Evaluating PET-CT in the detection and management of recurrent cervical cancer: systematic reviews of diagnostic accuracy and subjective elicitation.

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Running title

PET-CT in recurrent cervical cancer

Background
PET-CT scan is recommended to triage patients for exenterative surgery and surveillance after treatment for advanced cervical cancer.

Objective

To evaluate diagnostic accuracy of additional whole body PET-CT compared to CT/MRI in women with suspected recurrent/persistent cervical cancer and in asymptomatic women as surveillance

Design
Systematic reviews. Subjective elicitation to supplement diagnostic information

Search strategy/Selection criteria/Data collection and Analysis
Searching of electronic databases to May 2010. Studies in women with suspected recurrent/ persistent cervical cancer and in asymptomatic women undergoing follow-up with sufficient numeric data included. We calculated sensitivity, specificity, and corresponding 95% confidence intervals. Meta-analyses employing bivariate model that included random-effects term for between-study variation.

Subjective elicitation
Prevalence of recurrence and the accuracy of imaging elicited using the allocation of point's technique. Coherence of elicited subjective probabilities with estimates in the literature examined.

Results
We identified 12 relevant studies. None directly compared additional PET-CT to MRI or CT separately. CT and MRI studies used older protocols and majority did not distinguish between asymptomatic and symptomatic women. Meta-analysis of PET-CT studies showed sensitivity of 92.2% (95% CI 85.1-96.0) and specificity of 88.1% (95% CI 77.9-93.9). Sensitivity and specificity for MRI was 82-100% and 78-100% and CT between 78-93% and 0-95%. Subjective elicitation provided estimates comparable to literature. Subjective estimates of increase in accuracy from additional PET-CT were less than elicited increase required to justify use in surveillance.

Conclusion

Evidence to support additional PET-CT is scarce, of poor quality and does not distinguish between application for surveillance and diagnosis. Guidelines recommending PET/CT in cervical cancer need to be reconsidered.

Key words PET-CT, CT, MRI, recurrent cervical cancer, exenteration, accuracy

Introduction

Cervical cancer was diagnosed in 2,851 women in the UK in 2010 and 936 deaths from cervical cancer in the UK were noted. [1]Early stage cervical cancer is treated by surgery or chemoradiation (stages 1-IIA) whilst advanced stage cervical cancer (IIB-IIIB) is treated predominantly by chemoradiation. Chemotherapy alone is reserved for metastatic cancer at presentation. Recurrence is more common in advanced cervical cancer (30%) than in early stage cervical cancer (6%). [2] [3] Currently surveillance is based on clinical examination at regular follow-up visits to detect recurrence. If recurrence is suspected, either on the basis of symptoms or examination, computed tomography (CT) or magnetic resonance imaging is used to confirm and define the extent of recurrence. [4] Neither modality can distinguish between radiation induced fibrosis and malignancy.

Survival in women presenting with symptoms of recurrence – e.g. pain/bleeding/fistulae from locally advanced cancer or cachexia from distant metastases is substantially worse than in asymptomatic women detected at surveillance. [5-7] Treatment options for recurrent cervical cancer encompass radical surgery (salvage hysterectomy or pelvic exenteration), chemoradiotherapy and palliative treatment (which can be chemotherapy or radiotherapy).

In carefully selected patients, with pelvis confined or central recurrence, exenterative surgery involving the removal of bladder, uterus and vagina, and/or rectosigmoid is potentially curative. It is therefore reasonable to assume that improving early detection of recurrence in asymptomatic women will improve survival by identifying women with pelvis confined recurrence where salvage surgery can be undertaken. However, salvage surgery carries risk for significant morbidity and mortality, particularly where the pelvis has been irradiated. The long term impact on the patient, including psychosocial is also considerable. Accurately triaging patients with distant metastases to receive palliative therapy and patients with potentially curative central pelvic recurrence to exenterative surgery is critical to the management of women with recurrent cervical cancer.

Positron emission tomography (PET) uses 18-F fluorodeoxyglucose (FDG) uptake in metabolically active tissues for detection. PET-CT combines PET with CT to define anatomical images. The CT images are used for localization and characterization of abnormal activity on the PET scans, and therefore to improve the specificity of the PET scan

interpretation. However, registration CT scans performed as part of an integrated PET-CT study are almost universally done to a relatively low-dose protocol using lower exposure factors and thicker slices than dedicated diagnostic CT. Intravenous and oral contrast are not generally used. As a consequence resolution and sensitivity for lesions for the registration CT alone will be lower than for a dedicated diagnostic CT.

Whole body PET-CT has shown promise in surveillance, improved detection of recurrence and distant metastasis and can predict survival outcome if performed three months after treatment.[8 9] However, PET-CT is also expensive, the equipment alone costing about 2 million pounds Sterling. False positives can occur in other metabolically active conditions e.g. inflammation or sepsis.

PET-CT has been recently introduced into clinical practice to triage patients for exenterative surgery and is endorsed for this use by national guidelines.[10 11] PET-CT is also recommended as surveillance after treatment for advanced stage cervical cancer. [10] However, the effectiveness of PET-CT in accurately triaging patients to potentially curative or palliative treatment and the diagnostic accuracy of PET-CT in asymptomatic women as surveillance for recurrence are not known. We performed systematic reviews of test accuracy and subjective elicitation to determine diagnostic accuracy of whole body PET-CT in addition to CT/ MRI in women following treatment for cervical cancer. .

In identifying the additional value of PET/CT over standard CT/MRI imaging, we sought evidence to answer 3 specific questions – 1. Value of routine PET-CT in follow-up of *asymptomatic* women after treatment for cervical cancer
2 Value of PET-CT imaging in detecting a recurrence in *symptomatic* women
3. Value of PET-CT imaging in recurrence to define a treatment strategy

Methods

Systematic reviews of test accuracy

A generic protocol was developed for undertaking the systematic reviews of test accuracy, diagnostic and therapeutic yield. Systematic reviews of test accuracy were conducted using established methods in line with the recommendations of the Cochrane Diagnostic Test Accuracy

Working Group (http://srdta.cochrane.org/handbook-dta-reviews). Comprehensive searches from inception to May 2010 were conducted in MEDLINE, Embase, Science Citation Index, The Cochrane Library, MEDION, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, Clinical Trials.com as well as a search of internet resources (UK Clinical Research Network Portfolio, specialist search gateways (OMNI and The National Cancer Institute), Google and Copernic). Electronic searches were supplemented by checking of reference lists, handsearching Gynecologic Oncology and contact with authors of included studies. No language restrictions were applied.

Inclusion and exclusion criteria

Population

- Included were
    - 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, tests (including imaging and histology).
    - any women who had had advanced stage cervical cancer (IB2-IV) treated previously, for example with chemoradiation with a minimum gap between completion of treatment and imaging of 3 months and were currently asymptomatic and undergoing routine follow up.
- Excluded were:
    - studies where the population contained women within three months of completion of treatment for primary disease, due to problems associated with distinguishing treatment complications and inflammatory response from recurrence in this patient group

Index test

- Included was:
    - PET-CT using 18F-fluorodeoxyglucose as radioisotope tracer
- Excluded was:
    - PET alone without concurrent CT

Comparator tests

- Included were:

- CT, local or whole body
- MRI, local or whole body

Reference standard

- Included were:
    - histopathological findings or clinical follow up for 6 months or more or both for all participants (differential reference standard was accepted because of the difficulty of biopsy where there was no indicated lesion to biopsy in test negative patients)
- Excluded were:
    - studies where only some of the participants undergoing the index test also received any reference standard

Outcome

- Included were:
    - studies that provided numerical data sufficient to create 2 x 2 tables of test results comparing index or comparator tests to the reference standard to provide information on test accuracy, giving TP,TN, FP, FN results
    - studies that provided any information on diagnostic impact: change in diagnosis and / or staging after PET-CT compared to existing tests or to reference standard
    - studies that provided therapeutic impact: change in treatment plan after PET-CT compared to existing tests or reference standard.

Study design

- Included were:
    - 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 more than 10 participants;
- Excluded were:
    - 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

Study selection, data extraction and Quality assessment

Inclusion of studies, data extraction and quality assessment were carried out in duplicate using predesigned and piloted data extraction forms and the QUADAS quality assessment tool for evaluations of test accuracy. [12] Differences were resolved by consensus and/or arbitration involving a third reviewer. Information on the technical quality of imaging technologies were also collected.

Statistical analysis

Data were extracted as two-by-two tables (true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN). RevMan version 5.1 and STATA version 11 were used for analysis. Equivocal results were used in sensitivity analyses by adding the total number of equivocal results to each of TP, FP, FN, TN in turn to derive maximum and minimum variation in sensitivity and specificity. Results were displayed graphically on Forest and ROC plots. [13] A bivariate model that included a random-effects term for variation in accuracy and threshold between studies was fitted where adequate results were available to derive summary estimates of sensitivity and specificity and summary ROC curves. [14] Where 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.

The bivariate model has two levels corresponding to variation within and between studies in the meta-analysis.[15] At the first level, the within study variability for both sensitivity and specificity is assumed to follow a binomial distribution.The sensitivity - specificity pair for each study must be modelled jointly within study at level one of the analysis because they are correlated.

Methods for Subjective elicitation

An elicitation exercise with specialists in gynaecological imaging, radiation oncology and gynaecological oncology was planned in anticipation of a lack of evidence with which to undertake an economic analysis (ref linked paper); in particular disaggregation of estimates of prevalence and test performance in asymptomatic and symptomatic women and direct comparisons of testing strategies (CT and/or MRI versus routine addition of PETCT to CT and/or MRI). [16]

The subjective elicitation exercise aimed to answer 1. Value of routine PET-CT in follow-up of *asymptomatic women* after treatment for cervical cancer
2 Value of PET-CT imaging in detecting a recurrence in *symptomatic women*

Probabilities elicited

Informed by the preliminary results of the systematic reviews of test accuracy, 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, where patients are assumed to be disease free for a minimum of three months post-completion of primary treatment:- in women presenting with symptoms suggestive of recurrence , and in asymptomatic women.

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 three months post-completion of primary treatment: in women presenting with symptoms suggestive of recurrence , and in asymptomatic women (CT/MRI as surveillance).

3) To determine the test accuracy of CT and/or MRI performed at the discretion of clinicians and of PETCT (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 a minimum of three months post-completion of primary treatment: in women presenting with symptoms suggestive of recurrence , and in asymptomatic women (CT and/or MRI +PETCT used for surveillance).

The initial elicitation exercise (N=9) was facilitated during an educational meeting in order to evaluate the accessibility of materials for respondents. Following the success of the initial elicitation, as judged by the face validity of findings fed back to participants, elicitations from subsequent specialists (N=12) were conducted using self-completed questionnaires. Subjective estimates of the prevalence of cervical cancer recurrence in two hypothetical cohorts of symptomatic and asymptomatic women and the accuracy of two testing strategies (CT and/or MRI performed at the discretion of clinicians and the routine addition of PET-CT (performed regardless of the result of CT and/or MRI) were elicited. Participants completed the elicitation exercise independently in order to ensure that any variation within and across

disciplines could be captured. The elicitation exercise comprised an 11 page anonymous self-administered questionnaire (Appendix S1). We collected data on experience, use of current imaging techniques and participant's use of PET-CT. We asked what participants considered to be the minimum important clinical difference (in terms of test error rates) in accuracy between imaging with CT and/or MRI alone compared to routine addition of PET-CT to CT and/or MRI that they would require before the introduction of one or other imaging strategy into practice.

Accuracy data were elicited in the form of the proportion of test errors (false positive and false negatives). We chose test errors as a metric of accuracy based on research suggesting that the clinical utility of a test is commonly conceptualised in this way. [15] [17] Subjective estimates of test error rates and of the prevalence of cervical cancer recurrence were used to derive positive predictive vales and negative predictive values for asymptomatic and symptomatic women separately.

We defined PPV as the proportion of women who test positive on either CT and/or MRI (and separately the routine addition of PET-CT) who are confirmed as having recurrence of on the basis of histology. NPV is defined as the proportion of women who test negative on either CT and/or MRI (and separately routine addition of PET-CT) who are confirmed as not having recurrence on the basis of a minimum of 6 months clinical follow up. Elicitation of prevalence and test accuracy information was undertaken using the allocation of point's 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). Value ranges differed depending on the question being asked to. For example the spread of value ranges for subjective estimates of the prevalence of recurrence in *asymptomatic* women was 0-49% including a single category for >50%. The spread of value ranges for subjective estimates of the prevalence of recurrence in *symptomatic* women was 51-100% including a single category of <50%. For elicitation of test accuracy (FP and FN) the spread of value ranges was between 0 and 50% to reflect the fact that a test error rate greater than 50% equates to a test accuracy that is worse than chance. In this way probability functions were obtained for each individual and aggregated mathematically to derive an average distribution for the sample. [17]An aggregated mean value

was estimated using the average distribution and the mid-point of each value range. The variability of this aggregated mean was estimated by calculating the standard deviation across the value ranges.

Results

Results of systematic review of test accuracy

Study selection and characteristics of included studies

From 7,524 potentially relevant citations, we selected 252 full-text articles for assessment. 240 articles were excluded, most commonly for different patient population or incorrect study design. Figure 1 shows the PRISMA diagram of selection process. Six studies evaluated PET-CT, [8 18-22] two evaluated MRI, [23 24] three evaluated CT [25-27] one evaluated both MRI and CT[28] . Only one study gave results for both CT and / or MRI versus CT and/or MRI with whole body PET-CT with the same reference standard of histology or clinical evidence of disease in one table so comparisons can be drawn. [19] Unfortunately the study did not specify the part of the body imaged by CT/MRI. Supplementary Tables S1,S2,S3,S4,S5 describe characteristics of included patients. The total number of patients in the studies ranged from 20 to 75 but some of the studies included women with any gynaecological cancers and others reported imaging results for both recurrent and primary cervical cancer.

Of note, the MRI/CT studies were published between 1981-2000 and none used current standard imaging methods. The quality of the studies was poor; in particular very little clinical information about participants was given and incorporation bias was inevitable for index test negative patients as a result of the reference standard being clinical follow up which is likely to have included imaging. (Supplementary Table -S6)

Included studies for each study question

1. Value of routine PET-CT in follow-up of women after treatment for cervical cancer. Two included studies included asymptomatic women but did not present data for asymptomatic women separately from women with symptoms. [21 24]
2. Value of PET-CT imaging in detecting a recurrence in case of symptoms. We found six relevant studies , [8 18-22] .

3. Value of PET-CT imaging in order to define the treatment strategy. Only one included PET-CT study reported information on diagnostic and therapeutic impact.[8]

Statistical results for accuracy of imaging

The sensitivities and specificities of detection of local and distant recurrence with PET-CT ranged between 83%-100% and 71%-100% respectively. For distant recurrence alone the sensitivity of PETCT was 86% and the specificity 100%. The summary estimate of the sensitivity of PET-CT for detection of cervical cancer recurrence was 92.2 (95%CI 85.1, 96.0) and specificity 88.1 (95% CI 77.9, 93.9). (Figures 2, 3) A sensitivity analysis, omitting one study (Amit et al, 2006)[18] that reported accuracy for distant recurrence only did not affect accuracy estimates to any significant degree (sensitivity 92.6 (95%CI 85.3, 96.4); specificity 87.3 (95%CI 76.6, 93.5). Only one study (N=12) gave results 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 in one table. Unfortunately the part of the body imaged with standard imaging was not mentioned in the paper. This demonstrated sensitivity and specificity of CT and/or MRI of 25% and 50% respectively whilst the addition of PET-CT to this imaging strategy resulted in a sensitivity and specificity of 100%.[19]

Meta-analysis for MRI or CT test accuracy studies was not possible because of considerable clinical heterogeneity. The sensitivity and specificity of MRI in pelvic recurrence varied between 82% - 100% and 78% - 100% respectively. The sensitivity and specificity of CT in pelvic recurrence (excluding equivocal results) varied between 78% - 93% and 0% - 95% respectively. (data not shown)

Results for Subjective elicitation

Subjective estimation of the prevalence of recurrence was elicited from all twenty one respondents and subjective estimation of accuracy from 18 respondents. Responses from individuals who received pre-elicitation education in the form of a lecture did not appear to differ from those completing self-administered questionnaires only. The self-reported characteristics of respondents and their reported use of imaging technologies are outlined in Supplementary Table S7 and Figure 4. The mean elicited prevalence of recurrence in women presenting with symptoms a minimum of three months after completion of primary treatment

was 47.8% (sd 20.8) and for asymptomatic women was 16.7% (sd 13.1). Subjective estimates of the accuracy of the two testing strategies and the minimum important difference between them considered sufficient to warrant the routine addition of PET-CT for the detection of cervical cancer recurrence are shown in Table 1. Mean elicited estimates of the increase in PPV of CT and/or MRI plus PET-CT compared to CT and/or MRI alone in symptomatic women was 2.6 and the increase in NPV 3.6. For asymptomatic women the mean elicited increase in PPV was 4.6 and in NPV 3.4.

The minimum important elicited increase in accuracy of the addition of PET-CT to CT and/or MRI considered necessary to warrant introduction of PET-CT as a routine investigation in this sample of clinical experts was similar for asymptomatic (a mean 8.7% reduction in false positives and 6.3% reduction in false negatives) and symptomatic women (a mean 7.7% reduction in false positives and 6.4% reduction in false negatives). Thus the subjective estimate of incremental accuracy resulting from the routine addition of PET-CT to MRI and/or CT was estimated to be smaller than the elicited minimum important difference in accuracy required to justify its use for the investigation of women after completion of primary treatment for cervical cancer.

Comparison with systematic review results

We found that elicited estimates of the accuracy of CT and/or MRI plus PET-CT compared to CT and/or MRI alone in symptomatic women were similar to estimates of accuracy in the literature (Table 2). The absence of published estimates of accuracy in asymptomatic women precluded a comparison in this group. Elicited specificities of CT and/or MRI and CT and/or MRI plus PET-CT were comparable to literature based estimates in mixed symptomatic and asymptomatic populations whilst elicited sensitivities were lower. A lower sensitivity would be expected in a homogenous asymptomatic population compared to a mixed symptomatic and asymptomatic population and therefore this finding supports the validity of elicited estimates.

DISCUSSION

Intercollegiate guidelines recommend the use of PET-CT in patients with recurrent cervical cancer considered for exenterative surgery or where prior imaging is equivocal. The evidence

underpinning these recommendations were largely derived from studies of diagnostic accuracy of PET-CT in primary cervical cancer to predict lymph node metastasis. [29-31]. In addition, SIGN guidelines also recommend a PET-CT scan 9 months after chemoradiotherapy based on limited evidence [32 33]

We evaluated evidence to answer three relevant questionsvalue of PET/CT in routine follow-up in asymptomatic women, the value of PET/CT in women with symptoms suspicious of recurrence and the value of PET/CT in defining therapy. In particular, we sought to identify the additional value of PET/CT over conventional CT/MRI imaging in these clinical scenarios. Our systematic review finds that evidence of diagnostic accuracy to support the use of whole body PET-CT in addition to standard CT or MRI imaging in all 3 scenarios is scarce and of poor quality . We found that published studies often do not distinguish between applications for surveillance versus diagnosis in suspected recurrence. There was scanty information on imaging as routine follow up for asymptomatic patients. Only one paper on diagnostic impact was found[8]. In particular the MRI and CT studies did not reflect current practice standards and thus the true additional value of PET/CT in these scenarios is unclear. In fact, most included PET/CT studies present results of diagnostic accuracy of PET/CT alone rather than the accuracy of PET/CT in comparison to CT/MRI. Thus the additional value of PET-CT in these settings is unclear. Only meta-analysis of PET-CT results was possible and results from the literature were coherent with findings of the subjective elicitation exercise.

The elicited 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.

Our systematic review was comprehensive in its scope and search. We conducted the review in line with contemporary recommendations. Our search of literature aimed to minimise the risk of selection and publication bias. We made considerable efforts to find appropriate input values on effectiveness of treatment for the decision analytic model which is based on best available evidence. All assumptions used in the model were agreed by the team based on expert advice *a priori*.

Experts used in the elicitation exercise were representative in specialty and expertise of decision makers in recurrent cervical cancer. The subjective elicitation exercise was carried out using expert opinion, before any economic analysis was undertaken and produced data not available in the published literature. The definition of expert for the purposes of subjective elicitation is not considered restricted to hands-on experience of a technology as subjective beliefs are shaped by factors other than first-hand experience such as interaction with colleagues, published estimates of accuracy and knowledge of the technology. [17]

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 compared to asymptomatic women. In addition, the pattern of elicited estimates of accuracy in asymptomatic women is plausible given the lower prevalence of recurrence in asymptomatic women. Elicited estimates of accuracy also reflect a greater likelihood of an improvement in NPV compared to 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.

We did not evaluate selective use of PET-CT subsequent to initial CT/MRI imaging, which is recommended practice. [10] [11] However, the systematic searches did not identify any papers to support a selective approach either. In fact only one paper reports impact of PET-CT on guiding therapy. [8] This work is part of a larger National Institute of Health Research/Health Technology Assessment (HTA reference 09/29/02) funded evaluation of the accuracy and cost effectiveness of PET-CT in recurrent cervical cancer.[16] We identified the best inputs from evidence in order to construct a decision analytic model to determine the cost effectiveness of additional PET-CT in recurrent cervical cancer (linked submission).

Current guidelines support the use of PET-CT in suspected recurrent or persistent disease after initial imaging and as surveillance in asymptomatic women after completion of chemoradiation for primary treatment. This is not supported by evidence from this systematic review of the literature or by the elicitation exercise. Few test accuracy studies were

identified as being relevant to current imaging practice. This study finds that the accuracy of PET-CT in recurrent cervical cancer is not yet proven. However the authors acknowledge that lack of evidence of value (of PET-CT) is not the same as evidence to support lack of value .

Good quality, adequately powered studies directly comparing the test accuracy of the addition of PET-CT to MRI and/or CT imaging alone in women with recurrent and persistent cervical cancer are needed. Studies also need to investigate the impact of additional PET-CT on change in diagnosis, work-up and change in the treatment plan. We also recommend that a national register of women considered for exenterative surgery for recurrent cervical cancer be established to prospectively collect data on imaging, decision making and outcomes of treatment. To our knowledge, although conditional probabilities have been undertaken this is the first specific example of elicitation of test accuracy estimates and demonstrates the value of this approach to inform subsequent modelling where primary data is scanty or unreliable. [17] 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 on the validity of responses is warranted as this has an impact on the methods of elicitation that are possible (for example the use of postal and internet based questionnaires), the resources required and response rate.

Conclusions

Our study (and the linked economic evaluation) raises two important issues – firstly the paucity of robust evidence on which to base decision making in the diagnosis and treatment of recurrent cervical cancer and secondly a broader question on how rapidly evolving, often 'glamorous' technology can be robustly evaluated prior to incorporation into routine clinical care. The use of PET-CT in recurrent cervical cancer and its endorsement by national guidelines is not supported by published literature. Consideration to revise national guidelines and/or prospective study in a national registry of exenterative surgery for recurrent cervical cancer to evaluate the effectiveness of PET-CT in this setting is necessary.

Box

What is currently known on the topic?

- PET-CT scan is currently used to triage patients for exenterative surgery and is recommended for surveillance after treatment for advanced stage cervical cancer. These indications for use are endorsed by national guidelines.
- However, the diagnostic accuracy of additional PET-CT in either indication is not known.

What this study adds

- Test accuracy studies in recurrent cervical cancer lack currency, are of poor quality and of limited applicability to current practice. Published literature does not support the use of additional PET-CT in selecting patients for exenterative surgery or its use for surveillance in asymptomatic patients after completion of primary treatment.
- The elicited estimated increase in accuracy of adding PET-CT to MRI and/or CT is 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.
- There is an urgent need to revise national guidelines and/or prospectively investigate the test accuracy of additional PET/CT in recurrent cervical cancer.

Contribution to Authorship

SS, KK, TER contributed to the design of the whole project and obtained funding. CM and CD designed and supervised the systematic review with input from SS, TER, PB, PA, P M-H, PG. The systematic searches and meta-analysis was performed by AZ, SM, MK, AZ, EB. CM and CD designed and conducted the subjective elicitation with input from SS, P M-H, TER, PB, PG and PA. SS and CM prepared the manuscript as lead writers. All authors contributed to critical review and input into the final manuscript. CM is the Guarantor.

Details of ethics approval

No ethical approval was required for this systematic review and subjective elicitation. Subjective elicitation was performed with written consent from participants

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Figure 1. PRISMA diagram of selection process – diagnostic systematic review

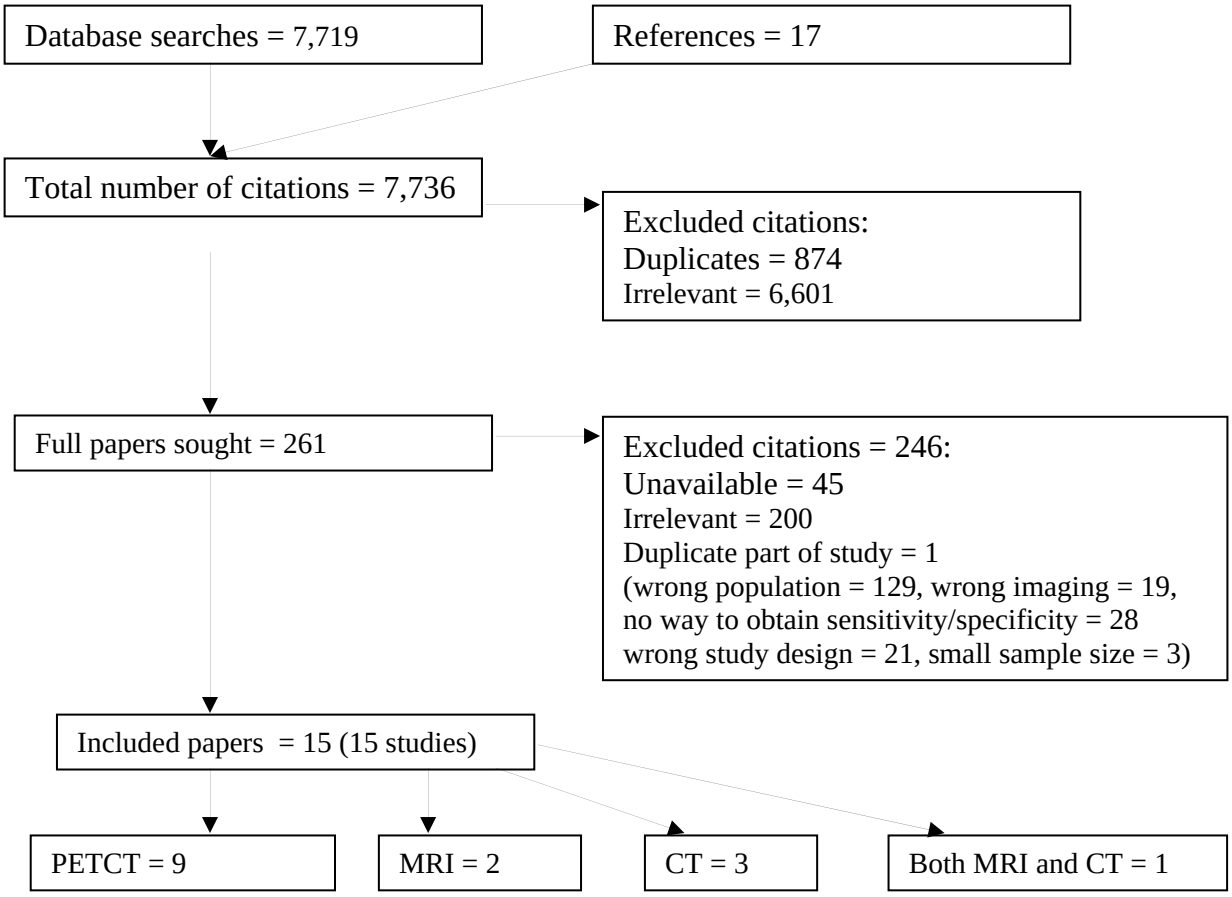
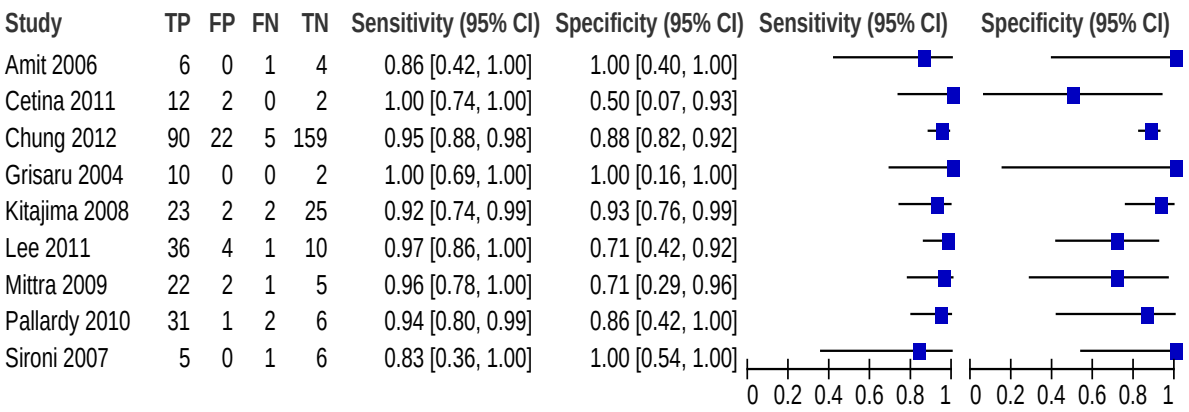
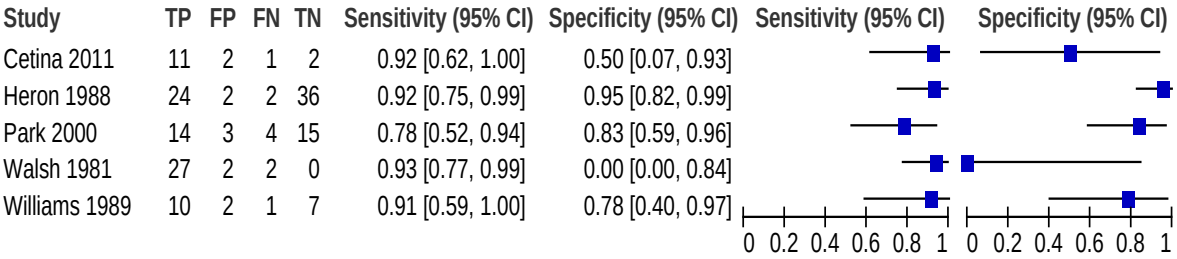


Fig: 2. Forest Plot: Sensitivity and Specificity PETCT studies



The bivariate model failed to converge for estimation of the accuracy of PETCT and estimates are therefore based on a univariate random effects meta-analyses for sensitivity and specificity separately. The summary estimate of the sensitivity of PET-CT for detection of cervical cancer recurrence was 94.8% (95%CI 91.2, 96.9) and specificity 86.9 (95% CI 82.2, 90.5).

Fig: 3. Forest Plot: Sensitivity and Specificity CT studies



Summary estimate of sensitivity of CT from a bivariate meta-analysis: 89.64 (95% CI 81.59, 94.41). Summary estimate of specificity of CT 76.00 (95% CI 43.68, 92.82)

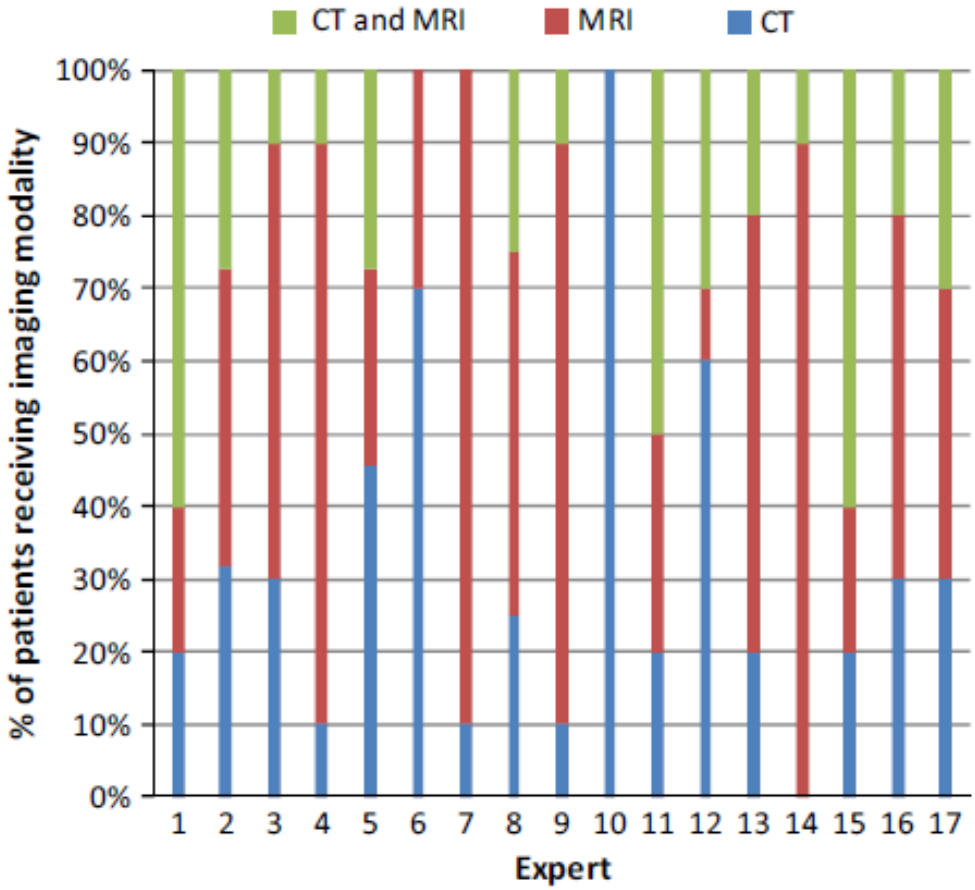


Figure 4. Use of imaging (MRI and/or CT in women presenting with suspected cervical cancer recurrence.

Table 1. Summary of accuracy results from subjective elicitation exercise

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

Table 2. Comparison of test accuracy results from elicitation exercise and systematic review of literature

Presentation	Asymptomatic				Symptomatic			
	Literature		Elicited***		Literature		Elicited***	
Accuracy	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
Clinical follow up and MRI ± CT	–	–	45.43	98.47			85.09	89.78
CT	–	–	–	–	78–93*	78–95**	–	–
MRI	–	–	–	–	82–100*	78–100**	–	–
Clinical follow up, MRI ± CT and PET-CT	–	–	65.25	98.58	83–100*	71–100**	89.71	91.88

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

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

Supplementary Table 1 Studies included in the diagnostic review

Study name, date	Index test (s)	Reference standard	Suspected recurrence/ asymptomatic	Number evaluable in study
Amit 2005	CT then whole body PET-CT	Histopathology	Suspected	11**
Cetina 2011	1. Abdominal or pelvic CT and PET-CT 2. Abdominal or pelvic CT alone	Histopathology, serial imaging studies or clinical follow up. Length of follow up not specified	Suspected	16
Chung 2012	Whole body PET-CT	Histopathology, radiology and/or clinical follow up. (range 6 – 307 months; median 24 months)	Asymptomatic (56.9%) or suspected (43.1%)	276
Grisaru 2004	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	Imaging then whole body PET-CT	Histopathology, clinical follow up for >1 yr, tumour marker levels alone or with CT or PET-CT	Suspected	52
Lee 2011	Imaging then whole body PET-CT	Histopathology, radiology and/or clinical follow up, or reaction to post-CHRT treatment (follow up 6 months)	Suspected	51
Mittra 2009	Imaging then whole body PET-CT	Histopathology or clinical follow up	Suspected and symptomatic (disaggregation not possible)	30
Pallardy 2010	1. CT and / or MRI then head, thorax and abdominal PET-CT 2. CT or MRI alone	Histopathology or clinical follow up (range 23.6 – 69.8 months; median 48 months)	Suspected	40
Sironi 2007	Imaging then whole body PET-CT	Histopathology, clinical follow up with radiology for >6 months	Suspected	12
Hatano 1999	MRI (pelvic)	Histopathology	Unclear	35*
Weber 1995	MRI (pelvic)	Histopathology, clinical follow up for up to 4 yrs	Suspected	37*
Heron 1988	CT (abdomen)	Histopathology, clinical follow up	Suspected	70*
Park 2000	CT (chest, abdomen and pelvis)	Histopathology, tumour marker, CT	Suspected	36
Walsh 1981	CT (abdomen and pelvis)	Histopathology	Probably suspected	33*
Williams 1989	CT and / or MRI (both pelvic)	Histopathology	Suspected	20*

* gives test results for local recurrence only, not for all recurrence
** gives test results for extra-cervical lesions only

Supplementary Table 2 Definitions of reference standards presented in included studies

Study	Reference standard		
	histopathological findings	follow-up	
		clinical	radiological
PET-CT			
Amit 2005	histopathological examination during biopsy, random sampling of nodes	-	-
Cetina 2011	histopathological examination during biopsy	Clinical course (lemgth not specified)	Serial imaging (length not specified)
Chung 2012	histopathological examination during biopsy	physical and gynaecological examination, tumour marker levels (6-307 months)	Serial imaging (6-307 months)
Grisaru 2004	histology during surgical exploration or guided biopsies	clinical outcomes (all negative tissue diagnosis were followed to confirm negative histology)	radiological
Kitajima 2008	histopathological examination (n=21)	clinical follow-up for periods longer than 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), tumour marker levels alone (n=5)	
Lee 2011	histopathology	Follow up lasting for 6 months or longer: reacted to post-CHRT treatment.	Follow up lasting for 6 months or longer, increase in size or number of affected areas
Mittra 2009	histological evaluation (n=23)	clinical follow-up (n=7)	-
Pallardy 2010	Histological evaluation	Follow up range 23.6-69.8 (median) 48 months according to RECIST criteria	Follow up range 23.6-69.8 (median) 48 monthsCT or MRI according to RECIST criteria
Sironi 2007	histopathological findings during surgery or imaging-guided FNA biopsy in patients who were positive on PET-CT	If –ve on PETCT - clinical outcomes with CT or MR imaging over at least 6 months	
MRI			
Hatano 1999	histopathological findings during multiple punch biopsies and cytology of tumour site only	-	-
Weber 1995	Histopathology and/or surgical outcomes (n=34)	clinical follow up for at least 4 years (n=3)	
CT			
Heron 1988	histological evaluation: at EUA (n=4), by laparotomy(n=7) and by CT-guided biopsy (n=3)	unequivocal progressive clinical course (n=25): inc 2 post-mortem proof,. 17 - supportive evidence of deterioration on follow-up. For 31 patients with –ve test was only considered to	-

Study	Reference standard		
	histopathological findings	follow-up	
		clinical	radiological
		be free of recurrence if clinical condition remained stable for > 2 years and/or histology	
Park 2000	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	histological evaluation (n=29): by laparotomy (n=10), parametnial biopsy (n=6), cervical and vaginal biopsy (n=6), penineal biopsy (n=2), lymph node aspiration (n=2), autopsy (n=2), and bone biopsy (n=1)	-	-
MRI and CT			
William s 1989	histological biopsies (n=10), hysterectomy specimens (n=4); open biopsy at laparotomy (n=2); histological proof of distant metastatic disease (n=4).	-	-

Supplementary Table 3 Population characteristics of studies evaluating PET-CT

Characteristics	Amit 2005	Cetina 2011		Chung 2012	Grisaru 2004	Kitajima 2008	Lee 2011	Mittra 2009	Pallardy 2010	Sironi 2007
Total N in study	75	26		430	53	52	51	30	40	25
Number with recurrent cervical cancer and imaging results	11	16		276	12	52	51	30	40	12
Mean age, year (range)	NR	47.2 (31-66)		52 (22-81) (median)	NR	58 (37; 78) (median)	53 (28-76)	50 (28; 87)	45.5 (35-81)	49.6
FIGO Initial stage	NR	IB2- (n=2), IIB (n=8), IIIB (n=3), IVA(n=1), IVB (n=2)		IA2 (n =30); IB1 (n=118); IB2 (n=16) IIA (n=41); IIB (n=45); IIIA (n=2) IIIB (n=9); IVA (n=8) IVB (n=7)	NR	I (n=12); II (n=15); III (n=21); IV (n=4)	0 – (n=2), I (n=20), II (n=25), III (n=3), IV (n=1)	IB2 (n=2); IIA (n=4); IIB (n=10); IIIA (n=1); IIIB (n=11); IVA (n=2)	I (n=7); II (n=16); III (n=13); IV (n=4)	IIB (n=6); IIIA (n=5); IIIB (n=1)
Type of tumour pathology	NR	SCC (n=15), ADC (n=1)		SCC (n=235), ADC (n=27), Other (n=14)	NR	SCC (n=42); ADC (n=8); ASC (n=2)	SCC (n=46), other (n=5)	SCC (n=22); ADC (n=5); other (n=3)	SCC (n=39), ADC (n=1)	NR
Prior treatment per person	NR	RT (n=1), CHRT (n=13), SR+RT (n=1), SR + CHRT (n=1)		NR	NR	SR+CHRT (n=20); SR + CH (n=12); CHRT (n=12); SR (n=8)	SR (n=5), SR+RT (n=4), SR + CHRT (n=19), CHRT (n=23)	NR	SR+CHRT (n=36); CHRT (n=2); RT (n=1); SR (n=1)	SR + CH (n=6); SR + RT (n=1); SR +CH +RT (n=5)

Inclusion criteria	patients with proven recurrent cervical cancer.	Patients with previous cervical cancer who underwent CT and PET-CT due to suspicion of persistent or recurrent disease		(1) had symptoms suspecting recurrence; (2) had new lesions on surveillance imaging studies; (3) had elevated serum tumor markers with or without abnormal imaging studies; (4) had abnormal results on physical or cytologic examination on routine surveillance; (5) wanted surveillance PET-CT scan for fear of recurrence without evidence of disease.	patients with proven gynaecological malignancy	patients who had undergone treatment for histopathologically proven uterine cervical cancer; who had suspected recurrence	Cases at risk for recurrence on the basis of clinical symptoms, signs or raised antigen levels or who had abnormal imaging results.	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.	Suspected recurrence from physical examination and / or cervical smear and / or antigens and / or conventional imaging every 6 months over a 5 year period, minimum 3 month follow up after the post treatment PET-CT scan	patients who had undergone primary surgical treatment and postoperative adjuvant therapy for uterine cancer.

Exclusion criteria	NR	NR		(1) previous diagnosis of another malignant disease (2) follow up duration less than 6 months (3) skin or pulmonary lesions or impaired renal function likely to raise SCC antigen levels.	NR	NR	Other malignancies. Refused PETCT for financial reasons	other malignancies, had an initial diagnosis of advanced cancer cervix not suitable for treatment with curative intent, or did not achieve complete remission.	NR	negative (normal) findings at routine follow-up examinations, serum glucose level of more than 200 mg/dl.

Supplementary Table S4. Quality of included studies in systematic review

Study name, date	Test	1	2	3	4	5	6	7	8	9	10	11	12	Comments
Amit 2005	PET CT	Y	N	Y	U	Y	Y	N	U	N	N	N	Y	Extra–pelvic recurrence only
Cetina 2011	PET-CT CT	- N	N	 U	U	N Y	 U	Y	U	N	N	 Y	xxx	
Chung 2012	PET-CT	Y	Y	Y	U	N	 U	Y	 U	N	N	 NA	xxx	
Grisaru 2004	PET CT (CT +/- MRI)	U	N	Y	U	Y	Y	N	Y	N	N	NA	Y	
Kitajima 2008	PET CT	Y	Y	Y	U	Y	Y	N	Y	Y	N	NA	Y	
Lee 2011	PET-CT	Y	Y	N	U	 Y	U	Y	U	Y	N	NA	xxx	
Mittra 2009	PET CT	Y	Y	Y	U	Y	U	N	U	Y	N	NA	Y	
Pallardy 2010	PET-CT	Y	Y	Y	U	Y	U	Y	U	U	N	NA	xxx	
Sironi 2007	PET CT	Y	Y	Y	Y	Y	Y	N	Y	Y	N	NA	Y	
Hatano 1999	MRI	Y	U	Y	U	Y	Y	N	U	Y	N	N	N	Tumour site only
Weber 1995	MRI	U	U	Y	U	Y	Y	N	U	N	N	NA	N	Pelvic recurrence only
Heron 1988	CT	Y	U	N	U	N	Y	N	U	Y	N	NA	N	Local recurrence only
Park 2000	CT	U	U	N	U	Y	N	N	U	U	N	NA	N	
Walsh 1981	CT	Y	Y	Y	Y	Y	Y	N	U	N	Y	Y	N	Pelvic recurrence only
Williams 1989	MRI/CT	Y	U	Y	U	Y	Y	N	Y	N	N	NA	N	Local (central) recurrence

														only
Y = yes, N = no , U = unclear, NA = not applicable														
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.														

Supplementary Table 5. Characteristics of respondents to the elicitation exercise - Speciality/ Designation; years of experience; years of using PETCT

Speciality & years of experience*	**Use of imaging technologies (% of symptomatic consultations for recurrence)**			
	MRI	**CT**	**MRI and CT**	**Experience with PETCT**
Gynaecological oncology (8 yrs)	20	20	60	No
Gynaecological oncology (15 yrs)	70	90	60	No
Radiology (10 yrs)	NA	NA	NA	NA
Radiology (20 yrs	NA	NA	NA	NA
Obstetrics and Gynaecology (SPR) (5 yrs)	30	60	10	*1 yr.* *"To decide on treatment planning: Need surgery?"*
Gynaecological oncology (5 yrs)	10	80	10	*4 yrs.* *"To decide on treatment planning: Prior to exenteration"*
Gynaecological oncology (21 yrs)	NS	NS	NS	No
Not reported (7 yrs)	*"depends on symptoms...MRI 100% if pelvic symptoms"*			3 yrs. *"To exclude distant recurrence in patients with proven local recurrence"*
Gynaecological oncology (10 yrs as a consultant)	50	30	30	5 yrs. *"Patients undergoing primary chemoradiation to determine extent of any lymphadenopathy. Patients with local recurrence after surgery prior to chemoradioation to determine extent of lymphadenopathy. Prior to consideration of exenteration"*
Gynaecological oncology (15 yrs)	70	30	0	3 yrs. *"Isolated central pelvic recurrence to confirm no metastatic disease prior to exenteration"*
Gynaecological oncology (3 yrs as a consultant)	10	90	0	3 yrs. *"To clarify nature of lesions seen on CT or MRI and to rule out other sites of disease if further surgey contemplated."*
Gynaecological oncology (15 yrs)	25	50	25	2 yrs. *"Suspected recurrence. Consideration for exenterative surgery."*
Gynaecological oncology (10 years)	10	80	10	3 yrs *"If recurrence suspected on the basis of clinical examination / CT / MRI."*
Gynaecological oncology (28 years)	100	0	0	*"Assessment of multiple site recurrence"*
Gynaecological oncology (5 yrs)	20	30	50	2 yrs *"Pre-exenteration or if biopsy difficult / inconclusive"*
Gynaecological oncology (3 yrs as a consultant)	60	10	30	3 yrs *"After initial imaging to determine*

				suitability for radical salvage treatment to help exclude occult distant mets"
Oncology (NS)	20	60	20	3 yrs *"? local recurrence where MRI cannot differentiate between recurrence and effects of radiotherapy.* *Proven local recurrence for staging prior to exenteration"*
Gynaecological oncology (34 yrs)	0	90	10	8 yrs *"Those with advanced disease or recurrent disease. Those requiring surgery following radiotherapy or chemoradiation."*
Gynaecological oncology (3 yrs)	20	20	60	1 yr *"If CT/MRI positive for central recurrence and considering exenteration as a management option"*
Gynaecological oncology (30 yrs)	30	50	20	3 yrs *"If further treatment is being considered - especially exenteration"*
Gynaecological oncology (30 yrs)	30	40	30	3 yrs *"Exenteration candidates.Equivocal CT/MRI "*
All respondents were consultants in their discipline with the exception of one specialist registrar (SPR). Both Consultants in Radiology had experience in PET-CT but declined to comment on requests for imaging based on clinical scenarios *Years of experience were variably reported as years practising in a discipline or years practising as a consultant. Where respondents clarified this it is indicated in the table. NS: not stated				

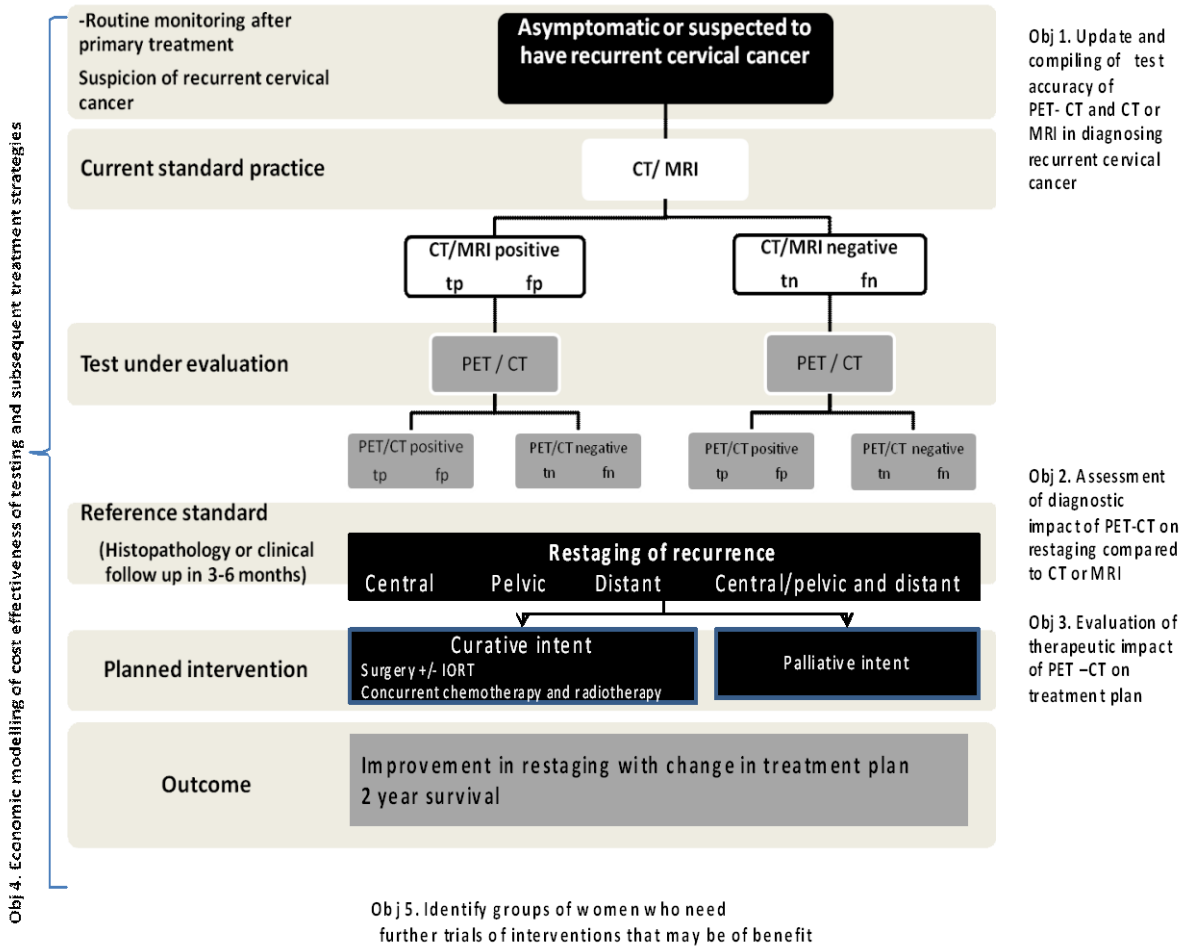
Appendix S1. Questionnaire for Subjective elicitation of probabilities

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 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 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)**