse: preliminary study.] *J Gynecol Obstet Biol Reprod* 2006;**35**:136–45	Wrong study design – case reports
Vera MI. Quality of life fallowing pelvic exenteration. *Gynecol Oncol* 1981;**12**:355–66	Waiting to be received
Viswanathan AN, Lee H, Hanson E, Berkowitz RS, Crum CP. Influence of margin status and radiation on recurrence after radical hysterectomy in stage IB cervical cancer. *Int J Radiat Oncol Biol Phys* 2006;**65**:1501–7	Wrong population – only some patients underwent radiotherapy for primary disease
Walji N, Chue AL, Yap C, Rogers LJ, El-Modir A, Chan KK, *et al*. Is there a role for adjuvant hysterectomy after suboptimal concurrent chemoradiation in cervical carcinoma? *Clin Oncol* 2010;**22**:140–6	Wrong population – chemotherapy plus adjuvant hysterectomy
Webb GA. The role of ovarian conservation in the treatment of carcinoma of the cervix with radical surgery. *Am J Obstet Gynecol* 1975;**122**:476–84	Wrong population – primary treatment
Wrigley JV, Prem KM, Fraley EE. Pelvic exenteration: complications of urinary diversion. *J Urol* 1976;**116**:428–30	Wrong population – different types of cancer

continued

TABLE 94 Effectiveness review list of excluded studies with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Wydra D, Emerich J, Sawicki S, Ciach K, Marciniak A. Major complications fallowing exenteration in cases of pelvic malignancy: a 10-year experience. *World J Gastroenterol* 2005;**12**:1115–19	Wrong population – different types of cancer
Wydra D, Emerich J, Ciach K, Sawicki S, Marciniak A. The role of pelvic exenteration for treatment of pelvic malignancy – a nine-year experience. *Eur J Gynecol Oncol* 2005;**26**:418–22	Wrong population – different types of cancer
Xu H, Chen Y, Li Y, Zhang Q, Wang D, Liang Z. Complications of laparoscopic radical hysterectomy and lymphadenectomy for invasive cervical cancer: experience based on 317 procedures. *Surg Endosc* 2007;**21**:960–4	Wrong population – patients after surgery in primary treatment

Appendix 14 Baseline characteristics of chemotherapy randomised controlled trials

TABLE 95 Baseline characteristics of chemotherapy RCTs

Study	Participants	Interventions	Outcomes	Comments
Alberts 1987[60]	**Inclusion criteria:** 1. Patients with incurable squamous cell carcinoma of the uterine cervix who were not candidates for surgery or radiotherapy 2. Microscopic proof of this malignancy and documentation of dissemination or recurrence were required 3. Life expectancy of at least 6 weeks 4. SWOG performance status of at least 2 5. At least one measurable lesion 6. Written informed consent Note: all patients had adequate haematopoietic, renal and hepatic function and spirometry within 50% of normal **Exclusion criteria:** 1. Uncontrolled active or potentially active sites of infection 2. Clinical or chemical evidence of biliary obstruction and/or 3. Previous treatment with any of the drugs being used in this protocol	MVBC – mitomycin C: 10 mg/m^2 i.v. on days 2 and 44; vincristine: 0.5 mg/m^2 i.v. on days 2, 4, 44 and 46; bleomycin: 30 mg in 1000 ml dextrose and water continuous i.v. infusion over 24 hours on days 1–4 and 43–46; cisplatin: 50 mg/m^2 i.v. bolus on days 1, 22, 43 and 64 MC – mitomycin C: 12 mg/m^2 i.v. every 6 weeks, days 1 and 43; cisplatin: 50 mg/m^2 i.v. every 3 weeks, days 1, 22, 43 and 64 Cisplatin: 50 mg/m^2 i.v. every 3 weeks, days 1, 22, 43 and 64 **Treatment duration:** Not reported	For response and toxicity, criteria of SWOG were used Mortality Toxicity	ITT analysis was not implemented Number of patients in cisplatin group was definitely lower than numbers in the other groups The cisplatin treatment arm was dropped early because of poor accrual

Study	Participants	Interventions	Outcomes	Comments
Barlow 1973[61]	**Inclusion criteria:** 1. Patients with disease no longer amenable to therapy with surgery or irradiation, or who represented failures of chemotherapy with agents considered effective for their disease 2. Patients with sarcomas and rare ovarian tumours, without previous therapy (their disease was considered too extensive for surgical excision) **Exclusion criteria:** Not reported	BLEO alone: total cumulative dose of ≤ 250 mg/m^2; when this dosage was approached patients were crossed over to treatment with ADM alone (30 mg/m^2/day × 3) ADM + BLEO: maximum dose of BLEO (250 mg/m^2); treatment was then continued with ADM alone (30 mg/m^2/day × 3) in these patients whether or not they had responded to the combination ADM alone: total cumulative dose of 600 mg/m^2, then no further therapy with ADM **Treatment duration:** Patients were treated in the hospital with courses of therapy repeated at intervals of 4 weeks or when haematopoietic and mucosal recovery had occurred 53 patients received two or more courses of treatment; three patients received only one course of therapy but were closely observed for ≥ 1 month following treatment	Response rate: complete remission – disappearance of all clinical evidence of tumour; partial remission – ≥ 50% decrease in the product of the largest two perpendicular diameters of all measurable lesions with no increase in size of any lesion or appearance of any new lesions Toxicity	ITT analysis was not implemented Two patients with squamous cell tumours were mistakenly randomised as non-squamous cell tumours and received ADM alone (group of 21 + 2 patients)

continued

TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
Bezwoda 1986[62]	**Inclusion criteria:** 1. Histological proof of malignancy and adequate documentation of the extent of the disease at primary and metastatic sites 2. Assessment included pelvic examination, biopsy of lesions of the cervix and vagina, Pap smear, i.v. pyelogram, bone scan and radiography of the chest, lumbar spine and pelvis **Exclusion criteria:** Not reported	Hydroxyurea 1.5 g/m^2 p.o. daily for 10 days followed by a rest period of 14 days and then maintenance therapy with hydroxyurea 1 g/m^2 p.o. daily for 2 weeks in each 4-week cycle DDP 20 mg/m^2 i.v. daily for 3 days plus methotrexate 100 mg/m^2 i.v. on day 3 followed by folinic acid rescue (15 mg, 6-hourly × eight doses) given 24 hours after the methotrexate After a preliminary analysis of the results, the hydroxyurea arm of the study was discontinued and a further 25 patients received the DDP plus methotrexate regimen **Treatment duration:** Combination chemotherapy was given at 4-week intervals and patients who had either stable disease or evidence of objective response were continued on monthly therapy as long as response was maintained	Response was assessed after re-evaluation of all initially involved sites of disease and assessments were performed at 12-week intervals Survival Toxicity	Only the initial 25 patients were randomised between treatment arms; after a preliminary analysis the hydroxyurea arm was discontinued and all subsequent patients received cisplatin and methotrexate Method of randomisation – no description Allocation concealment – not reported No blinding used

Study	Participants	Interventions	Outcomes	Comments
Bloss 2002[63]	**Inclusion criteria:** 1. Histologically confirmed, advanced (stage IVB), recurrent or persistent squamous cell carcinoma of the cervix not suitable for curative treatment with surgery and/or radiotherapy 2. GOG performance score of 0, 1 or 2 (Karnofsky 50–100) 3. Recovered from effects of recent surgery, chemoradiotherapy or radiotherapy 4. Free of clinically significant infection 5. Adequate pulmonary, renal, haematological and hepatic function 6. Results of pretreatment pulmonary function tests to include diffusing capacity of the lung for carbon monoxide within institutional norms **Exclusion criteria:** 1. Cervical neoplasms other than squamous cell carcinoma or with non-measurable cervical cancer 2. White blood count < 4000/μl, neutrophil count < 1500/μl and/or platelet count < 100,000/μl, abnormal liver function (bilirubin, AST or alkaline phosphatase level > two times normal not related to the cancer), bilateral hydronephrosis not relieved by stenting or percutaneous drainage 3. Past or concomitant malignancy other than non-metastatic skin cancer (excluding melanoma) 4. Previous therapy with cytotoxic drugs except when used as a radiation sensitiser 5. Radiotherapy within 3 weeks of entry 6. Lesions measurable only by ultrasound 7. Pregnancy or lactation 8. Brain metastasis or other central nervous system diseases of clinical significance	Cisplatin: 50 mg/m^2 with adequate hydration on day 1 plus ifosfamide 5.0 g/m^2 over 24 hours plus mesna 6 g/m^2 given concurrently with ifosfamide and for the following 12 hours Bleomycin: 30 units over 24 hours on day 1 followed by cisplatin, ifosfamide and mesna as in the first regimen **Treatment duration:** In both arms treatment was administered every 3 weeks for a maximum of six courses Additional cycles of treatment – after approval of the study chair	Toxicity was graded according to standard GOG criteria Response rate: complete response – the disappearance of all gross evidence of disease for at least 4 weeks; partial response – > 50% reduction in the product obtained from the bidimensional measurements of each lesion Duration of response Survival time Progression-free survival	Patients were centrally randomised with equal probability to receive treatment Description of allocation concealment – not reported No blinding used Six patients did not receive the randomised study treatment (classified as non-responders and grouped by randomised treatment in an ITT analysis but not included in the summary of toxicity)

continued

TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
Bonomi 1985[64]	**Inclusion criteria:** 1. Patients with biopsy-proven squamous cell carcinoma of the cervix who were considered incurable with surgery or radiotherapy 2. Leucocyte count >4000/μl, platelet count > 100,000/μl, BUN level <25 mg/dl, serum creatinine level < 1.5 mg/dl 3. Measurable or evaluable lesions 4. Recovery from previous surgery or radiotherapy 5. GOG performance status <3.3 **Exclusion criteria:** Not reported	Patients were randomly assigned to one of the following cisplatin regimens: 50 mg/m^2 i.v. every 21 days (regimen 1); 100 mg/m^2 i.v. every 21 days (regimen 2); 20 mg/m^2 daily dose for 5 days repeated every 21 days (regimen 3) **Treatment duration:** Treatment was continued for a total dose of 400 mg/m^2 for each of the regimens, providing that there was no evidence of tumour progression	Response rates Median response duration Time to tumour progression Median survival time Toxicity	Patients were stratified according to GOG performance status (0–1 vs 2–3), method of tumour measurement (physical examination and/or conventional radiographic vs computerised axial tomography) and site of disease 54 patients were excluded from analysis for the following reasons: no histological confirmation of tumour (five patients), wrong cell type (32 patients), inadequate renal function (three patients), second or wrong primary tumour (eight patients), GOG performance status >3 (two patients), and improper preprotocol treatment (four patients) 30 patients were considered unevaluable for the following reasons: inadequate pathological material (eight patients), improper randomisation (three patients), clerical error (two patients), never received cisplatin (11 patients), removed by investigator (one patient) and inadequate data (five patients) 30 had no measurable disease and 23 were unevaluable for response – ITT analysis was not completed

Study	Participants	Interventions	Outcomes	Comments
Cadron 2005[65]	**Inclusion criteria:** 1. Histologically proven cervical cancer with distant metastases after surgery or recurrent after radiotherapy 2. Absence of previous chemotherapy or other malignant diseases 3. At least one measurable tumour site 4. Performance status (WHO) ≤2 5. Life expectancy >3 months 6. Adequate renal function **Exclusion criteria:** 7. Brain or bone metastases were the only recurrence	Cisplatin monotherapy 37.5 mg/m^2 on days 1 and 2 of 4-week schedule PIF regimen: cisplatin as above, ifosfamide 2 g/m^2 on days 1 and 2 together with mesna 0.5 g/m^2, 5-fluorouracil 500 mg/m^2 on days 1 and 2, and folinic acid 30 mg/m^2 on days 1 and 2 **Treatment duration:** Cisplatin (number of courses): 1–2: 4 (36%); 3–4: 3 (27%); 5–6: 4 (36%); 7–8: 0 PIF (number of courses): 1–2: 4 (40%); 3–4: 1 (10%); 5–6: 3 (30%); 7–8: 2 (20%)	Response rate was evaluated according to WHO criteria Median of survival	ITT analysis was implemented Three patients did not receive any chemotherapy because of rapid progression Only 24 patients were entered and the study was stopped early (a target of 200 patients was estimated)
Garin 2001[66]	**Inclusion criteria:** 1. Patients with metastasis of squamous cell carcinoma of the cervix 2. Measurable disease outside the irradiated field 3. WHO performance status 1–2 4. No previous chemotherapy 5. Radiotherapy allowed if ended 3 months previously 6. Adequate liver, renal and haematological functions 7. Written consent **Exclusion criteria:** Not reported	Irinotecan 350 (or 250) mg/m^2 day 1 every 3 weeks Cisplatin 80 mg/m^2 + irinotecan 200 (or 160) mg/m^2 day 1 every 3 weeks Cisplatin 80 mg/m^2 day 1 every 3 weeks **Treatment duration:** Median duration of treatment: 12/20/12 weeks	Toxicity Overall response rate	
Greenberg 1977[67]	15% had previous chemotherapy and 100% had radiotherapy 25% had pelvic disease, 10% had distant disease and 65% had both	ADM ADM and BLEO (No platinum dose in either arm)	Response rates and survival rates reported, no definitions available	Data from Hirte *et al.*[59] systematic review

continued

TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
Lira-Puerto 1991[68]	**Inclusion criteria:** 1. Patients with progression (growth of 25% in cross-sectional area or new appearance of the disease) 2. Patients who underwent previous chemotherapy but without cisplatin (minimal time period from previous chemotherapy 6 weeks) 3. Patients with normal serum keratinise levels and acceptable haematological parameters 4. Pretreatment liver function values should not have exceeded twice the normal range **Exclusion criteria:** Not reported	Total dose, median (range): CHIP: 1320 mg/m^2 (390–4610 mg/m^2) CBDCA: 1800 mg/m^2 (550–6800 mg/m^2) **Treatment duration:** For both drugs the median number of cycles was three	Response rate: complete response – complete disappearance of all clinical evidence of tumour and symptoms for two consecutive measurements made at least 4 weeks apart; partial response – a decrease of at least 50% in the sum of the products of the perpendicular diameters of all index lesions for at least two consecutive measurements Survival was computed as the number of months from randomisation until death or until the last follow-up examination Toxicity was evaluated according to ECOG criteria	Parallel randomised phase II studies were planned in three institutions. On the termination of support, accrual was suspended in two institutions and insufficient numbers of patients (10 and 5, respectively) were entered for independent analysis ITT analysis was not implemented

Study	Participants	Interventions	Outcomes	Comments
Long 2005[71]	**Inclusion criteria:** 1. Patients with histologically confirmed advanced (stage IVB), recurrent or persistent carcinoma of the uterine cervix who were unsuitable candidates for curative treatment with surgery and/or radiotherapy 2. Squamous, adenosquamous and adenocarcinoma of the cervix 3. Measurable disease (by physical examination, radiography or CT/MRI) 4. GOG performance status 0–2 5. Recovered from the effects of recent surgery, chemoradiotherapy or radiotherapy and free of clinically significant infection **Exclusion criteria:** 1. Bilateral hydronephrosis that could not be alleviated by ureteral stents or percutaneous nephrostomy drainage 2. Absolute neutrophil count <1500/μl, platelet count <100,000/μl, serum creatinine level >1.5 mg/dl, abnormal liver function (bilirubin >1.5×normal, and/or AST/alkaline phosphatase level >3×normal) 3. Performance status 3–4 4. Concurrent malignancy 5. Past malignancy other than non-melanoma skin cancer within the last 5 years 6. Brain or spinal cord metastasis 7. Patients who were pregnant or lactating	C regimen: cisplatin 50 mg/m^2 i.v., repeated every 21 days CT regimen: topotecan 0.75 mg/m^2 i.v. during 30 minutes days 1, 2 and 3 followed by cisplatin 50 mg/m^2 i.v. on day 1, repeated every 21 days **Treatment duration:** All regimens were to be administered for a maximum of six cycles for non-responders or until disease progression or unacceptable toxicity prohibited additional therapy. Patients who achieved a partial response with an acceptable level of toxicity were permitted to continue treatment with their assigned regimen beyond six cycles after discussion with the study chair	Response – according to GOG criteria: complete response – disappearance of all gross evidence of disease for at least 4 weeks; partial response – >50% reduction in the product of the bidimensional measurements of each lesion maintained for at least 4 weeks; increasing disease was a >50% increase in the product of the bidimensional measurements of each lesion or development of any new lesion Progression-free survival – defined as the minimum amount of time until clinical progression, death or date of last contact Overall survival – measured to the date of death or, for patients who were still alive, the date of last contact	Randomly assigned the treatment regimens with equal probability using a fixed-block design; patients were stratified by treating institution only ITT analysis was implemented 63 patients were randomly allocated to receive MVAC before the treatment arm, with MVAC discontinued in July 2001. Results for the MVAC arm were not reported

continued

TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
McGuire 1989[74]	**Inclusion criteria:** 1. Patients with histologically proven squamous carcinoma of the uterine cervix 2. Recurrent disease with primary treatment 3. Patients with one or more lesions bidimensionally measurable in perpendicular diameters 4. GOG performance score of ≥2 5. Adequate haematological function as evidenced by white blood cell count 6. Adequate renal and hepatic function **Exclusion criteria:** 1. Previous chemotherapy	CBDCA: staring dose 400 mg/m^2 (reduced to 340 mg/m^2 for patients with previous radiotherapy) CHIP: starting dose 270 mg/m^2 (230 mg/m^2 for patients with previous radiotherapy) **Treatment duration:** Treatment cycles were repeated every 28 days when adverse criteria allowed	Response rate Survival (median) Progression-free survival Toxicity	No information about numbers of therapy cycles ITT analysis was not implemented Randomisation used a block design with balanced assignments both within and across institutions

Study	Participants	Interventions	Outcomes	Comments
Monk 2010[75]	**Inclusion criteria:** 1. ≥18 years 2. Histologically or cytologically confirmed advanced (FIGO stage IVB), recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix 3. At least one previous chemotherapy regimen for metastatic disease 4. 3 weeks had elapsed from the last administration of chemotherapy 5. At least one target lesion to be used to assess response as defined by RECIST 6. ECOG performance status of 0 or 1 7. Adequate bone marrow function (absolute neutrophil count >1500/μl, platelet count >100,000/μl, haemoglobin >9 g/dl), renal function (creatinine clearance >50 ml/minute and urine protein <1 g) and hepatic function (total bilirubin <1.5×upper limit of normal, AST and ALT <2.5×upper limit of normal) **Exclusion criteria:** 1. Previous therapy with inhibitors of VEGF, VEGF receptor or ErbB-1/ErbB-2 2. Hormonal therapy, biologic therapy, immunotherapy or tumour embolisation 3. Poorly controlled hypertension; QTc prolongation (defined as a QTc interval of >470 ms); class III or IV heart failure; or a history of cerebrovascular accident, myocardial infarction, unstable angina, cardiac angioplasty/stenting or untreated venous thrombosis within 6 months of screening	Pazopanib: 400 mg (800 mg daily) Lapatinib: 250 mg tablets (1500 mg daily) Combination arm: discontinued **Treatment duration:** Lapatinib 13 weeks, pazopanib 11 weeks Treatment with study medication continued until disease progression, unacceptable toxicity, death or discontinuation for other reasons (e.g. patient refused additional treatment, protocol was violated or patient was lost to follow-up)	Progression-free survival – the time interval between the date of random assignment and the date of progression or death Overall survival Tumour response based on RECIST criteria Adverse events and toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.14	ITT analysis was implemented Combination arm discontinued after interim analysis

continued

TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
Monk 2009[76]	**Inclusion criteria:** 1. Advanced (stage IVB), recurrent or persistent cervical cancer 2. Histological types of cancer: squamous, adenosquamous and adenocarcinoma 3. Histological documentation of the primary cervical cancer was required 4. Biopsy confirmation of metastatic disease was not required for lesions identified by CT/MRI if the lesion was >3 cm in diameter; in patients with small-volume metastatic disease (<3 cm), biopsy of at least one lesion was required 5. GOG performance status of 0 or 1 **Exclusion criteria:** 1. An absolute neutrophil count <1500/μl, platelet count <100,000/μl, bilirubin >1.5×institutional normal, AST level >3×institutional normal, alkaline phosphatase level >3×institutional normal or a serum creatinine level >1.2 mg/dl (patients with serum creatinine level >1.2 mg/dl but <1.5 mg/dl were eligible if a creatinine clearance determination was >50 ml/minute 2. Previous chemotherapy for metastatic disease 3. Concurrent or past malignancy 4. Central nervous system metastasis or had bilateral hydronephrosis that could not be alleviated by ureteral stents or percutaneous nephrostomy	1. Paclitaxel 135 mg/m^2 over 24 hours plus cisplatin 50 mg/m^2 day 2 every 3 weeks (PC, reference arm) 2. Vinorelbine 30 mg/m^2 days 1 and 8 plus cisplatin 50 mg/m^2 day 1 every 3 weeks (VC) 3. Gemcitabine 1000 mg/m^2 day 1 and 8 plus cisplatin 50 mg/m^2 day 1 every 3 weeks (GC) 4. Topotecan 0.75 mg/m^2 days 1, 2 and 3 plus cisplatin 50 mg/m^2 day 1 every 3 weeks (TC) **Treatment duration:** A maximum of six cycles for non-responders, including those with stable disease. Those with a partial response with an acceptable level of toxicity were permitted to continue treatment with their assigned regimen beyond six cycles after discussion with the study chair	Survival was defined as the time from random assignment until death or the date of last contact Progression-free survival was defined as the time from random assignment until the date of last contact, disease progression or death, whichever came first Quality of life was assessed before random assignment (baseline), before cycles 2 and 5, and 9 months post study entry. Quality-of-life measures included the FACT-Cx TOI, the FACT/GOG-NTX and the BPI 0–10 pain intensity item Response was defined according to the criteria adopted by RECIST Toxicity – the NCI CTC version 2.0 was used for characterising adverse events and dose modifications	The random assignment of the treatment regimen was balanced at registration for disease status (recurrent, persistent or advanced stage IVB primary) and performance status (0 or 1) Allocation concealment – not reported No blinding used Until January 2004 this study consisted of only two arms comparing PC with VC. The primary analyses excluded these 41 patients

Study	Participants	Interventions	Outcomes	Comments
Moore 2004[78]	**Inclusion criteria:** 1. Squamous cell carcinoma of the cervix confirmed by GOG central Pathology Committee review 2. Recurrent or persistent disease, stage IVB, not amenable to curative treatment with surgery or radiotherapy 3. Bidimensional tumour measurable by physical examination, radiography, CT or MRI 4. Adequate bone marrow function (absolute neutrophil count >1500/μl, platelet count >100,000/μl), renal function (serum creatinine <2.0 mg/dl) and liver function (bilirubin <1.5× institutional normal; AST and alkaline phosphatase <3× institutional normal) 5. GOG performance status score of 0–2 6. Patients must have recovered from the effects of surgery, radiotherapy or chemoradiotherapy 7. At least 6 weeks must have elapsed since the last administration of chemoradiotherapy, and at least 3 weeks must have elapsed from the last administration of radiotherapy alone **Exclusion criteria:** 1. Non-squamous or non-measurable cervical cancer or bilateral hydronephrosis 2. Previous chemotherapy (except when used for radiation sensitisation) 3. Pregnant or lactating 4. Craniospinal metastasis 5. Patients with a previous history of malignant disease were eligible provided that they had been disease free for ≥5 years and had received no chemotherapy or radiotherapy for that malignancy	Single-agent cisplatin (C) was administered at an dose of 50 mg/m^2 i.v. at the rate of 1 mg/minute Combination arm (C + P) with paclitaxel at a dose of 135 mg/m^2 i.v. as a 24-hour infusion followed immediately by cisplatin at a dose of 50 mg/m^2 **Treatment duration:** Total of six cycles unless disease progression or toxicity prohibited further therapy. Patients who continued to respond to treatment were permitted to continue beyond six treatment courses with the consent of the study chair	Response rate Toxicity Progression-free survival Survival	Randomisation with equal probability to each of the treatment arms was carried out using a block design, which balances the sequence of assigned arms within parent institutions

continued

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TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
Mountzios 2009[79]	**Inclusion criteria:** 1. Histologically documented primary metastatic or recurrent carcinoma of the uterine cervix no longer amenable to surgery and/or radiotherapy and had not received chemotherapy for advanced disease with the exception of previous cisplatin administration given as a radiation sensitiser 2. ECOG performance status of 0–2 3. One or more lesions measurable in perpendicular diameters by imaging studies 4. Neutrophil count >1500/μl, platelet count >100,000/μl, creatinine clearance >50 ml/minute, serum bilirubin <2.0 mg/dl and ALT and AST levels <2×the institutional upper limit of normal 5. 3 weeks from previous surgery and 4 weeks from radiotherapy **Exclusion criteria:** 1. Brain metastases 2. Active infection 3. Serious concurrent medical illnesses 4. Pre-existing clinically significant peripheral neuropathy of any cause	Ifosfamide given at a dose of 1500 mg/m^2 i.v. over 1 hour on days 1–3, diluted in 1000 ml of 0.9% saline. Mesna was given at a dose of 300 mg/m^2 i.v. over 15 minutes before each dose of ifosfamide. The same dose of mesna was given orally at home 4 and 8 hours after the administration of ifosfamide. On day 2, before ifosfamide administration, patients received 900 ml of 0.9% saline with 100 ml of 20% mannitol over 1 hour, immediately followed by cisplatin 70 mg/m^2 diluted in 1000 ml of 0.9% saline and infused over 3 hours. Subsequently, the patients received an additional litre of normal saline with potassium and magnesium to minimise cisplatin-induced renal toxicity (IP arm) Ifosfamide (as above) plus on day 1 of each cycle paclitaxel 175 mg/m^2 diluted in 500 ml of 0.9% saline was infused i.v. over 3 hours before ifosfamide administration. All patients in this arm received a pretreatment regimen designed to abrogate allergic reactions to paclitaxel. Granulocyte colony-stimulating factor was systematically administered s.c. from day 7 to day 11 of each cycle at a dose of 5 mg/kg/day in both arms. Because chemotherapy courses were administered every 28 days instead of the usual 21-day schedule, the cisplatin dose was adjusted to 70 mg/m^2 instead of the standard 50 mg/m^2 to maintain equivalent dose intensity of the drug (ITP arm) **Treatment duration:** Target of six cycles. Treatment discontinued in case of progressive disease or unacceptable toxicity (achieved in 54% and 63% of patients who received the IP and the ITP regimens respectively)	Response rate: WHO criteria for response were used Survival was estimated from the initiation of treatment to the date of last follow-up or until the patient's death Progression-free survival was calculated from the initiation of treatment to the first documented progression of disease Toxicity (WHO criteria)	Assessment of treatment outcome was blinded to the treatment group assignment Description of method of randomisation and allocation concealment – not reported

Study	Participants	Interventions	Outcomes	Comments
Omura 1997[80]	**Inclusion criteria:** 1. Women with histologically confirmed advanced (stage IVB), recurrent or persistent squamous cell carcinoma of the cervix not suitable for curative treatment with surgery and/or radiotherapy 2. Written informed consent 3. GOG performance score of 0, 1 or 2 (Karnofsky 50–100) 4. Patients were to have recovered from the effects of recent surgery or radiotherapy and to be free of clinically significant infection **Exclusion criteria:** 1. Patients with cervical neoplasms other than squamous cell carcinoma or with non-measurable cervical cancer 2. White blood cell count <4000/μl and/or platelet count <100,000/μl 3. Abnormal liver function (bilirubin, AST or alkaline phosphatase level >2× normal not related to the cancer) 4. Bilateral hydronephrosis 5. GOG performance status 3 or 4 6. Past or concomitant malignancy other than skin (excluding melanoma) 7. Previous therapy with cytotoxic drugs except when used as a radiation sensitiser 8. Radiotherapy within 3 weeks of entry 9. Lesions measurable only by ultrasound 10. Pregnancy or lactation	Cisplatin 50 mg/m^2 with appropriate hydration every 3 weeks for a maximum of six courses (C arm) Cisplatin 50 mg/m^2 on day 1 plus mitolactol 180 mg/m^2 orally for 5 days on days 2 through 6 every 3 weeks (CM arm) Cisplatin 50 mg/m^2 plus ifosfamide 5 g/m^2 over 24 hours plus mesna 6 g/m^2 given concurrently with ifosfamide and for 12 hours after, every 3 weeks, for a maximum of six courses (CIFX arm) **Treatment duration:** Median number of courses: CIFX and C 4 (range 0–8); CM 3 (range 0–7)	Toxicity (including toxicity deaths) Response rate: complete response was defined as the disappearance of all gross evidence of disease for at least 4 weeks; partial response was a >50% reduction in the product obtained from the measurement of each lesion for at least 4 weeks Median duration of response Progression-free survival Survival	Patients were prospectively stratified according to whether they had received previous radiation-sensitiser treatment (hydroxyurea, cisplatin or fluorouracil) and by performance status and were then centrally randomised ITT analysis was implemented. A total of 10 patients did not receive the randomised study treatment. They were classified as non-responders and grouped by randomised treatment in a ITT analysis. They are also included in the analysis of overall survival and progression-free survival but are not included in the summary of toxicity

continued

TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
Thomsen 1998[81]	**Inclusion criteria:** 1. Recurrent or advanced cervical cancer no longer amenable to curable treatment with surgery and/or radiotherapy 2. Lesions measurable or evaluable according to WHO criteria 3. WHO performance status of ≥2 4. White blood cell count >3500/μl and platelet count >100,000/μl 5. Histological confirmation of the diagnosis 6. Informed consent **Exclusion criteria:** 1. Impaired renal function 2. Progressive disease after one course	CBDCA: 400 mg/m^2 on day 1 i.v. over 30 minutes every 4 weeks Teniposide: 125 mg/m^2 on days 1, 2 and 3 i.v. over 60 minutes every 4 weeks Dose reduction: five patients treated with CBDCA, two in the teniposide group **Treatment duration:** After four courses only patients with a complete response or a partial response received further treatment Median time to treatment failure was 20 (95% CI 11 to 31) weeks for CBDCA and 17 (95% CI 12 to 32) weeks for teniposide ($p = 0.93$)	Survival time was calculated as the time from randomisation until death from any reason Response rate was defined in accordance with WHO criteria Toxicity was defined in accordance with WHO criteria	ITT analysis was implemented

Study	Participants	Interventions	Outcomes	Comments
Vermorken 2001[82]	**Inclusion criteria:** 1. Histologically confirmed advanced (stage IVB) or recurrent squamous cell carcinoma of the uterine cervix not suitable for curative treatment with surgery and/or radiotherapy 2. Measurable lesions at distant sites outside previously irradiated areas 3. Informed consent (this had to be obtained according to the operative regulations followed in the individual participating institutions) **Exclusion criteria:** 1. Malignancies of the cervix other than squamous cell carcinoma of the uterine cervix 2. Age >75 years 3. Life expectancy <3 months 4. WHO performance status 3 or 4 5. Previous chemotherapy 6. Previous extensive radiotherapy within 8 weeks 7. Previous or concurrent cancer at other sites with the exception of adequately treated basal cell carcinoma of the skin 8. A serum creatinine level >1.5 mg/dl (or >132 μmol/1) and/or creatinine clearance <60 ml/minute/1.73 m^2 9. White blood cell count <4000/μl and/or platelet count <100,000/μl, bilirubin >1.5 mg/dl (or >25.6 μmol/l) 10. Severe pulmonary dysfunction (maximum breathing capacity <30 l/minute, FEV_1 <1000 ml) 11. Neurological conditions that could interfere with evaluation of neurological toxicity, or conditions of impaired mobility in which neurological toxicity might cause an unacceptable degree of incapacity 12. Bone lesions detectable only on bone scans, sclerotic bone metastases and serous effusions as single tumour response parameters, signs or symptoms of brain involvement or leptomeningeal disease 13. Overt psychosis or senility	BEMP: E 3 mg/m^2 day 1, P 50 mg/m^2 day 1, B 15 mg (24-hour infusion) days 2–4 and M 8 mg/m^2 (at alternate cycles) Cisplatin (P): 50 mg/m^2 **Treatment duration:** The first four cycles were given every 3 weeks (induction phase). Subsequent cycles were given every 4 weeks (maintenance phase) during which B was deleted from BEMP (MEP) Median number of treatment cycles was four (range 0–16) in the BEMP arm and six in the P arm (range 0–17) ($p = 0.0017$)	Toxicity Response rate: complete response was defined as complete disappearance of all clinically detectable tumour(s) together with a return of relevant blood chemistries to normal values for at least 4 weeks; partial response was defined as a ≥50% decrease in total tumour size of the lesions(s), which was measured or evaluated to determine the effect of therapy by two observations not less than 4 weeks apart Median response duration Median survival Median progression-free survival	ITT analysis was implemented Sample size was calculated 45 patients from the P group received BEMP as second-line treatment

continued

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TABLE 95 Baseline characteristics of chemotherapy RCTs (*continued*)

Study	Participants	Interventions	Outcomes	Comments
Wallace 1978[83]	No details available	ADM ADM and vincristine ADM and cyclophosphamide	Response rates and survival rates reported, no definitions available	Data from Hirte *et al.*[59] systematic review

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BLEO, bleomycin; BUN, blood urea nitrogen; C, cisplatin; CIFX, cisplatin, ifosfamide; CM, cisplatin, mitolactol; FEV_1, forced expiratory volume in 1 second; GC, gemcitabine, cisplatin; IP, cisplatin, ifosfamide; ITP, cisplatin, ifosfamide, paclitaxel; ITT, intention to treat; i.v., intravenously; MBC, mesna, sodium-2-mercaptoethane sulphate; PC, paclitaxel, cixplatin; PIF, cisplatin, ifosfamide, 5-fluorouracil; p.o., by mouth; RECIST, Reponse Evaluation Criteria in Solid Tumors; s.c., subcutaneously; SWOG, Southwest Oncology Group; TC, topotecan, cisplatin; VC, vinorelbine, cisplatin; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

Appendix 15 Quality assessment of case series: radiotherapy and chemoradiotherapy

TABLE 96 Quality assessment of case series: radiotherapy and chemoradiotherapy

	Population[a]			Method of allocation[a]										Outcomes[a]						Analysis[a]					
Study	1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5	4.6
Ciatto 1980[84]	+	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Deutsch 1974[85]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	–	++	NA	+	NA	NA	NA	NA	+	NA
Grigsby 2004[93]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Haasbeek 2008[94]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Hille 2003[86]	++	NA	+	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Ijaz 1998[95]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Ito 1997[87]	+	NA	+	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Jain 2007[88]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	+	+	++	++	–	++	NA	+	NA	NA	NA	NA	++	NA
Jobsen 1989[89]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Lucraft 1981[90]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	–	++	NA	+	NA	NA	NA	NA	+	NA
Maneo 1999[96]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	–	++	NA	+	NA	NA	NA	NA	++	NA
Potter 1990[91]	+	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Tan 1991[92]	++	NA	+	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Thomas 1987[97]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Tsuda 2003[98]	++	NA	++	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	–	++	NA	++	NA	NA	NA	NA	+	NA
Virostek 1996[99]	++	NA	+	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA

+, some of the checklist criteria have been fulfilled; where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter; ++, all or most of the checklist criteria have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter; –, few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter; NA, not applicable.

a Items correspond to the classifications in the case series quality assessment form in *Appendix 5*.

Appendix 16 Quality assessment of case series: surgery

TABLE 97 Quality assessment of case series: surgery

	Population[a]			Method of allocation[a]										Outcomes[a]						Analysis[a]					
Study	1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5	4.6
Adcock 1979[100]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Coleman 1994[101]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Ibsen 1988[102]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Maneo 1999[103]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Rubin 1987[104]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Terada 1987[105]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Tupper 1965[106]	+	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Anthopoulos 1989[107]	+	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	–	++	NA	+	NA	NA	NA	NA	–	NA
Barber 1971[108]	+	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Beitler 1997[109]	++	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Bricker 1960[110]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Brunschwig 1960[111]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Chung 1983[112]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	–	++	NA	+	NA	NA	NA	NA	+	NA
Deckers 1972[113]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Hatch 1990[114]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	–	++	NA	+	NA	NA	NA	NA	++	NA
Ketcham 1970[115]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA

	Population[a]			Method of allocation[a]										Outcomes[a]						Analysis[a]					
Study	1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5	4.6
Kraybill 1988[116]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Mikuta 1960[117]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Mikuta 1967[118]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	+	NA
Palmer 1953[119]	+	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	–	++	NA	+	NA	NA	NA	NA	+	NA
Pinelo 2002[120]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	+	++	++	–	++	NA	+	NA	NA	NA	NA	+	NA
Rutledge 1977[121]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Shingleton 1989[122]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Stanhope 1990[123]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	–	NA
Symmonds 1975[124]	+	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	–	–	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Teran-Porcayo 2006[125]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	+	++	NA	++	NA	NA	NA	NA	++	NA
Vieira 2009[126]	++	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	–	+	++	++	–	++	NA	+	NA	NA	NA	NA	+	NA

+, some of the checklist criteria have been fulfilled; where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter; ++, all or most of the checklist criteria have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter; –, few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter; NA, not applicable.

a Items correspond to the classifications in the case series quality assessment form in *Appendix 5*.

Appendix 17 Systematic review of single cisplatin treatment in cervical cancer

Methods

Searches were conducted in MEDLINE (Ovid) and the Cochrane database (CENTRAL; from inception to January 2012) for any studies evaluating cisplatin in cervical cancer. The search terms used were 'cisplatin' and 'cervical cancer'. Both MeSH terms and text words were used and a therapy clinical query maximising sensitivity was used in MEDLINE. Reference lists from relevant systematic reviews and guidelines were also searched. Included were any fully published RCTs in women with diagnosed cervical cancer (any stage, recurrent or primary) investigating cisplatin (including synonyms such as cis-platinum, cis-DDP) compared with no treatment and presenting any clinical outcomes but specifically interested in overall survival curves. The best-quality evidence for input into the economic model was sought. Preliminary and final inclusion decisions were made by one researcher (CM). Data extraction and quality assessment for the chosen RCT were performed by two researchers (CM, PA). If more than one large recent good-quality study was available meta-analysis would have been performed but this proved not to be necessary.

Results

Database searches yielded 1524 citations. Two published papers that nearly met the inclusion criteria were excluded: the study by Bonomi *et al.*[64] is a RCT that evaluates three different doses of cisplatin but has no control arm, and the study by Thigpen *et al.*[149] is a case series of cisplatin in recurrent cervical cancer and has no control arm without cisplatin. Three abstracts[66,150,151] were also excluded. One paper[152] was not available but as this did not give a sample size (as reported in Tzorias *et al.*[146]) it would be unlikely that this would be the best paper available. Four full papers[127,153–155] were evaluated and all compared cisplatin plus radiotherapy with radiotherapy only. Pearcey *et al.*[127] was chosen as the best paper for several reasons: participants were enrolled between 1991 and 1996 (i.e. after 1990), it had the largest sample size (259 patients), patients had a variety of FIGO stages including IVA and a survival curve for both arms was presented for up to 10 years.

Appendix 18 Health economics

TABLE 98 Branch probabilities used in model 1

	Label	Stage: early	Range (95% CI)	Probability distribution
Surgical treatment for initial cervical cancer				
Asymptomatic without cancer (A)				
Surviving within 3 months having received clinical follow-up	a1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	a2	0.0103	0.0098 to 0.0108	Beta(506.35, 48,654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	a3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Remaining asymptomatic without cancer within 3 months given no recurrence	a4	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Asymptomatic cancer at 3 months (B)				
Surviving within 3 months after treatment	b1	0.9307	0.8807 to 0.9807	Beta(102.90, 7.66)
Surviving within 3 months if cancer is undetected and untreated	b2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	b3	0.9000	0.8550 to 0.9450	Beta(123.47, 13.72)
Asymptomatic recurrence (C)				
Surviving within 3 months after treatment	c1	0.9307	0.8807 to 0.9807	Beta(89.25, 6.65)
Surviving within 3 months if cancer is undetected and untreated	c2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	c3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Symptomatic recurrence (D)				
Surviving within 3 months after treatment	d1	0.9307	0.8807 to 0.9807	Beta(89.25, 6.65)
Surviving within 3 months following undetected cancer	d2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Symptomatic cancer at 3 months (E)				
Surviving within 3 months after treatment	e1	0.9307	0.8807 to 0.9807	Beta(89.25, 6.65)
Surviving within 3 months following undetected cancer	e2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)

TABLE 98 Branch probabilities used in model 1 (*continued*)

	Label	Stage: early	Range (95% CI)	Probability distribution
Symptomatic without cancer (F)				
Surviving within 3 months following false symptoms	f1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	f2	0.0103	0.0094 to 0.0112	Beta(506.35, 48654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	f3	0.4000	0.3800 to 0.4200	Beta(915.02, 1372.53)
Remaining asymptomatic without cancer within 3 months given no recurrence	f4	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Post treatment: asymptomatic cancer at 3 months (G)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer at 3 months	g	0.9307	0.8807 to 0.9807	Beta(89.25, 6.65)
Post treatment: asymptomatic (H)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer	h	0.9307	0.8807 to 0.9807	Beta(89.25, 6.65)
Post treatment: symptomatic cancer at 3 months (I)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer at 3 months	i	0.9307	0.8807 to 0.9807	Beta(89.25, 6.65)
Post treatment: symptomatic (J)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer	j	0.9307	0.8807 to 0.9807	Beta(89.25, 6.65)
Dead (absorbing state)				

TABLE 99 Transition probabilities used in model 2

	Label	Stage: early	Range (95% CI)	Probability distribution
Surgical treatment for initial cervical cancer				
Asymptomatic without cancer (A)				
Surviving within 3 months having received clinical follow-up	a1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	a2	0.0103	0.0098 to 0.0108	Beta(506.35, 48654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	a3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Remaining asymptomatic without cancer within 3 months given no recurrence	a4	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Asymptomatic cancer at 3 months (B)				
Surviving within 3 months after treatment	b1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months if cancer is undetected and untreated	b2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	b3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Asymptomatic recurrence (C)				
Surviving within 3 months after treatment	c1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months if cancer is undetected and untreated	c2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	c3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Symptomatic recurrence (D)				
Surviving within 3 months after treatment	d1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months following undetected cancer	d2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Symptomatic cancer at 3 months (E)				
Surviving within 3 months after treatment	e1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months following undetected cancer	e2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Symptomatic without cancer (F)				
Surviving within 3 months following false symptoms	f1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	f2	0.0103	0.0094 to 0.0112	Beta(506.35, 48,654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	f3	0.4000	0.3800 to 0.4200	Beta(915.02, 1372.53)
Remaining asymptomatic without cancer within 3 months given no recurrence	f4	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)

TABLE 99 Transition probabilities used in model 2 (*continued*)

	Label	Stage: early	Range (95% CI)	Probability distribution
Post treatment: asymptomatic cancer at 3 months (G)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer at 3 months	g	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Post treatment: asymptomatic (H)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer	h	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Post treatment: symptomatic cancer at 3 months (I)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer at 3 months	i	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Post treatment: symptomatic (J)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer	j	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Dead (absorbing state)				

TABLE 100 Transition probabilities used in model 3

	Label	Stage: late	Range (95% CI)	Probability distribution
Surgical treatment for initial cervical cancer				
Asymptomatic without cancer (A)				
Surviving within 3 months having received clinical follow-up	a1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	a2	0.0103	0.0098 to 0.0108	Beta(506.35, 48,654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	a3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Remaining asymptomatic without cancer within 3 months given no recurrence	a4	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Asymptomatic cancer at 3 months (B)				
Surviving within 3 months after treatment	b1	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Surviving within 3 months if cancer is undetected and untreated	b2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	b3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Asymptomatic recurrence (C)				
Surviving within 3 months after treatment	c1	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Surviving within 3 months if cancer is undetected and untreated	c2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	c3	0.9000	0.8550 to 0.9450	Beta(149.37, 16.60)
Symptomatic recurrence (D)				
Surviving within 3 months after treatment	d1	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Surviving within 3 months following undetected cancer	d2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Symptomatic cancer at 3 months (E)				
Surviving within 3 months after treatment	e1	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Surviving within 3 months following undetected cancer	e2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Symptomatic without cancer (F)				
Surviving within 3 months following false symptoms	f1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	f2	0.0103	0.0098 to 0.0108	Beta(506.35, 48,654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	f3	0.4000	0.3800 to 0.4200	Beta(915.02, 1372.53)
Remaining asymptomatic without cancer within 3 months given no recurrence	f4	0.9000	0.8448 to 0.9442	Beta(149.37, 16.60)

TABLE 100 Transition probabilities used in model 3 (*continued*)

	Label	Stage: late	Range (95% CI)	Probability distribution
Post treatment: asymptomatic cancer at 3 months (G)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer at 3 months	g	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Post treatment: asymptomatic (H)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer	h	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Post treatment: symptomatic cancer at 3 months (I)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer at 3 months	i	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Post treatment: symptomatic (J)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer	j	0.9779	0.8530 to 0.9969	Converted from log-normal distribution for hazard rate
Dead (absorbing state)				

TABLE 101 Transition probabilities used in model 4

	Label	Stage: early	Range (95% CI)	Probability distribution
Surgical treatment for initial cervical cancer				
Asymptomatic without cancer (A)				
Surviving within 3 months having received clinical follow-up	a1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	a2	0.0103	0.0098 to 0.0108	Beta(506.35, 48,654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	a3	0.9000	0.8448 to 0.9442	Beta(149.37, 16.60)
Remaining asymptomatic without cancer within 3 months given no recurrence	a4	0.9000	0.8448 to 0.9442	Beta(149.37, 16.60)
Asymptomatic cancer at 3 months (B)				
Surviving within 3 months after treatment	b1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months if cancer is undetected and untreated	b2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	b3	0.9000	0.8448 to 0.9442	Beta(149.37, 16.60)
Asymptomatic recurrence (C)				
Surviving within 3 months after treatment	c1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months if cancer is undetected and untreated	c2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Remaining asymptomatic with untreated cancer conditional on surviving within 3 months	c3	0.9000	0.8448 to 0.9442	Beta(149.37, 16.60)
Symptomatic recurrence (D)				
Surviving within 3 months after treatment	d1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months following undetected cancer	d2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Symptomatic cancer at 3 months (E)				
Surviving within 3 months after treatment	e1	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Surviving within 3 months following undetected cancer	e2	0.8406	0.7986 to 0.8826	Beta(241.05, 45.71)
Symptomatic without cancer (F)				
Surviving within 3 months following false symptoms	f1	0.9993		Fixed
Progressing to recurrent cervical cancer after having a biopsy and survived within 3 months	f2	0.0103	0.0094 to 0.0112	Beta(506.35, 48,654.06)
Recurrence being asymptomatic given recurrence occurred within 3 months	f3	0.4000	0.3800 to 0.4202	Beta(915.02, 1372.53)
Remaining asymptomatic without cancer within 3 months given no recurrence	f4	0.9000	0.8448 to 0.9442	Beta(149.37, 16.60)

TABLE 101 Transition probabilities used in model 4 (*continued*)

	Label	Stage: early	Range (95% CI)	Probability distribution
Post treatment: asymptomatic cancer at 3 months (G)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer at 3 months	g	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Post treatment: asymptomatic (H)				
Mean survival time following treatment for those who were diagnosed with asymptomatic cancer	h	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Post treatment: symptomatic cancer at 3 months (I)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer at 3 months	i	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Post treatment: symptomatic (J)				
Mean survival time following treatment for those who were diagnosed with symptomatic cancer	j	0.9778	0.8526 to 0.9968	Converted from log-normal distribution for hazard rate
Dead (absorbing state)				

Description of the pathways for the model structure

Asymptomatic without cancer

At cycle 2 and onwards, that is, at 6 months' follow-up and onwards, these women, in accordance with the schedule, will receive standard practice together with PET-CT. Women with an abnormal examination will receive a biopsy. Women who survived 3 months following the biopsy can either become recurrent or remain without recurrence. For those women who become recurrent, the disease can be either asymptomatic or symptomatic. Those women who remain without recurrence can remain asymptomatic without cancer or symptomatic without cancer. Women who survived after normal examination or no examination can become recurrent or remain free of recurrent cervical cancer. Again, women in this group can also remain free of recurrence or remain asymptomatic without cancer or symptomatic without cancer. In the model structures below (specifically *Figures 39* and *40*) the term 'No examination' relates to cycles in the process in which the frequency of examination has dropped from every 3 months to every 6 months so at that point in the cycle there is no examination conducted.

Symptomatic without cancer

Women with symptoms that they suspect are related to recurrent cervical cancer will receive standard practice and PET-CT. Women who received an abnormal result will receive a biopsy. In this group the biopsy will confirm no recurrent cervical cancer and women will not receive any treatment. Women who survive at 3 months following biopsy can either become recurrent or remain without recurrence. For those women who are recurrent, the disease can be either asymptomatic or symptomatic. Those women who remained free of recurrence can remain asymptomatic without cancer or symptomatic without cancer. Women who survive after normal examination can become recurrent or remain free of recurrent cervical cancer.

Asymptomatic cancer at 3 months

At 3 months following treatment for initial cervical cancer, these women, in accordance with the schedule, will receive standard practice and PET-CT. Women with an abnormal examination will receive a biopsy. On confirmatory biopsy, women will receive treatment for persistent cancer. Women who survive 3 months following treatment will remain in the post-treatment asymptomatic with cancer state. Women with

no examination or a normal examination who survive 3 months will become either asymptomatic or symptomatic recurrent in the next cycle of the model.

Asymptomatic recurrence

Women who have asymptomatic recurrence will receive standard practice and PET-CT. Women with an abnormal examination will receive a biopsy. On confirmatory biopsy, women will receive treatment for asymptomatic recurrent cancer. Women who survive for 3 months following treatment will remain in the post-treatment asymptomatic with cancer state. Women with no examination or a normal examination who survive 3 months will become either asymptomatic or symptomatic recurrent in the next model cycle.

Symptomatic recurrence

Women who have symptomatic recurrence will receive standard practice and PET-CT. Women with an abnormal examination will receive a biopsy. On confirmatory biopsy, women will receive treatment for symptomatic recurrent cancer. Women who survive 3 months following treatment will remain in the post-treatment symptomatic recurrence state. Women with a normal examination who survive 3 months will remain symptomatic in the next model cycle.

Symptomatic cancer at 3 months

Women who have symptomatic recurrence will receive standard practice and PET-CT. Women with an abnormal examination will receive a biopsy. On confirmatory biopsy, women will receive treatment for symptomatic persistent cancer. Women who survive 3 months following treatment will remain in the post-treatment symptomatic persistent state. Women with a normal examination who survive 3 months will remain symptomatic in the next model cycle and would be considered as recurrent once detected.

Post-treatment asymptomatic cancer at 3 months

Women will remain in this state until death.

Post-treatment symptomatic cancer at 3 months

Women will remain in this state until death.

Post-treatment asymptomatic recurrence

Women will remain in this state until death.

Post-treatment symptomatic recurrence

Women will remain in this state until death.

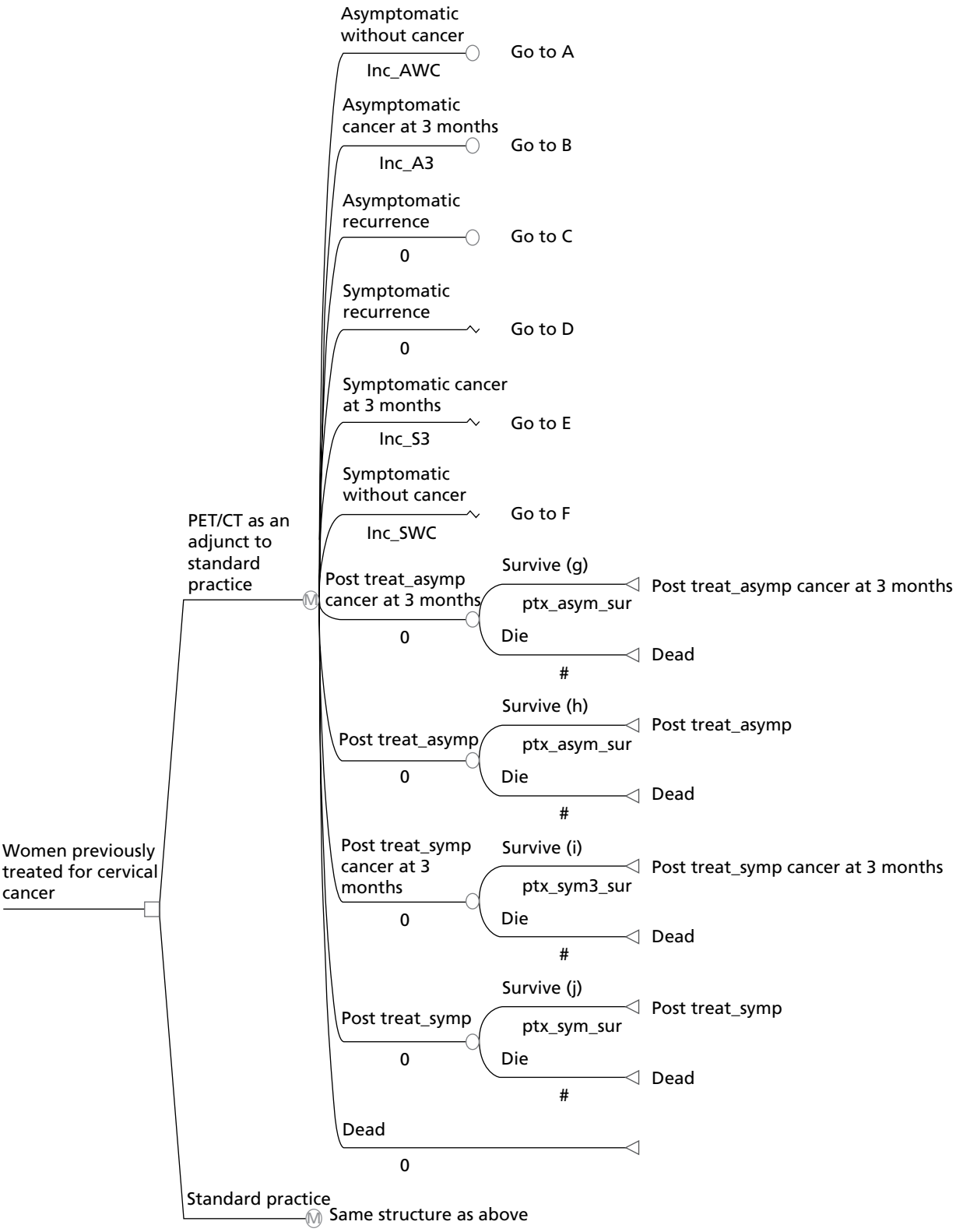

FIGURE 37 Decision tree-like model structure.

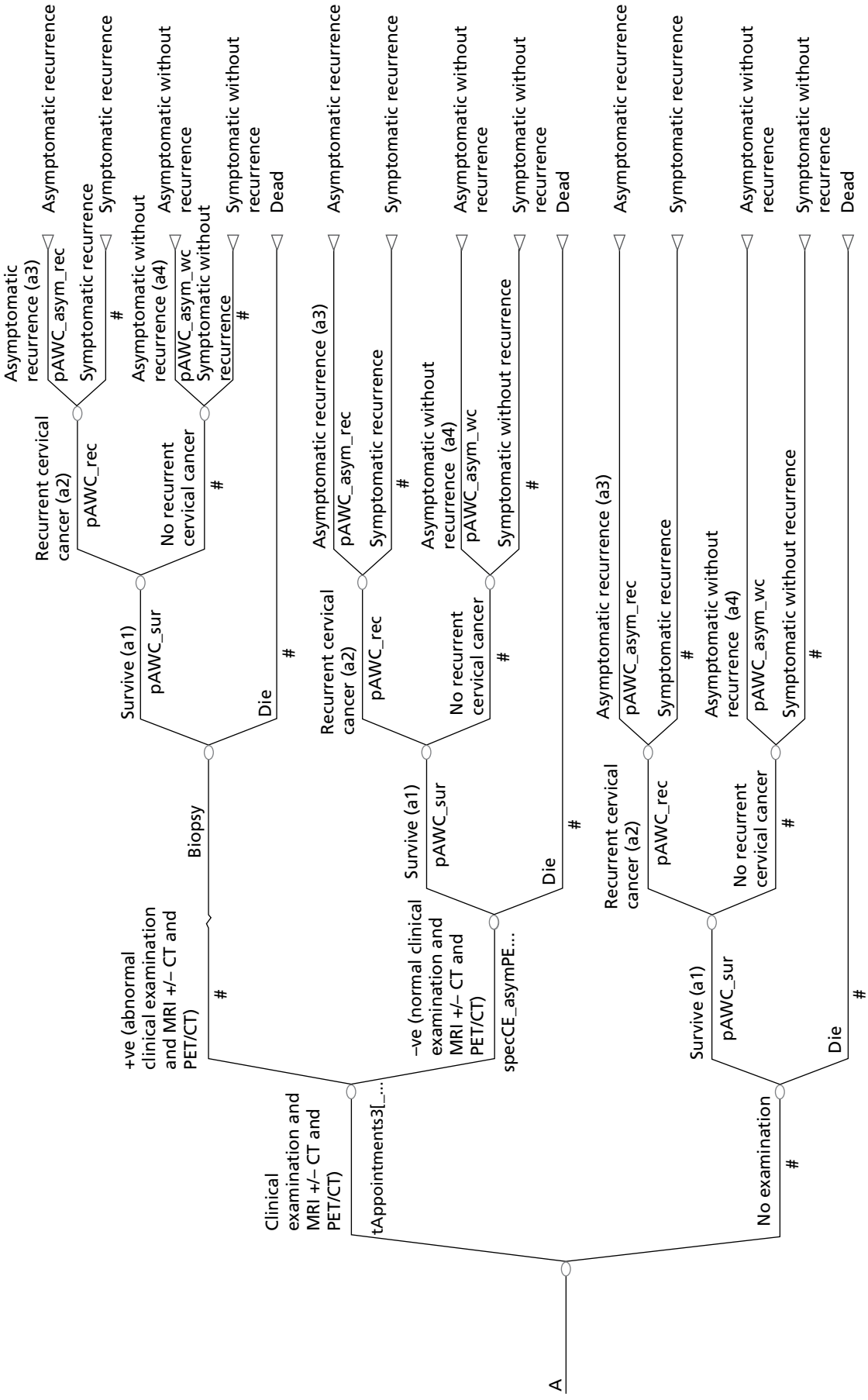

FIGURE 38 Pathway for the PET-CT as an adjunct to standard practice strategy for women who are asymptomatic without recurrence.

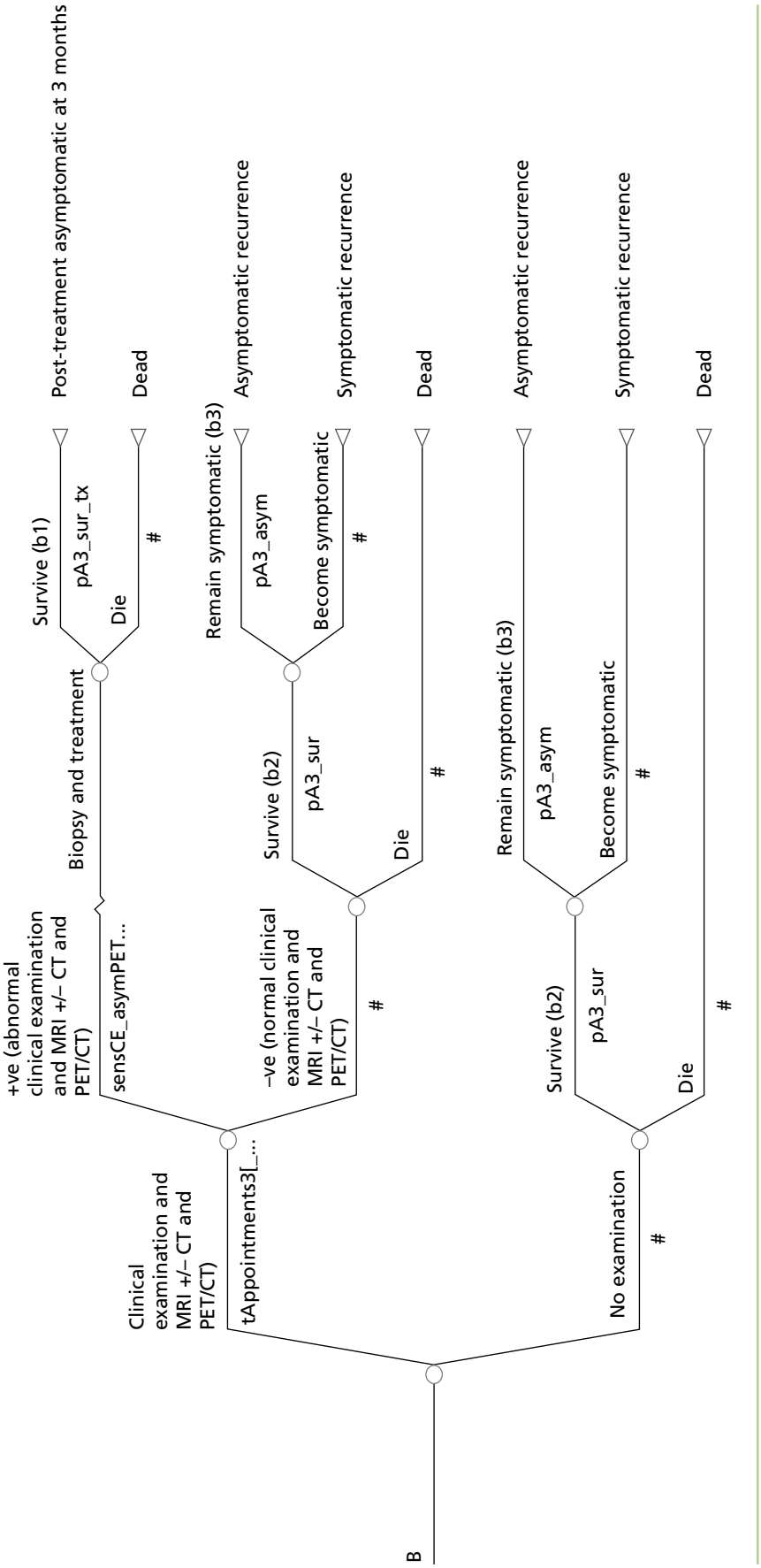

FIGURE 39 Pathway for the PET-CT as an adjunct to standard practice strategy for women who are asymptomatic at 3 months (persistent).

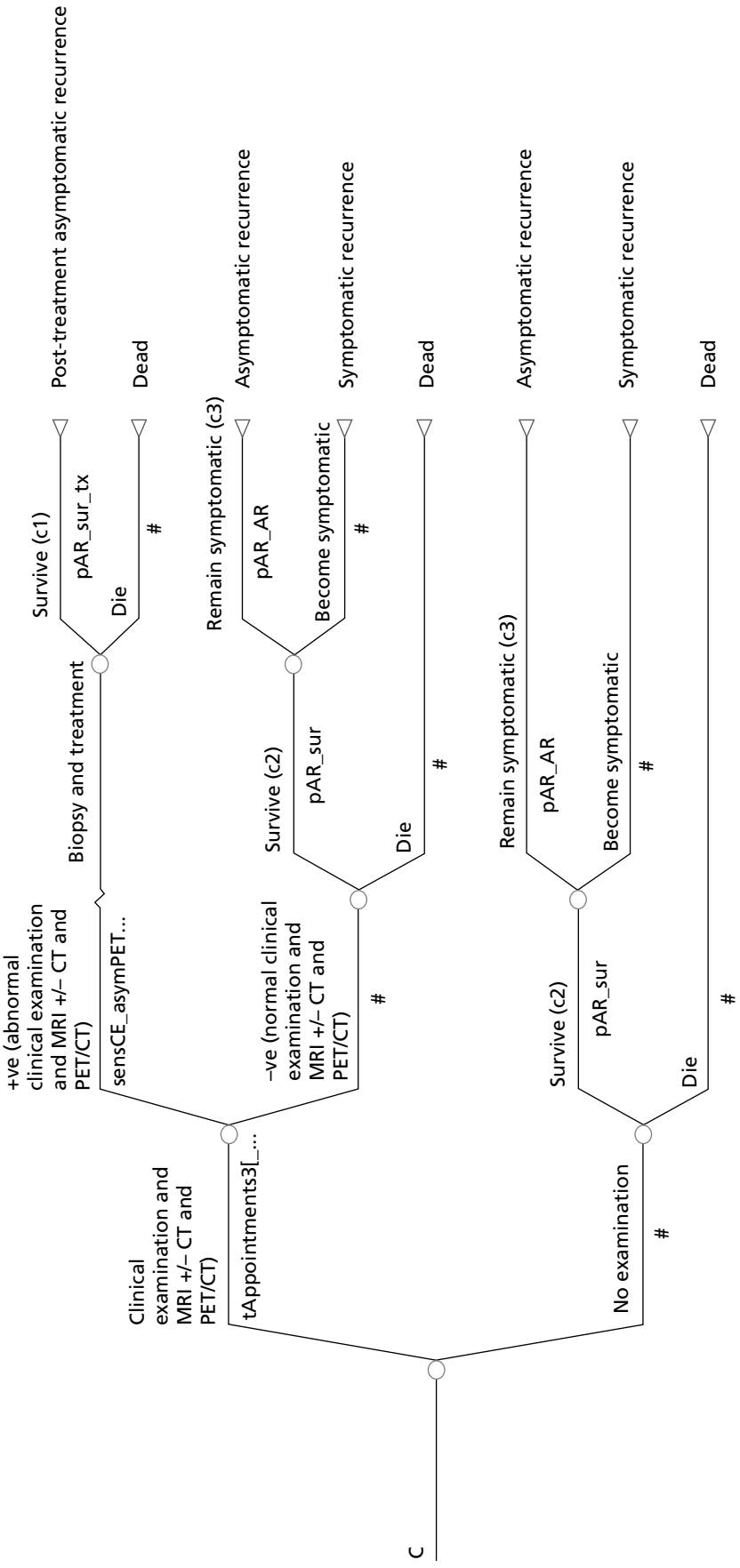

FIGURE 40 Pathway for the PET-CT as an adjunct to standard practice strategy for women who have recurrent asymptomatic cancer.

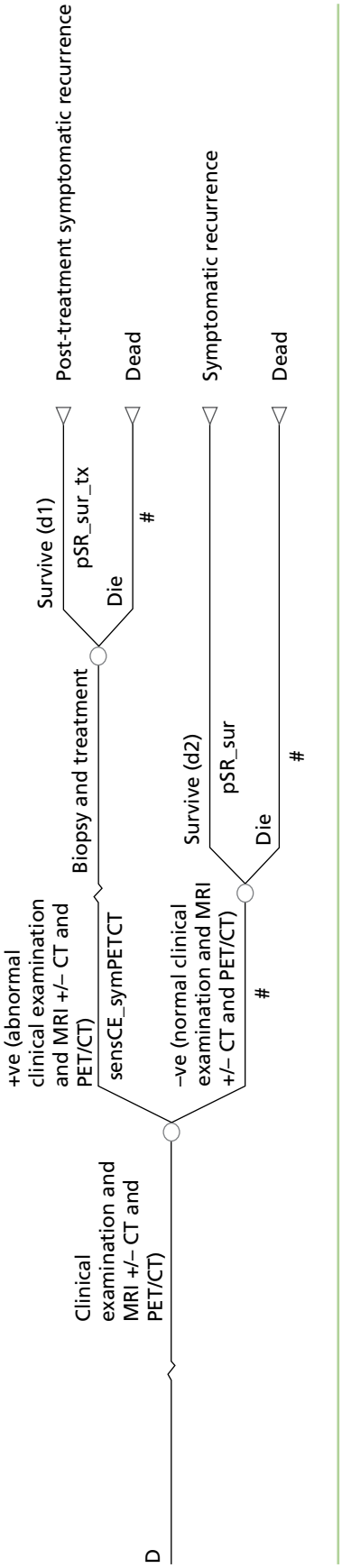

FIGURE 41 Pathway for the PET-CT as an adjunct to standard practice strategy for women who have recurrent symptomatic cancer.

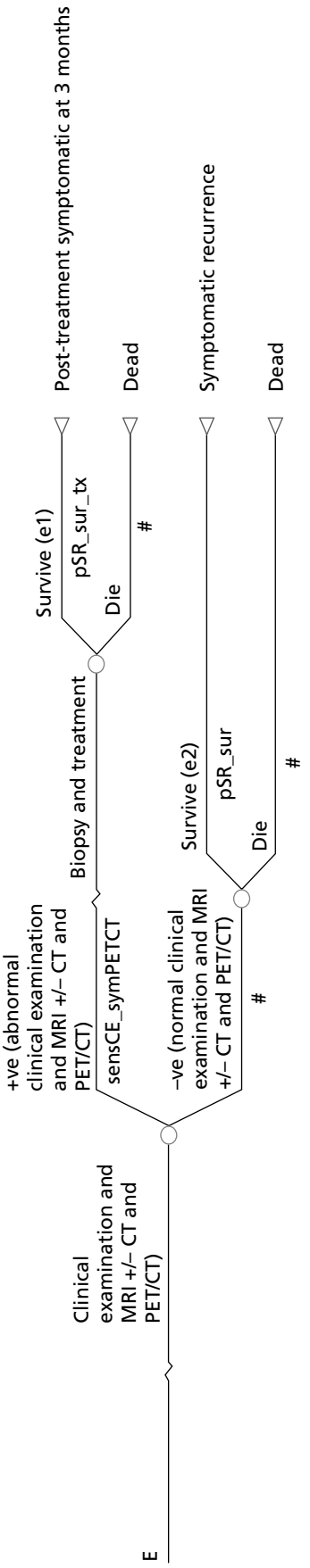

FIGURE 42 Pathway for the PET-CT as an adjunct to standard practice strategy for women who have symptomatic cancer at 3 months (persistent).

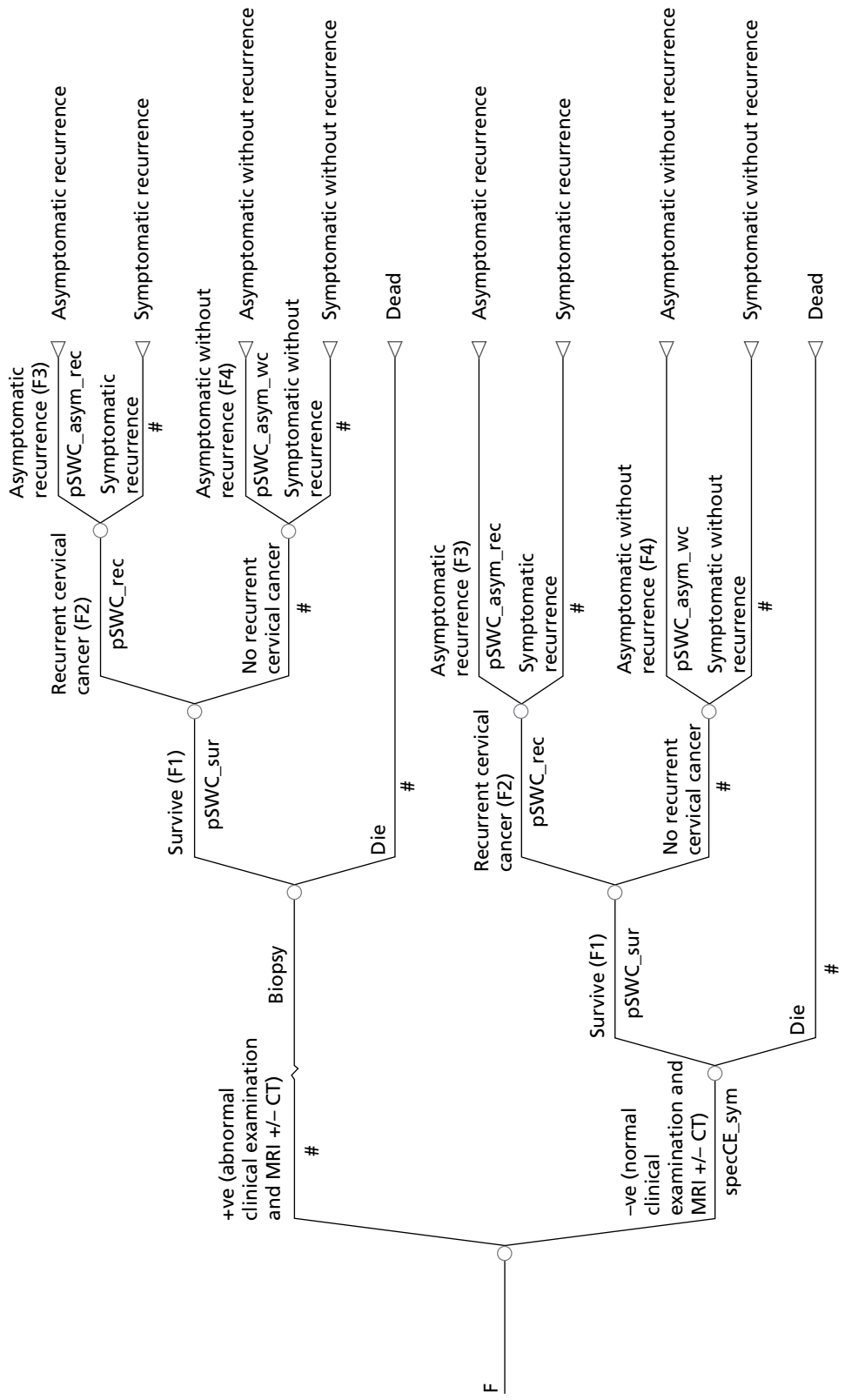

FIGURE 43 Pathway for the PET-CT as an adjunct to standard practice strategy for women who are symptomatic without recurrent cancer.

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