Ontario
Cancer Care Ontario
Action Cancer Ontario

PET Recommendation Report 6

PET Imaging in Cervical Cancer

A Fyles and C Walker-Dilks

Report Date: January 19, 2009

PET Recommendation Report 6 is comprised of 2 sections and is available on the CCO Web site (https://www.cancercare.on.ca)
PEBC PET Recommendation Reports page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/petrecs/

Section 1: Recommendations
Section 2: Evidentiary Base

For further information about this report, please contact:

Dr. Anthony Fyles,
Princess Margaret Hospital, 610 University Avenue, Toronto,
Ontario, Canada M5G 2M9
Telephone (416) 946-6522; Fax (416) 946-2111; Email anthony.fyles@rmp.uhn.on.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

Citation (Vancouver Style): Fyles A, Walker-Dilks C. PET Imaging in cervical cancer. Toronto (ON): Cancer Care Ontario; 2009 Jan 19. Program in Evidence-based Care PET Recommendation Report No.: 6.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Recommendation Report – PET #6: Section 1

PET Imaging in Cervical Cancer: Recommendations

A Fyles and C Walker-Dilks

Report Date: January 19, 2009

QUESTIONS

- What benefit to clinical management does positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) contribute to the diagnosis or staging of cervical cancer?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for cervical cancer?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of cervical cancer is suspected but not proven?
- What benefit to clinical management does PET or PET/CT contribute to restaging at the time of documented recurrence for cervical cancer?
- What is the role of PET when a solitary metastasis is identified at the time of recurrence and a metastectomy is being contemplated?

TARGET POPULATION

Patients with cervical cancer.

INTENDED PURPOSE

- This recommendation report is primarily intended to guide the Ontario PET Steering Committee in their decision making concerning indications for the use of PET imaging.
- This recommendation report may also be useful in informing clinical decision making regarding the appropriate role of PET imaging and in guiding priorities for future PET imaging research.

RECOMMENDATIONS AND KEY EVIDENCE

These recommendations are based on an evidentiary foundation consisting of one recent high-quality systematic review from the U.S. Agency for Health Research and Quality (AHRQ) (1) that included primary study literature for the period from 2003 to March 2008.

Diagnosis/Staging

PET is not recommended for diagnosis of cervical cancer.
PET is not recommended for staging early stage cervical cancer.
A recommendation cannot be made for or against the use of PET for staging advanced stage cervical cancer due to insufficient evidence. However, ongoing studies will clarify the role of PET in advanced disease.
Multiple prospective and retrospective clinical trials have evaluated the diagnostic accuracy of PET or PET/CT for determining involvement of pelvic and para-aortic nodes compared to surgical staging or CT/magnetic resonance imaging (MRI). A 2008 meta-analysis by Selman et al (2) on diagnostic tests for lymph node status in cervical cancer included seven studies on PET. Of the seven studies, two were included in the Alberta 2008 AHRQ review (1), and five were included in the Duke University AHRQ review (3). In pooled estimates of test prediction of lymph node status, PET was inferior to sentinel node biopsy, but superior to MRI and CT. Selman et al (2) also compared post-test probabilities of PET in early versus (vs.) advanced disease and showed PET to perform well in advanced disease compared with early disease. For the staging workup of patients with cervical cancer who are potential candidates for curative therapy, there is insufficient evidence to indicate that PET benefits clinical management by improving the accuracy of staging for nodal and metastatic disease, particularly in women with early disease treated surgically. One trial (Bjurberg et al [4]) demonstrated a change in management (i.e., change in radiation fields or conversion from curative to palliative intent) in four of 17 (24%) women with locally advanced disease, due to the identification of new metastases on PET/CT. The impact on treatment outcome is not clear, and for women with advanced disease treated with chemoradiation, further (ideally randomized) trials evaluating clinical impact are needed.

Qualifying Statements

- Most cervix cancers take up fluorodeoxyglucose (FDG) and are easily visualized on PET scan; however, as biopsy is needed for the diagnosis, there is little benefit to clinical management in using PET for assessment of the primary tumour.
- The impact of the detection of otherwise occult metastases of uncertain biology is unknown. In addition, although detection of metastases may render treatment palliative in intent, patients should not be deprived of aggressive chemoradiation to achieve pelvic control and optimal palliation.

Assessment of Treatment Response

PET is not recommended (following or early during therapy) for the purpose of predicting response to chemoradiation therapy.
Studies have demonstrated that chemo-radiation responders (defined at various times after treatment) have a better outcome than those with partial response or new development of metastases (Schwarz et al [5]). This is not surprising, and since salvage treatment of poor responders is unlikely to be effective, the clinical impact of using PET for response assessment remains to be determined.

Qualifying Statement

None.

Recurrence/Restaging

A recommendation cannot be made for or against the use of PET for evaluation of suspected recurrence, due to insufficient evidence.
Several trials have evaluated PET in women without clinical evidence of recurrence but with elevated serum SCC antigen. Chang et al (6) included 27 patients with elevated SCC-Ag levels but no evidence of recurrent disease. PET results were positive in 19 patients, only two of whom had local recurrence alone. Two patients had false-positive PET studies on further investigation and follow up. For women with clinical or imaging suspicion of recurrence, PET will only be of use in those with salvageable disease in the pelvis or regional nodes, and the clinical impact of PET in this situation is unknown.

Qualifying Statement

None.

PET is recommended for women with recurrence who are candidates for pelvic exenteration or chemoradiation with curative intent.
Several studies have demonstrated significant changes in management in women with documented recurrent disease. In 12 patients with histologically confirmed relapsed disease (Bjurberg et al [4]), the treatment strategy was changed in three patients (25%). Lai et al (7) included 40 patients with documented recurrent or persistent cervical carcinoma after definitive radiotherapy or surgery and potentially curable disease. Fifteen of 40 women (37.5%) were spared futile curative treatment, and in seven, curative treatment was continued but the treatment field or modality was changed following the demonstration of metastases on PET scan. Maximizing risk benefit ratios and avoiding the morbidity of major surgery is a meaningful endpoint in this admittedly small group of women. Schwarz et al (5) (cited in the AHRQ report but not in data tables) showed that three-month posttherapy PET results provided an indication of response to treatment and were predictive of survival.

Qualifying Statement

None.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Contact Information
For further information about this report, please contact:

Dr. Anthony Fyles, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario Canada M5G 2M9, telephone (416) 946-6522, fax (416) 946-2111, email anthony.fyles@rmp.uhn.on.ca

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

REFERENCES

1. McEwan AJ, Gulenchyn K, Ospina M, Horton J, Seida J, Vandermeer B, et al. Positron emission tomography for nine cancers (bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small cell lung, testicular). Rockville, Maryland: Agency for Healthcare Research and Quality; August 2008. Draft.
2. Selman TJ, Mann C, Zamora J, Appleyard TL, Khan K. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. CMAJ. 2008 Mar 25;178(7):855-62.
3. Matchar DB, Kulasingam SL, Havrilesky L, Mann LO, Myers ER, McCrory DC, et al. Positron emission tomography for six cancers (brain, cervical, small cell lung, ovarian, pancreatic, and testicular). Rockville, Maryland: Agency for Healthcare Research and Quality; 2004 Feb [cited 2009 Jan 19]. Available from: http://www.cms.hhs.gov/mcd/viewtechassess.asp?where=search&tid=21
4. 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(11):1385-91. Epub 2007 Sep 4.
5. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. JAMA. 2007 Nov 21;298(19):2289-95.
6. Chang TC, Law KS, Hong JH, Lai CH, Ng KK, 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 Jul 1;101(1):164-71.
7. Lai CH, Huang KG, See LC, Yen TC, Tsai CS, Chang TC, et al. Restaging of recurrent cervical carcinoma with dual-phase [18F]fluoro-2-deoxy-D-glucose positron emission tomography. Cancer. 2004 Feb 1;100(3):544-52.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Recommendation Report – PET #6: Section 2

PET Imaging in Cervical Cancer: Evidentiary Base and Consensus Process

A Fyles and C Walker-Dilks

Report Date: January 19, 2009

QUESTIONS

- What benefit to clinical management does positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) contribute to the diagnosis or staging of cervical cancer?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for cervical cancer?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of cervical cancer is suspected but not proven?
- What benefit to clinical management does PET or PET/CT contribute to restaging at the time of documented recurrence for cervical cancer?
- What is the role of PET when a solitary metastasis is identified at the time of recurrence and a metastectomy is being contemplated?

INTRODUCTION

The Ontario PET Steering Committee made a special request to the Clinical Council of Cancer Care Ontario to co-lead the development of guidance regarding the clinical uses of PET imaging. The Program in Evidence-based Care (PEBC), working together with PEBC Disease Site Groups (DSGs), synthesized the clinical research and drafted recommendations for 10 disease sites. Recommendations for the use of PET in colorectal cancer, esophageal cancer, head and neck cancer, and melanoma were reviewed at a consensus meeting on 19 September 2008, and recommendations for the use of PET in brain, ovarian, cervical, testicular, small-cell lung, and pancreatic cancer were reviewed at a consensus meeting on 25 November 2008.

METHODS

Overview

In order to develop the recommendations and achieve consensus, a three-step methodology was undertaken.

Step 1 – Systematic review. A systematic review of the published literature was undertaken (see details below). This was conducted by one clinical lead author,

nominated by the PEBC Gynecology (GYN) DSG and a PEBC methodologist. The systematic review served as the evidentiary foundation for a set of draft recommendations developed by this team.

Step 2 – Consensus by the PEBC GYN DSG. The draft recommendations were refined during a DSG teleconference. The GYN DSG is comprised of gynecologic, medical, and radiation oncologists and supported by a PEBC research methodologist.

Step 3 – Provincial PET imaging consensus meeting. The draft recommendations were vetted at a larger provincial PET imaging consensus meeting co-hosted by Cancer Care Ontario and the Provincial PET Steering Committee. The meeting was facilitated and supported by members of the PEBC team. Participants included representatives of the PEBC DSGs, other clinical experts in the areas of nuclear and diagnostic medicine, members of the Cancer Care Ontario clinical leadership team, and representatives from the Ontario PET Steering Committee and the Ontario Health Technology Assessment Committee.

The systematic review and companion recommendations are intended to promote evidence-based decisions in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

SYSTEMATIC REVIEW

Literature Search

The PEBC was aware of a technology assessment being produced by the University of Alberta Evidence-based Practice Center for the U.S. Agency for Healthcare Research and Quality (AHRQ) evaluating the use of PET imaging in nine cancers (1) (referred to as the AHRQ review from this point forward). This review updated a previous AHRQ report produced by Duke University in 2004 (2). The Alberta update included individual primary studies dating from 2003 to March 2008 on six of the 10 cancer sites targeted by this project. Because the AHRQ review sufficiently covered the questions and methodologies of interest to this recommendation report, a draft of the AHRQ review was made available to the PEBC, and its results were used for the evidentiary base.

Study Selection Criteria

All primary studies in the AHRQ review that addressed the questions of interest in this recommendation report (diagnosis, staging, treatment response, recurrence, and restaging) were included.

The inclusion criteria for primary studies included in the AHRQ review were:

- prospective or retrospective clinical study evaluating the use of FDG PET or FDG PET/CT in primary cancer;
- study not duplicated or superseded by a later study with the same purpose from the same institution;
- study reported numeric data on at least one objective outcome of interest for the key questions of the technology assessment (diagnostic performance, treatment decisions and management strategy, changes in therapy, patient-centred outcomes, and economic outcomes);
- study included ≥ 12 patients with the cancer of interest;
- study used a suitable reference standard (pathological confirmation and clinical follow-up) when appropriate.

Synthesizing the Evidence

In some cases where sufficient evidence existed, meta-analyses were included with pooled likelihood ratios. The AHRQ review included evidence tables that summarized the characteristics and results of each study according to the outcomes the study addressed. For diagnostic performance, the evidence tables recorded details on the source of the publication and the evidence grade, study design, patient characteristics, PET technical characteristics, criteria for interpretation, and results. In addition to the diagnostic performance of PET, the AHRQ review also sought to evaluate PET in terms of its impact on physician decision making approaches to diagnosis and management (referred to as diagnostic thinking) and its impact as part of a management strategy to improve patient-centred outcomes (referred to as management strategy). Full text and data extractions of the studies were provided to the clinical lead author to aid in the formulation of the recommendations. Telephone conferences and email correspondence between the clinical lead and the PEBC methodologist took place to clarify details and answer questions.

CONSENSUS

DSG Consensus Process

The clinical lead author wrote summaries of the key evidence, draft recommendations, and qualifying statements for the questions pertaining to diagnosis/staging, assessment of treatment response, and recurrence/restaging. The ensuing documents were circulated to all members of the GYN DSG and discussed during a teleconference. The recommendations that were generated during this process are referred to below as the DRAFT DSG Recommendations. The intent of these recommendations was to guide discussion at the consensus meeting.

Provincial Consensus Process

The consensus meeting on 25 November 2008 was conducted as follows:

- Presentations by each of the clinical lead authors on the DRAFT DSG recommendations and supporting evidence were made to the meeting participants.
- The recommendations were refined by the large group, and in some cases a revised recommendation was proposed resulting in a FINAL recommendation.
- The participants voted on the FINAL recommendations to indicate their extent of agreement on a scale from 1 to 7 (1 indicating strong agreement, 5 indicating no agreement or disagreement, and 7 indicating strong disagreement).

RESULTS

Literature Search Results

The AHRQ review results for cervical cancer included 35 primary studies. Data from the evidence tables are summarized in Appendix 1. In addition to data for diagnostic performance, summaries of results for diagnostic thinking and management strategy are also presented where they apply. The key evidence is described below in an abbreviated fashion.

Key Evidence

Diagnosis/Staging

- Multiple prospective and retrospective clinical trials have evaluated the diagnostic accuracy of PET or PET/CT for determining involvement of pelvic and para-aortic nodes compared to surgical staging or CT/MR imaging. A 2008 meta-analysis by Selman et al (3) on diagnostic tests for lymph node status in cervical cancer included 7 studies on PET. Of the seven studies, twp were included in the Alberta 2008 AHRQ review (1), and five were included in the Duke University 2004 AHRQ review (2). In pooled estimates of test

prediction of lymph node status, PET was inferior to sentinel node biopsy, but superior to MRI and CT. Selman et al (3) also compared post-test probabilities of PET in early vs. advanced disease and showed PET to perform well in advanced disease compared with early disease.

- For the staging workup of patients with cervical cancer who are potential candidates for curative therapy, there is insufficient evidence to indicate that PET benefits clinical management by improving the accuracy of staging for nodal and metastatic disease, particularly in women with early disease treated surgically. One trial (Bjurberg et al [4]) demonstrated a change in management (i.e., change in radiation fields, or conversion from curative to palliative intent) in four of 17 (24%) women with locally advanced disease, due to identification of new metastases on PET/CT. The impact on treatment outcome is not clear, and for women with advanced disease treated with chemo-radiation, further (ideally randomized) trials evaluating clinical impact are needed.

Assessment of Treatment Response

- Studies have demonstrated that chemoradiation responders (defined at various times after treatment) have a better outcome than those with partial response or new development of metastases (Schwarz et al [5]). This is not surprising, and since salvage treatment of poor responders is unlikely to be effective, the clinical impact of using PET for response assessment remains to be determined.

Recurrence/Restaging

- Several trials have evaluated PET in women without clinical evidence of recurrence but with elevated serum SCC antigen. Chang et al (6) included 27 patients with elevated SCC-Ag levels but no evidence of recurrent disease. PET results were positive in 19 patients, only two of whom had local recurrence alone. Two patients had false-positive PET studies on further investigation and follow-up.
- For women with clinical or imaging suspicion of recurrence, PET will only be of use in those with salvageable disease in the pelvis or regional nodes, and the clinical impact of PET in this situation is unknown.
- Several studies have demonstrated significant changes in management in women with documented recurrent disease. In 12 patients with histologically confirmed relapsed disease (Bjurberg et al [4]), the treatment strategy was changed in three patients (25%).
- Lai et al (7) included 40 patients with documented recurrent or persistent cervical carcinoma after definitive radiotherapy or surgery and potentially curable disease. Fifteen of 40 women (37.5%) were spared futile curative treatment, and in seven, curative treatment was continued but treatment field or modality was changed following the demonstration of metastases on PET scan. Maximizing risk benefit ratios and avoiding the morbidity of major surgery is a meaningful endpoint in this admittedly small group of women.
- Schwarz et al (5) (cited in the AHRQ report but not in data tables) showed that three-month posttherapy PET results provided an indication of response to treatment and were predictive of survival.

RECOMMENDATIONS
DIAGNOSIS/STAGING
Clinical Question
What benefit to clinical management does PET or PET/CT contribute to the diagnosis or staging of cervical cancer?

DRAFT DSG Recommendations
a) PET is not recommended for the diagnosis of cervical cancer.
b) PET is not recommended for staging early-stage cervical cancer.
c) A recommendation cannot be made for or against the use of PET for staging advanced-stage cervical cancer, due to insufficient evidence. However, ongoing studies will clarify the role of PET in advanced disease.

Provincial Consensus Meeting Deliberations

No major issues were raised during discussion of these recommendations. Whether brachytherapy would still be done was questioned, and the response was yes, for local control if the woman was healthy and otherwise fit.

FINAL Recommendation Put to Vote
a) PET is not recommended for the diagnosis of cervical cancer.

	1 – Strongly Agree		4 – Neither Agree nor Disagree			7 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	
Total	17	4			1			

Votes = 21

FINAL Recommendation Put to Vote
b) PET is not recommended for staging early-stage cervical cancer.

	1 – Strongly Agree		4 – Neither Agree nor Disagree			7 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	
Total	14	6	1					

Votes = 21

FINAL Recommendation Put to Vote
c) A recommendation cannot be made for or against the use of PET for staging advanced-stage cervical cancer due to insufficient evidence. However, ongoing studies will clarify the role of PET in advanced disease.

	1 – Strongly Agree		4 – Neither Agree nor Disagree			7 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	
Total	11	6	3	1				

Votes = 21

Qualifying Statements
- Most cervix cancers take up FDG and are easily visualized on PET scan; however, as biopsy is needed for the diagnosis, there is little benefit to clinical management in using PET for the assessment of the primary tumour.

- The impact of the detection of otherwise occult metastases of uncertain biology is unknown. In addition, although detection of metastases may render treatment palliative in intent, patients should not be deprived of aggressive chemoradiation to achieve pelvic control and optimal palliation.

ASSESSMENT OF TREATMENT RESPONSE

Clinical Question

What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for cervical cancer?

DRAFT DSG Recommendation

PET is not recommended (following or early during therapy) for the purpose of predicting response to chemoradiation therapy.

Provincial Consensus Meeting Deliberations

No major issues were raised during the discussion about this recommendation.

FINAL Recommendation Put to Vote:

PET is not recommended (following or early during therapy) for the purpose of predicting response to chemoradiation therapy.

	1 – Strongly Agree		4 – Neither Agree nor Disagree			7 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	
Total	11	7	1	2				

Votes = 21

Qualifying Statement

None.

RECURRENCE/RESTAGING

Clinical Question

What benefit to clinical management does PET or PET/CT contribute when recurrence of cervical cancer is suspected but not proven? What benefit to clinical management does PET or PET/CT contribute to restaging at the time of documented recurrence for cervical cancer?

DRAFT DSG recommendation

A recommendation cannot be made for or against the use of PET for evaluation of suspected recurrence, due to insufficient evidence.

Provincial Consensus Meeting Deliberations

No major issues were raised during the discussion of this recommendation.

FINAL Recommendation Put to Vote

A recommendation cannot be made for or against the use of PET for evaluation of suspected recurrence due to insufficient evidence.

	1 – Strongly Agree			5 – Neither Agree nor Disagree				9 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	8	9	
Total	8	10	2		1					

Votes = 21

Qualifying Statement

None.

DRAFT DSG Recommendation

PET is recommended for women with pelvic recurrence who are candidates for pelvic exenteration or pelvic chemoradiation.

Provincial Consensus Meeting Deliberations

During group discussion, the issue was raised about the value of PET in patients who recur in the paraaortic region rather than in the pelvis. The Schwarz et al study (5) was cited as indicating that early detection of paraaortic recurrence leads to positive effects on clinical outcomes. Although the evidence is based on a single study, the group agreed that PET should not be limited to only pelvic recurrence.

FINAL Recommendation Put to Vote

PET is recommended for women with recurrence who are candidates for pelvic exenteration or chemoradiation with curative intent.

	1 – Strongly Agree			5 – Neither Agree nor Disagree				9 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	8	9	
Total	13	7	1							

Votes = 21

Issues raised on voting questionnaire:

-This is uncommon, like with SCLC and pancreas “curative” recurrence.

Qualifying Statement

None.

Solitary Metastasis Identified at Time of Recurrence

Clinical Question

What is the role of PET when a solitary metastasis is identified at the time of recurrence and a metastectomy is being contemplated?

This question was not addressed in the cervical evidence review.

FUTURE RESEARCH

Areas for future research were not discussed in the process of drafting these recommendations.

ACKNOWLEDGEMENTS

The GYN DSG would like to thank Dr. Anthony Fyles for taking the lead in drafting this systematic review.

For a complete list of the Gynecology DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Contact Information

For further information about this report, please contact:

Dr. Anthony Fyles, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario Canada M5G 2M9, telephone (416) 946-6522, fax (416) 946-2111, email anthony.fyles@rmp.uhn.on.ca

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

REFERENCES

1. McEwan AJ, Gulenchyn K, Ospina M, Horton J, Seida J, Vandermeer B, et al. Positron emission tomography for nine cancers (bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small cell lung, testicular). Rockville, Maryland: Agency for Healthcare Research and Quality; August 2008. Draft.
2. Matchar DB, Kulasingam SL, Havrilesky L, Mann LO, Myers ER, McCrory DC, et al. Positron emission tomography for six cancers (brain, cervical, small cell lung, ovarian, pancreatic, and testicular). Rockville, Maryland: Agency for Healthcare Research and Quality; 2004 Feb [cited 2009 Jan 19]. Available from: http://www.cms.hhs.gov/mcd/viewtechassess.asp?where=search&tid=21
3. Selman TJ, Mann C, Zamora J, Appleyard TL, Khan K. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. CMAJ. 2008 Mar 25;178(7):855-62.
4. 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(11):1385-91. Epub 2007 Sep 4.
5. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. JAMA. 2007 Nov 21;298(19):2289-95.
6. Chang TC, Law KS, Hong JH, Lai CH, Ng KK, 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 Jul 1;101(1):164-71.
7. Lai CH, Huang KG, See LC, Yen TC, Tsai CS, Chang TC, et al. Restaging of recurrent cervical carcinoma with dual-phase [18F]fluoro-2-deoxy-D-glucose positron emission tomography. Cancer. 2004 Feb 1;100(3):544-52.
8. Chang YC, Yen TC, Ng KK, See LC, Lai CH, Chang TC, 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(6):647-52.
9. Amit A, Beck D, Lowenstein L, Lavie O, Bar Shalom R, Kedar Z, et al. The role of hybrid PET/CT in the evaluation of patients with cervical cancer. Gynecol Oncol 2006;100(1):65-9.
10. Choi HJ, Roh JW, Seo SS, Lee S, Kim JY, Kim SK, 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(4):914-22.
11. Chou HH, Chang TC, Yen TC, Ng KK, 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(1):123-8.
12. Hope AJ, Saha P, Grigsby PW. FDG-PET in carcinoma of the uterine cervix with endometrial extension. Cancer 2006;106(1):196-200.
13. 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(1):73-6.
14. 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(1):29-34

15. Ma SY, See LC, Lai CH, Chou HH, Tsai CS, Ng KK, et al. Delayed (18)F-FDG PET for detection of paraaortic lymph node metastases in cervical cancer patients. J Nucl Med 2003;44(11):1775-83
16. 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(5):260-4.
17. Roh JW, Seo SS, Lee S, Kang KW, Kim SK, 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(14):2086-92.
18. 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(1):272-9.
19. 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(3):572-6.
20. Unger JB, Ivy JJ, Ramaswamy MR, Charrier A, Connor P. Whole-body [18F]fluoro-2-deoxyglucose positron emission tomography scan staging prior to planned radical hysterectomy and pelvic lymphadenectomy. Int J Gynecological Cancer 2005;15(6):1060-4.
21. Wright JD, Dehdashti F, Herzog TJ, Mutch DG, Huettner PC, Rader JS, et al. Preoperative lymph node staging of early-stage cervical carcinoma by [18F]-fluoro-2-deoxy-D-glucose-positron emission tomography. Cancer 2005;104(11):2484-91.
22. Yen TC, Ng KK, Ma SY, Chou HH, Tsai CS, Hsueh S, et al. Value of dual-phase 2-fluoro-2-deoxy-d-glucose positron emission tomography in cervical cancer.[erratum appears in J Clin Oncol. 2004 Jan 1;22(1):209]. J Clin Oncol 2003;21(19):3651-8.
23. 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(1):154-9.
24. Chang WC, Hung YC, Lin CC, Shen YY, Kao CH. Usefulness of FDG-PET to detect recurrent cervical cancer based on asymptomatically elevated tumor marker serum levels: a preliminary report. Cancer Invest 2004;22(2):180-4.
25. Chung HH, Jo H, Kang WJ, Kim JW, Park NH, Song YS, et al. Clinical impact of integrated PET/CT on the management of suspected cervical cancer recurrence. Gynecol Oncol 2007;104(3):529-34.
26. Chung HH, Kim SK, Kim TH, Lee S, Kang KW, Kim JY, et al. Clinical impact of FDG-PET imaging in post-therapy surveillance of uterine cervical cancer: from diagnosis to prognosis. Gynecol Oncol 2006;103(1):165-70.
27. 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(1):186-90.
28. Lin CT, Yen TC, Chang TC, Ng KK, Tsai CS, Ho KC, et al. Role of [18F]fluoro-2-deoxy-D-glucose positron emission tomography in re-recurrent cervical cancer. Int J Gynecological Cancer 2006;16(6):1994-2003.
29. Ryu SY, Kim MH, Choi SC, Choi CW, Lee KH. Detection of early recurrence with 18F-FDG PET in patients with cervical cancer. J Nucl Med 2003;44(3):347-52.
30. 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(3):601-7.
31. Sironi S, Picchio M, Landoni C, Galimberti S, Signorelli M, Bettinardi V, et al. Post-therapy surveillance of patients with uterine cancers: value of integrated FDG PET/CT in the detection of recurrence. Eur J Nucl Med Mol Imaging 2007;34(4):472-9.

32. 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(1):212-6.
33. Van Der Veldt AAM, 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(12):1408-16.
34. Yen TC, Lai CH, Ma SY, Huang KG, Huang HJ, Hong JH, 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(12):1399-407.
35. Yen TC, See LC, Chang TC, Huang KG, Ng KK, Tang SG, et al. Defining the priority of using 18F-FDG PET for recurrent cervical cancer. J Nucl Med 2004;45(10):1632-9.
36. Grisaru D, Almog B, Levine C, Metser U, Fishman A, Lerman H, et al. The diagnostic accuracy of 18F-Fluorodeoxyglucose PET/CT in patients with gynecological malignancies. Gynecol Oncol 2004;94(3):680-4.
37. 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(1):55-62.

Appendix 1. PET for cervical cancer: summary of the evidence from 2003 to March 2008.

CERVICAL Diagnostic performance						
Citation (ref #)	Study design	PET imaging	Reference std	Sens	Spec	Evid grade
Primary diagnosis and recurrence						
Chang 2005 (8)	Prospective	PET	Hist/bx or clin fup	Met lesns 92% 1° tum/ loc rec 88% All lesns 91%	Met lesns 98% 1° tum/ loc rec 100% All lesns 98%	B
Staging						
Amit 2006 (9)	Prospective	PET/CT	Hist/bx or clin fup	60%	94%	B
Choi 2006 (10)	Prospective	PET/CT	Hist/bx	57%	92%	B
Chou 2006 (11)	Prospective	PET	Hist/bx	10%	94%	B
Hope 2006 (12)	Prospective	PET	Hist/bx	69%	76%	B
Lin 2003 (13)	Prospective	PET	Hist/bx	86%	94%	B
Loft 2007 (14)	Prospective	PET/CT	Hist/bx or clin fup	100%	88%	A
Ma 2003 (15)	Prospective	PET	Hist/bx & imag fup	82%	97%	B
Park 2005 (16)	Retrospective	PET	Hist/bx	43%	100%	C
Roh 2005 (17)	Prospective	PET	Hist/bx	40%	97%	B
Sironi 2006 (18)	Prospective	PET/CT	Hist/bx	72%	99%	A
Tran 2003 (19)	Retrospective	PET	Hist/bx	100%	100%	C
Unger 2005 (20)	Retrospective	PET	Hist/bx	29%	100%	C
Wright 2005 (21)	Retrospective	PET & PET/CT	Hist/bx	Pelvic LN met 52% Paraaort LN met 25%	Pelvic LN met 90% Paraaort LN met 97%	C
Yen 2003 (22)	Prospective	PET	Hist/bx or clin fup	92%	99%	B
Yildirim 2008 (23)	Prospective	PET/CT	Hist/bx	50%	83%	B
Recurrence						
Chang 2004 (6)	Prospective	PET	Hist/bx or clin fup	Local 88% Dist 100%	Local 50% Dist 100%	B
Chang 2004 (24)	Retrospective	PET	Hist/bx or clin fup	Local 88% Dist 100%	Local 50% Dist 100%	C
Chung 2007 (25)	Retrospective	PET/CT	Hist/bx or clin fup	90%	81%	C
Chung 2006 (26)	Retrospective	PET	Hist/bx or clin fup	96%	84%	C
Havrilesky 2003 (27)	Retrospective	PET	Hist/bx	85%	86%	C
Lin 2006 (28)	Prospective	PET	Hist/bx or clin fup	Peritoneum 57% Bone 50% Liver/spleen 100% Lung 75% Mediastinal LN 100% Supraclav LN	Peritoneum 89% Bone 96% Liver/spleen 100% Lung 100% Mediastinal LN 88% Supraclav LN	B

				75% Paraaort LN 90% Pelvic LN 50%	95% Paraaort LN 94% Pelvic LN 100%	
Ryu 2003 (29)	Retrospective	PET	Hist/bx or clin fup	90%	76%	C
Sakurai 2006 (30)	Prospective	PET	Hist/bx	91%	57%	D
Sironi 2007 (31)	Prospective	PET/CT	Hist/bx or clin fup	83%	100%	B
Unger 2004 (32)	Retrospective	PET	Hist/bx or clin fup	Asympt women 80% Sympt women 100%	Asympt women 100% Sympt women 100%	C
Van der Veldt 2006 (33)	Retrospective	PET	Hist/bx or clin fup	96%	100%	C
Yen 2006 (34)	Prospective	PET	Hist/bx or clin fup	Peritoneum 65% Bone 100% Liver/spleen 67% Lung 92% Mediastinal LN 100% Supraclav LN 81% Paraaort LN 88% Pelvic LN 83%	Peritoneum 98% Bone 97% Liver/spleen 99% Lung 97% Mediastinal LN 96% Supraclav LN 98% Paraaort LN 99% Pelvic LN 98%	B
Yen 2004 (35)	Prospective	PET	Hist/bx or clin fup	Peritoneum 88% Bone Not calc Liver/spleen 100% Lung 78% Mediastinal LN 100% Supraclav LN 85% Paraaort LN 88% Pelvic LN 91%	Peritoneum 96% Bone 98% Liver/spleen 98% Lung 100% Mediastinal LN 98% Supraclav LN 98% Paraaort LN 100% Pelvic LN 98%	B
Restaging						
Lai 2004 (7)	Prospective	PET	Hist/bx or clin fup	91%	98%	C
Staging and recurrence						
Grisaru 2004 (36)	Prospective	PET	Hist/bx	Stag 100% Recur 100%	Stag 100% Recur 100%	B
Staging and restaging						
Bjurberg 2007 (4)	Prospective	PET/CT	Hist/bx or clin fup	Early dis Not calc. Loc adv 94%. Relapse 92%.	Early dis 100% Loc adv Not calc Relapse 100%	B

Wong 2004 (37)	Retrospective	PTE	Hist/bx or clin fup	Stag dist 100% Restag loc 84% Restag dist 100% Loc 89% Dist 100%	Stag dist 100% Restag loc 96% Restag dist 89% Loc 96% Dist 90%	C

Abbreviations: Asympt, asymptomatic; bx, biopsy; calc, calculated; clin, clinical; CT, computed tomography; dis, disease; Dist, distant; fup, follow up; Hist, histology; imag, imaging; lesns, lesions; LN, lymph node; loc adv, locally advanced; loc rec, local recurrence; Met, metastasis; PET, positron emission tomography; Sens, sensitivity; Spec, specificity; std, standard; Supraclav, supraclavicular; Sympt, symptomatic; tum, tumour.

Meta-analysis: Studies evaluating diagnostic performance with purpose of detecting recurrence.
Imaging: PET
Design: Prospective
Reference standard: Histology/biopsy or clinical follow-up
3 studies: Lin et al (28), Yen et al (34), Yen et al (35)

Pooled +LR
Peritoneum = 15.75
Bone = 26.56
Liver/spleen = 45.89
Lung = 33.32
Mediastinal lymph node = 15.24
Supraclavicular lymph node = 29.06
Paraaortic lymph node = 40.24
Pelvic lymph node = 41.42
Inguinal lymph node = 27.92
Pooled –LR
Peritoneum = 0.37
Bone = 0.22
Liver/spleen = 0.25
Lung = 0.22
Mediastinal lymph node = 0.09
Supraclavicular lymph node = 0.19
Paraaortic lymph node = 0.12
Pelvic lymph node = 0.23
Inguinal lymph node = 0.17

Imaging: PET
Design: Retrospective
Reference standard: Histology/biopsy or clinical follow-up
3 studies: Chung et al (26), Ryu et al (29), Unger et al (32)
Pooled +LR = 5.33
Pooled –LR = 0.11

Meta-analysis: Studies evaluating diagnostic performance with purpose of staging
Imaging: PET
Design: Prospective
Reference standard: Any reference standard
5 studies: Chou et al (11), Hope et al (12), Lin et al (13), Ma et al (15), Roh et al (17)
Pooled +LR = 8.22
Pooled –LR = 0.38

Imaging: PET
Design: Retrospective
Reference standard: Histology/biopsy or clinical follow-up
3 studies: Park et al (16), Tran et al (19), Unger et al (20)
Pooled +LR = 32.90
Pooled –LR = 0.41

Imaging: PET/CT
Design: Prospective
Reference standard: Any reference standard
3 studies: Amit et al (9), Loft et al (14), Yildirim et al (23)
Pooled +LR = 6.89
Pooled –LR = 0.28

CERVICAL Diagnostic thinking					
Citation (ref #)	Study design	PET imaging	Purpose of PET	Management decision	Evidence grade
Bjurberg2007 (4)	Prospective	PET/CT	Staging & restaging	Pts with loc adv dis: -Rx strategy changed for 4/17 pts (24%) due to id of new mets. Pts with relapsing dis: -PET did not confirm clin suspicion of recurrence. -PET deemed true –ve in fup of 3/15 pts. -Rx strategy changed for 3/12 +ve recurrence pts (25%). -Add'l dx testing in 6/12 +ve recurrence pts.	B
Chang2004 (6)	Prospective	PET	Recurrence	Rx strategy changed for 17/27 pts (63%): Curative Rx (7 pts), palliative chemo (4 pts), supportive care (6 pts). 7/13 pts (39%) with recurrence rec'd curative Rx based on PET vs 16/30 (53%) in historic control.	B
Chung2007 (25)	Retrospective	PET/CT	Recurrence	Rx strategy changed for 12/52 pts (3%): -Initiated previously unplanned Rx (4 pts). -Changed previously planned Rx approach (5 pts). -Eliminated previously planned dx procedure (3 pts). PET guided add'l invasive dx procedures.	C
Lai2004 (7)	Prospective	PET	Restaging	Rx strategy changed for 22/40 pts (55%): -From curative to palliatve Rx (15 pts). -Curative Rx cont'd, Rx field or modality changed (7 pts). Dx testing impact due to PET findings in 14 pts: -Add'l guided bx (11 pts. -Exploratory surgery (3 pts).	C
Lin2006 (28)	Prospective	PET	Recurrence	Rx strategy changed for 12/26 pts (46%): -From curative to palliative Rx (9 pts). -Isolated in field failure successfully resected (3 pts). -PET led to unnecessary & invasive procedures (4 pts).	B

				-PET stated to have overall –ve imact on mgmt (2 pts).	
Yen2004 (35)	Prospective	PET	Recurrence	Rx strategy changed for 36/55 pts (65%): -Field or modality of rad'n changed (9 pts). -From curative to palliative Rx (27 pts).	B

Abbreviations: -ve, negative; +ve, positive; clin, clinical; dis, disease; dx, diagnostic; fup, follow up; id, identification; loc adv, locally advanced; mets, metastases; PET, positron emission tomography; pts, patients; Rx, treatment.

CERVICAL Management strategy					
Citation (ref #)	Study design	PET imaging	Purpose of PET	Patient centred outcomes and prognosis	Evidence grade
Chang2004 (6)	Prospective	PET	Recurrence	Comparison groups: PET (27 pts), historical control (30 pts). Mean overall survival: PET 22 mo vs. Historical cntrl 12.7 mo (P=0.0202)	B
Lai2004 (7)	Prospective	PET	Restaging	Comparison groups: Restaged with PET (40 pts), historical cntrols restaged w/o PET (125 pts). -All pts treated with a Rx field altered post-PET remained alive (7 pts). -Pts treated with primary RT or CCRT did not differ between groups (HR 0.99, CI 0.53 to 1.85; P=0.996). -In pts treated with surgery, PET group had higher survival than historical cntrls at 2 yr (HR 0.21, CI 0.05 to 0.83; P=0.020).	C

Abbreviations: CCRT, concurrent chemotherapy and radiotherapy; CI, confidence interval; HR, hazard ratio; mo, months; PET, positron emission tomography; pts, patients; RT, radiotherapy; yr, year.