



## Guideline 4-16 Version 2 IN REVIEW

A Quality Initiative of the  
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

### Follow-up for Cervical Cancer

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An assessment conducted in November 2022 placed Guideline 4-16 Version 2 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document

[\(PEBC Assessment & Review Protocol\)](#)

Guideline 4-16 comprises 5 sections. You can access the summary and full report here:

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/476>

Section 1:	Recommendations Summary
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IN REVIEW

## Follow-up for Cervical Cancer: Recommendations Summary

### GUIDELINE OBJECTIVE

This guideline was written to provide guidance on the most appropriate follow-up strategy for patients with cervical cancer who are clinically disease-free after receiving primary treatment. This guideline is an update of a previous version, which was published in 2009. The update was initiated when the members of the Program in Evidence-Based Care (PEBC) Gynecologic Cancer Disease Site Group become aware of new publications related to follow-up for the target population. The Disease Site Group members wanted to determine whether this new evidence would result in modifications to the existing recommendations.

### TARGET POPULATION

This practice guideline applies to women who are clinically disease free and asymptomatic after receiving potentially curative primary treatment for cervical cancer. This guideline does not apply to the follow-up of women who have been treated for cervical precancer.

### INTENDED USERS

This practice guideline is for clinicians involved in the care and follow-up of women who have received treatment for cervical cancer.

**Note:** the content of these recommendations has not changed since the 2009 version of this guideline, however the evidence-base has been updated and now includes studies published up to 2014.

### RECOMMENDATIONS

- Follow-up care after primary treatment should be conducted and coordinated by a physician experienced in the surveillance of patients with cancer. Continuity of care and dialogue between the healthcare professional and patient about symptoms of recurrence may enhance and facilitate early cancer recurrence detection because the majority of women who develop a recurrence have symptoms and signs that occur outside scheduled follow-up visits.

#### Follow-up to Five Years

- A reasonable follow-up strategy involves visits at the following intervals:
  - every three to four months within the first two years,
  - every six to 12 months from years 3 to 5.
- At a minimum, follow-up visits should include a patient history and a complete physical examination.
  - Symptoms elicited during the patient history should include general performance status, lower back pain (especially if it radiates down one leg), vaginal bleeding, or unexplained weight loss. Focused imaging or testing appropriate to findings is warranted.
  - A physical examination should attempt to identify abnormal findings related to general health and/or those that suggest vaginal, pelvic sidewall, or distant recurrence. Because central pelvic recurrences are potentially curable, the physical examination should include a speculum examination with bimanual and pelvic/rectal examination. Focused imaging or testing appropriate to findings is warranted.

- If vaginal vault cytology examination is used to detect new precancerous conditions of the vagina it should be performed no more frequently than once a year. An abnormal cytology result that suggests the possibility of neoplasia warrants colposcopic evaluation and directed biopsy for histological confirmation.
- Because their role has not been evaluated in a definitive manner, the following investigations *are not advocated*:
  - Positron emission tomography (PET) with computed tomography (PET-CT),
  - Other imaging or biomarker tests in asymptomatic patients.
- Although there is evidence showing that HPV DNA testing has promise as a method of detection of recurrence after radiotherapy, data are preliminary and need verification in higher quality studies with larger sample sizes, and HPV DNA testing is currently unfunded at this time in the province of Ontario.

#### **Follow-up Beyond Five Years**

- After five years of recurrence-free follow-up:
  - Patients may return to annual assessment with a history, general physical, including pelvic examination with cervical/vaginal cytology performed by the primary care physician that is consistent with standards for well-woman care; however, some patients with treatment complications such as those related to radiotherapy may require more prolonged follow-up at the cancer centre.
  - Routine lower genital tract screening to identify new pre-invasive disease according to population-based guidelines is recommended for patients who have undergone surgical treatment. Cytological follow-up is not recommended for patients who have been treated with radiotherapy.

## Follow-up for Cervical Cancer: Guideline

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### RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

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#### Key Evidence

New evidence that met the inclusion criteria for this guideline update was identified:

##### HPV Testing

- In one study [1], HPV test results at one, three, six, and 12 months after radiotherapy were evaluated for an association with local recurrence. A positive cervicovaginal HPV DNA test result at three months had the highest sensitivity (78%), specificity (82%), and overall accuracy (82%), and was more accurate than the results of testing at one month postradiotherapy (sensitivity, 64%; specificity, 78%; accuracy, 76%), possibly due to the presence of cellular debris immediately after radiotherapy.

##### Cervicovaginal Cytology

- There is no new evidence to suggest that cervicovaginal cytology should be performed in asymptomatic patients more frequently than annually.
- One study [2] found a very low yield with continued cytology surveillance among women who had completed five years of posttreatment surveillance without a recurrence. No cases of cancer were diagnosed among 61 women included in the study population. Seventeen abnormal Papanicolaou tests were reported, which led to the performance of three diagnostic procedures, and the diagnosis and treatment of one case of vaginal dysplasia.

##### Serum Biomarkers

- The results of one study [3] indicated that elevated serum levels of squamous cell carcinoma antigen (SCC-Ag) and high-sensitivity C-reactive protein (hsCRP) were associated with increased odds of having a disease recurrence ( $p=0.003$  and  $p<0.001$ , respectively). Diagnostic accuracy of both these biomarkers combined was 0.87 (95% confidence interval [CI], 0.805 to 0.935). Seven other biomarkers tested in the same study did not add significantly to the ability to predict recurrence rates. The SCC-Ag plus hsCRP combination can be considered promising

as a biomarker for disease recurrence; however, more research is needed before it can be recommended for routine surveillance.

#### *PET-CT*

- PET-CT was evaluated in a meta-analysis [4]. The overall estimate of sensitivity was 94.8% (95% CI, 91.2% to 96.9%), and specificity was 86.9% (95% CI, 82.2% to 90.5%); however, only two of nine studies in the analysis included asymptomatic patients, which is this guideline's population of interest. The authors of this meta-analysis conclude that there is a need for a prospective study.

#### *Cytology Follow-up After Radiotherapy*

- The accuracy of cervicovaginal cytology after treatment with radiotherapy for cervical cancer is compromised by the anatomical and tissue changes resulting from irradiation [5].

#### *Summary of 2009 Evidence Base [6]:*

- Seventeen retrospective studies reported follow-up strategies for women who were disease-free after primary treatment for cervical cancer.
  - In nine studies that reported short-term data, 62% to 89% of cervical cancer recurrences were detected within two years of primary treatment. In the six studies that reported long-term data, a minimum of 89% of recurrences were detected by five years.
  - Fifteen of the 17 retrospective studies reported whether recurrences were symptomatic or asymptomatic. Approximately two-thirds of patients presented with symptoms (range, 46% to 87%), and approximately one-third of patients were asymptomatic (range, 4% to 54%).
  - Scheduled follow-up visits varied from a low of nine visits to a potential high of 28 visits over five years. Most studies followed similar intervals: follow-up visits every three to four months within the first two years, every six months for the next three years, then annually to year 10 or discharge.
  - While not consistently reported, physical examination and vaginal vault cytology were the most common follow-up tests performed across the 17 retrospective studies. A median of 52% of recurrences across the studies were detected by physical examination, and a median of 6% were detected by vaginal vault cytology.
  - Of the studies that reported on the routine use of chest x-ray, abdominal and pelvic ultrasound, PET, computed tomography, magnetic resonance imaging, intravenous pyelography, or tumour markers, the reporting was generally inconsistent, and the impact of asymptomatic recurrence detection on survival rates was not known.

#### *Qualifying Statement:*

The National Advisory Committee on Immunization issued a statement in 2012 recommending the use of a quadrivalent human papillomavirus vaccine (Gardasil, Merck Canada, Inc.) or bivalent vaccine (Cervarix™, GalaxoSmithKline, Inc.) in girls and women to protect against dysplastic lesions caused by HPV 16/18. The quadrivalent vaccine is available for females 9 to 45 years and males 9 to 26 years of age. The bivalent vaccine is available for females 10 to 25 years of age. The vaccine may be used in females even if they have had previous Papanicolaou test abnormalities (including cervical cancer), and even if they have had genital warts or a known HPV infection [7].

#### *Interpretation of Evidence*

The body of evidence for this review consisted of a small group of mostly retrospective, highly heterogeneous studies. Therefore, in general, the consensus-based recommendations from the previous version of this guideline have been endorsed in this updated version, and future research for promising methods of recurrence detection is recommended.

## UPDATING

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the Cancer Care Ontario (CCO) website at: <https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true>. Guideline history is presented in Appendix 1.

#### **FUNDING**

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

#### **CONFLICT OF INTEREST**

Information regarding conflict of interest declarations can be found at the end of Section 5.

#### *Disclaimer*

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.



## Follow-up for Cervical Cancer: Guideline Methods Overview

### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario. The PEBC's mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups in the development of various PEBC products. The Guideline Development Groups are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. PEBC guidelines include an evidence review (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through periodic review and evaluation of the scientific literature and, where appropriate, integration of that literature with the original guideline information.

### Background

This guideline was identified for updating through the PEBC Document Assessment and Review Process, which regularly assesses all documents that are older than one year. New evidence was identified through this process. The members of the PEBC Gynecologic Cancer Disease Site Group (DSG) decided to proceed with a full update of this guideline in order to determine whether the new evidence would result in changes to the recommendations.

### Guideline Developers

This guideline was developed by the Cervical Cancer Follow-up Working Group, a group organized by the PEBC at the request of the PEBC Gynecologic Cancer DSG. The group comprised individuals with expertise in gynecologic oncology, radiation oncology, radiology, and health research methodology (Appendix 2). All members contributed to the interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Individuals with conflicts of interest were generally not allowed to participate as members of the Working Group; exceptions are noted in Appendix 2.

### Guideline Development Methods

The PEBC uses the AGREE II tool as its methodological framework [8]. The key steps in the process are: a project plan, systematic methods of evidence synthesis and/or adaptation, consensus of interpretation of evidence, drafting and contextualization of recommendations, and external review of the draft guideline. The PEBC's processes and methods are described in more detail in the [PEBC Handbook](#) and the [PEBC Methods Handbook](#).

A search for existing guidelines for adaptation or endorsement was conducted using the SAGE database (cancerviewcanada.ca) (to January 2013) and the National Guidelines Clearinghouse (www.guideline.gov). This search did not yield an appropriate source document; therefore, a search of the primary literature was required (see Section 4).

The methods used to search for systematic reviews and primary literature are outlined in Section 4. Using evidence from the primary literature search, recommendations were drafted and approved by the members of the Working Group. The draft document was circulated to an independent PEBC committee for internal review and to experts in the field for external review (see Section 5). Refinements to the document were made in response to the feedback received and the final recommendations were approved by a panel of content experts - the Expert Panel. The PEBC requires that 75% of the DSG membership must cast a vote, and of those, 75% must approve the document. If suggested changes resulted in substantial alteration of the recommendations, re-approval would be required.

### **Focus**

The primary focus of this guideline is on the clinical evidence. Other features related to the implementation of the recommendations, such as costs, human resources, unique requirements for special or disadvantaged populations, and development and measurement of quality indicators are addressed by other divisions at Cancer Care Ontario.

### **Details**

- Details of the evidence base can be found in Section 4: Evidence Review.
- Details of the internal and external reviews can be found in Section 5: Internal and External Review.

### **ACKNOWLEDGEMENTS AND AUTHORSHIP**

The Gynecologic Cancer DSG and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Sheila McNair, Hans Messersmith, Bill Evans, and Rebecca Wong, for providing feedback on draft versions.
- Kristy Yiu for conducting a data audit.
- Health Research Methodologists Fulvia Baldassare and Chika Agbassi for internal peer review of the document.
- Sara Miller and Janet Rowe for copy editing.

A complete list of the members of the Guideline 4-16 Version 2 Expert Panel and Working Group, with their affiliations and conflict of interest information, is provided in Appendix 2.

## Follow-up for Cervical Cancer: Evidence Review

### INTRODUCTION

There are approximately 580 new cases and 140 deaths from cervical cancer annually in the province of Ontario [9]. Most (approximately 70% to 80%) cervical cancers are squamous cell carcinomas (SCCs), and adenocarcinomas account for 10% to 15% [10]. Depending on disease stage, treatment consists of surgery, radiation therapy, or a combination of radiation and chemotherapy [10], and the risk of recurrence ranges from 13% to 17% [11]. The majority of cases are diagnosed at International Federation of Gynecology and Obstetrics stage I or II [11], and the five-year survival rate for these women is high, i.e., 80% to 85% for stage IB disease treated with radical hysterectomy and pelvic lymphadenectomy [12]. Across disease stages, the proportion of recurrences that are asymptomatic ranges from 4% to 50% (median, 26%) [6].

In 2009, the Program in Evidence-Based Care (PEBC) published a guideline for the follow-up of patients with cervical cancer who had experienced complete response to treatment [6]. The evidence base for that guideline was developed through a systematic review of follow-up studies of patients after complete response to cervical cancer treatment. Outcomes of interest included survival rates, recurrences detected during screening, and quality of life. The search identified 17 relevant studies, but none of them were prospective studies with direct comparisons of different follow-up regimens. Thus, the evidence base was deemed to be of low quality. Nonetheless, recommendations were made by consensus of the guideline Working Group, based on what was considered to be a reasonable schedule of follow-up that would allow for the detection of asymptomatic recurrences and the possibility of curative treatment.

The 2009 guideline [6] was identified as a candidate for updating during a routine assessment as part of the PEBC Document Assessment and Review Process. New evidence was identified through this process, and the members of the PEBC Gynecologic Cancer Disease Site Group decided to proceed with a full update of this guideline to determine whether the new evidence would impact the recommendations.

The purpose of follow-up for patients who have experienced complete response to cervical cancer treatment is to assess for signs and symptoms suggestive of recurrence, and to detect recurrences that may be early or asymptomatic and amenable to treatment that will result in response or significant improvement in overall survival rate. Potentially effective treatment options are available for the 40% to 50% of recurrences that are located centrally [6], and treatments that may prolong time free of symptoms may be available for recurrences outside the pelvis.

The impact of early detection of recurrence is not known and has been somewhat controversial [6,11]; some studies have found no difference in survival rate for women with asymptomatic recurrences in stage I or II [13] and stage IB cancer [14]. However, the largest study included in the previous version of this review found that patients with recurrences detected before symptoms became evident or were reported had a significantly better median overall survival rate, presumably due to early delivery of effective treatment [15].

In characterizing the patient population the authors of the previous version of this guideline [6] found a low rate of recurrence for early stage disease, ranging from 10% to 18% across studies, and most recurrences were detected within two years of primary treatment (range across studies: 62% to 89%). Almost all recurrences occurred within five years of follow-up (range across studies: 89% to 99%).

Key findings and recommendations of the 2009 report included the following:

- Follow-up visits were recommended every three to four months within the first two years, and every six to 12 months from years 3 to 5.

- Visits that included a patient history and complete physical examination, with speculum examination and bimanual pelvic examination, were determined to be the most effective method of detecting a recurrence [16].
- Vaginal vault cytology at an interval more frequent than one year did not appear to add significantly to the detection of early disease recurrence.
- Patients were advised to return to annual population-based screening after five years of recurrence-free follow-up.
- The routine use of other radiological or biological follow-up investigations in asymptomatic patients was not recommended.

The 2009 guideline noted that areas for future research included the role of positron emission tomography combined with computed tomography (PET-CT), and the role of tumour markers, in detecting recurrence. In the course of the regular guideline review process in 2014, the members of the PEBC Gynecologic Cancer Disease Site Group became aware that new evidence had been published on these methods of detection, as well as new information on the potential for human papillomavirus (HPV) testing in this patient population. This updated version of the guideline will assess the methods to detect recurrence during follow-up examinations that were not included in the previous version of the guideline, or that had an evidence base that was underdeveloped at that time.

This systematic review and accompanying guideline attempted to locate and assess new studies, published since the previous guideline search date, that compared follow-up intervals or that investigated the potential of follow-up modalities - both those covered in the previous version of this guideline, and newer ones. These modalities included PET/CT scanning, serum biomarkers, and HPV testing.

Various studies have identified different prognostic factors that influence risk of recurrence, including HPV-16 negativity of the tumour [17], lymph vascular space invasion [18], and tumour size [19]; however, consideration of tailoring follow-up intervals to risk of recurrence is outside the scope of this guideline. Also outside the scope are the identification and treatment of other complications related to treatment for cervical cancer, and psychosocial components of follow-up, including sexual health. The goal of this systematic review and accompanying guideline is to provide the most up-to-date strategy for follow-up and surveillance of women who have experienced complete response to treatment of cervical cancer. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

## **RESEARCH QUESTION**

**What is the most appropriate follow-up strategy for patients with cervical cancer who are clinically disease free after receiving primary treatment?**

## **METHODS**

### **Literature Search Strategy**

The literature was searched using MEDLINE (OVID: November 2007 through November 18, 2014) and EMBASE (OVID: November 2007 through November 18, 2014). The search strategy is given in Appendix 3. The search for articles related to HPV testing was extended to include the years 2000 to 2006, because this term was not captured in the previous version of this guideline. The Cochrane Library, the Canadian Medical Association Infobase, and clinicaltrials.gov were searched between 2007 and 2014. Reference lists of studies deemed eligible for inclusion in the systematic review were scanned for additional citations.

### **Study Selection Criteria and Outcomes of Interest**

Studies were included if they reported follow-up strategies for patients who were clinically disease free after potentially curative treatment for cervical cancer. The Working Group first looked for existing systematic reviews of follow-up strategies or methods, then, if none were found, searched randomized controlled trials, prospective comparative cohort studies, prospective single-cohort studies, or retrospective single-cohort studies for outcomes related to follow-up practices.

For studies of follow-up interval, the members of the Working Group chose to include only prospective or retrospective studies that compared two or more distinct study groups. The Working Group members were aware in advance that it was unlikely that the search results would include randomized controlled trials.

Outcomes of interest included comparisons of overall or progression-free survival rates for different follow-up strategies. For diagnostic accuracy studies, the outcomes of interest were sensitivity, specificity, positive predictive value, negative predictive value, and hazard ratios for disease recurrence. Patient quality of life was an additional outcome of interest.

Studies were excluded from the review if they were case reports, letters, or editorials that did not report original aggregate data. Papers published in a language other than English were not considered, nor were papers that reported data on fewer than 25 patients.

### **Data Extraction and Quality Assessment**

Systematic reviews identified in the search of electronic databases were assessed using the Assessment of Multiple SysTemAtic Reviews (AMSTAR) tool [20] (The assessment for the one systematic review included in this guideline can be found in Appendix 4).

For primary studies, important characteristics of the study populations were extracted, including primary treatment type, histological type of cervical cancer, and stage of disease. Intervention and comparison under study were extracted where applicable. Determination of study quality was based on an assessment of study design, and of risk of bias. Data extraction was conducted by the project methodologist and verified by a project research assistant. All the members of the Working Group reviewed and discussed a draft of the evidence summary, and strengths and weaknesses were evaluated with the aim of characterizing the quality of the evidence base as a whole.

### **Synthesizing the Evidence**

Meta-analysis of appropriate outcomes (hazard ratios, relative risks and/or odds ratios) from randomized controlled trials or prospective comparative cohort studies was planned. However, because no studies with these designs were identified, meta-analyses were not conducted.

## **RESULTS**

A flow diagram of the literature search results is available in Appendix 5.

### **Systematic Reviews**

Three systematic reviews that met the inclusion criteria were located in the search. One was a Cochrane systematic review [21] that aimed to assess follow-up protocols for women with cervical cancer after primary treatment. This review limited inclusion of studies to randomized controlled trials. No studies met their inclusion criteria; therefore, AMSTAR was not used to assess the quality of this review, and this study was eliminated from further consideration.

The other two systematic reviews were both authored by Meads et al [4,22] and covered the role of PET-CT in detecting disease recurrence after complete response to treatment for cervical cancer, among other topics. The two reviews evaluated largely the same studies and, therefore, the more up-to-date version [20] was retained and the older review [21] was excluded from further consideration. Meads et al [4] used the QUADAS tool to assess the quality of the included diagnostic accuracy studies and found that the overall quality was poor because very little information was provided on the characteristics of study participants and studies were subject to verification bias. The results of this review, based on a search that is current to June 2013, are summarized below.

#### **Meads et al 2014 [4] (PET-CT)**

The question of whether PET-CT adds any clinical benefit to conventional imaging techniques is difficult to determine, because direct comparisons are rare [4]. Meads et al conducted a systematic review and meta-analysis of the sensitivity and specificity for detecting cervical cancer recurrence using PET-CT in addition to routine imaging (computed tomography [CT] or magnetic resonance imaging). This review rated highly on the AMSTAR tool (Appendix 4). Studies of positron emission tomography (PET) alone or where only a portion of patients received PET-CT, were excluded from the review, and CT as a stand-alone modality was also assessed to provide a comparison with PET-CT. The overall summary estimates for sensitivity and specificity of PET-CT for the detection of recurrence were 94.8% (95% confidence interval [CI], 91.2% to 96.9%) and 86.9% (95% CI, 82.2% to 90.5%), respectively (Table 2). PET-CT was more sensitive for local recurrence, compared with distant. The meta-analysis was heavily weighted by one larger study (n=276), which accounted for 55% of the total patients. In this single-institution study, 57% of patients (n=157) underwent PET-CT for surveillance [23] at a median interval of 24 months after completion of therapy. Overall, sensitivity was found to be 95% (95% CI, 88% to 98%) and specificity was 88% (95% CI, 82% to 92%). Only two of nine studies included in the Meads et al review evaluated asymptomatic cases and therefore provide information on the utility of PET-CT for our target population. Information on the number of additional cases detected by PET-CT in excess of those detected via routine screening practices is not available. The authors conclude that the use of PET-CT is currently not supported by the existing literature and recommend prospective study of this technology.

#### **Study Characteristics and Quality Assessment of Individual Studies (Tables 1a and 1b)**

No studies were found that compared one regimen of follow-up frequency with another. Six individual studies were included that assessed various methods of follow-up [1-3,24-26]. Two studies evaluated HPV deoxyribonucleic acid (DNA) testing [1,26], one study addressed the role of serum biomarkers in detecting recurrence [3] and three studies addressed the role of vaginal vault cytology [2,24,25]). No studies were found that addressed the following methods of detection that were considered in the previous version of the guideline: chest x-ray, ultrasound, PET or magnetic resonance imaging as stand-alone modalities, or intravenous pyelography. Studies were conducted in India [24,26], South Korea [1], the United States [2,25], and the Netherlands [3]. Study sample size ranged from 56 [26] to >1500 patients [24]. Most studies were retrospective and two studies followed prospective cohorts [1,26]. A variety of data sources were used, including hospital records, cancer registries, patient databases, and a biobank (for the tumour marker study) [3]. Follow-up timelines ranged from a few days [3] to over five years [2]. Funding was provided by government sources, where reported [1,26]. Outcomes of interest included measures of diagnostic accuracy, and hazard ratios for disease recurrence. The predominant histological type across studies was SCC, with a minority having adenocarcinoma or other histological types. There was wide variation across studies in types of treatment and initial stage of the patient population (Table 1b). Institutional Review Board

approval was sought and obtained in all studies.

The overall quality of the evidence base was determined to be low, based on the predominantly retrospective nature of the included studies, and the bias introduced in many studies by incomplete verification of disease status using the reference standard test.

IN REVIEW

Table 1a. Study characteristics.

	Location	Sample	Comparison groups	Study design	Data source	Years of treatment	Follow-up	Funding source	Outcomes of interest
Gupta et al, 2013 [24]	India	1566 women who had undergone hysterectomy	Cytology-positive vs. cytology-negative	Retro cohort	Samples from a tertiary care hospital	2001 to 2010	2 to 10 yrs	Not stated	Diagnostic accuracy of vault cytology with gold standard biopsy
Rimel et al [25]	United States	929	Cytology-positive vs. cytology-negative	Retro cohort	Cancer registries and patient databases	2000 to November 2009	2.5 to 118.2 mo (median: 32 mo)	Not stated	% of recurrences detected by Pap test (liquid-based cytology)
Singh et al, 2006 [26]	India	56 postradiotherapy patients with cervical cancer	Presence of HPV vs. absence and high vs. low viral load	Pro cohort	Samples taken after last radiation	1988 and 2004	Range: 5 to 224 mo	Government	Prevalence of HPV in exfoliated cells and plasma
Song et al, 2011 [1]	South Korea	156 patients with HPV-positive cervical cancer	HPV cleared vs. persistent	Pro cohort	Hospital records	July 2003 to December 2006	Range: 6 to 66 mo (median: 41 mo)	National Cancer Centre Korea	Diagnostic accuracy of HPV test, LRFS
Hoogendam et al, 2013 [3]	The Netherlands	75	9 serum biomarkers: CA-15.3, CA-125, CEA, CYFRA 21-1, hsCRP, IL-6, SCC-Ag, TNF- $\alpha$ , VEGF	Retro cohort	Biobanked samples from patients with cervical cancer	January 1988 to January 2000	7 days to 5 yrs	Not stated	Diagnostic accuracy of nine serum biomarkers. OR for recurrence
Orr et al, 2011 [2]	United States	61 postsurgery or postradiotherapy patients	Single group	Retro cohort	Tumour registry database	1990 to 2003	Median: 143 mo (after 5 yrs recurrence-free follow-up)	Not stated	Yield of cytological screening

CA-15.3=cancer antigen 15-3, CA-125=cancer antigen 125, CEA=carcinoembryonic antigen, CYFRA 21-1=cytokeratin 19-fragments, HPV=human papillomavirus, hsCRP=high-sensitivity C-reactive protein, IL-6=interleukin 6, LRFS=local relapse-free survival rate, mo=months, OR=odds ratio; Pap=Papanicolaou test, Pro=prospective, Retro=retrospective, SCC-Ag=squamous cell carcinoma antigen, TNF- $\alpha$ =tumour necrosis factor-alpha, VEGF=vascular endothelial growth factor, vs.=versus, yrs=years



Table 1b. Descriptive characteristics of follow-up studies.

Author, year [reference]	Patients, n	Primary Treatment Type (%)					Histology (%)		Stage (%)					
		Surgery	Radiotherapy	Chemoradiation	Surgery + Radiotherapy	Surgery + Chemoradiation	Squamous	Adenosquamous and Adenocarcinoma	IA	IB	IIA	IIB	III	IV
Gupta et al, 2013 [24]	1566	All had surgery combined with unspecified other treatment					"carcinoma"		Early: 34 Advanced: 66					
Rimel et al, 2011 [25]	929	40	3	42	4	11	74	26	13	55	19		11	2
Singh et al, 2006 [26]	56	--	100	--	--	--	"carcinoma"		--	11	2	36	IIIB:46	IVB:5
Song et al, 2011 [1]	156	--	13	81	--	--	91.3	8.7	--	21	56		IIIA, IIIB, IVA=18	IVB=6
Hoogendam et al, 2013 [3]	75	51	--	47	--	3	84	16	5	47	11	17	15	5
Orr et al, 2011 [2]	61	69	10	18	--	2	77	20	80			20		

## Study Outcomes

### *Serum Biomarkers*

One new study was found that assessed the use of serum biomarkers [3]. Nine markers, including cancer antigen 15.3, cancer antigen 125, carcinoembryonic antigen, cytokeratin-19 fragments, high-sensitivity C-reactive protein (hsCRP), interleukin 6, SCC antigen (SCC-Ag), tumour necrosis factor-alpha, and vascular endothelial growth factor, were assessed in individual patients using a retrospective cohort derived from a single institutional biobank. The main outcome measure was diagnostic accuracy (a combination of sensitivity and specificity). Combined testing of SCC-Ag and hsCRP yielded the highest detection rate of disease recurrence during cervical cancer follow-up. The other seven biomarkers that were evaluated did not add anything to the model.

### *Vaginal Vault Cytology*

The previous version of this guideline evaluated 13 studies that assessed vaginal vault cytology and found that very few recurrences were discovered using this method, ranging from 0% to 17% across studies. Sensitivity has previously been found to be very low for this test [27,28]. Two studies [24,25] were found in this update that addressed the value of vaginal vault cytology during follow-up within five years posttreatment. The first study [24] was a retrospective examination of the value of vaginal vault and/or cervical smears and was designed to address the utility of this method of detection in a lower resource location in a population of women who mostly presented with an advanced stage disease. Confirmatory biopsies were conducted for smears that were indicative of malignancy or were inconclusive cases. One hundred forty recurrences were detected in 1972 women who had been treated previously for gynecological malignancies. In all cases where a biopsy was conducted based on a smear malignancy, the diagnosis was confirmed (specificity of 100%); however, a confirmatory biopsy was only conducted on 72% of positive smears. Sensitivity and false-negative rates could not be calculated for this study, because negative smears were not followed up with biopsy. In total, 65.7% of the 140 women who tested positive for recurrence with cytology presented with advanced disease, mostly within two years (92.1%) of initial treatment. In nearly 24% of cases, cytology testing was the method of detection, and the other 76% of women either presented with symptoms or had vaults that were “clinically unhealthy” on examination.

The second study, reported by Rimel et al [25], evaluated the utility of liquid-based cytology in detecting recurrent cervical cancer. No data were provided on recurrences detected by other methods. Cancer recurrence was documented in 147 (15.8%) of women in the study population, with 12 cases (8.1%) detected by Papanicolaou (Pap) test. Patients treated with radiation therapy had more abnormal Pap test results compared with those treated with surgery alone. In this study, Pap surveillance appears to have led to salvage for recurrence in three of 929 (0.3%) cervical cancer survivors. In this study population, 810 Pap tests would be required to detect at least one cancer with 90% probability. Patients in the study reported by Rimel et al [25] who had been treated with radiation therapy had more abnormal Pap test results (14.8%) compared with those treated with surgery alone (8.7%).

Orr et al [2] found a very low yield with continued cytology surveillance among women who had completed five years of posttreatment surveillance without a recurrence. No cases of cancer were diagnosed among 61 women included in the study population. They considered their study results to be evidence of the futility of Pap testing in the passive surveillance period (beyond five years without recurrence). Seventeen abnormal Pap tests were reported, which led to the performance of three diagnostic procedures, and the diagnosis and treatment of one case of vaginal dysplasia.

### ***Human Papillomavirus DNA Testing***

HPV testing was included in this version of the guideline as a potentially more sensitive option than cytology for detecting disease recurrence during follow-up.

In Singh et al [26], HPV DNA was detected in 44 of 56 patients in samples taken after radiotherapy. Recurrences were detected in 14 patients. Significant association (correlation) with recurrence was observed in cases with HPV-positive exfoliated cells ( $p=0.01$ ) as well as high viral load ( $\geq 100$  pg/mL) ( $p=0.007$ ). Presence of HPV in plasma was significantly associated with its presence in exfoliated cells, viral load and recurrence. Sensitivity and specificity are provided in Table 2. The disease-free survival rate was significantly higher in patients who tested negative for plasma HPV compared with those who tested positive ( $p=0.04$ ). The authors conclude that in postradiotherapy patients with cervical cancer, high viral load in exfoliated cells as well as HPV in plasma samples could be used to identify patients at increased risk for disease recurrence and progression.

In Song et al [1], HPV test results at one, three, six, and 12 months after radiotherapy were evaluated for an association with local disease recurrence. HPV test results at three months had the highest sensitivity, specificity (Table 2), and overall accuracy, and were more accurate than the results of testing at one month postradiotherapy, possibly as a result of the presence of cellular debris after radiotherapy. HPV status at 24 months was significantly associated with local relapse after radiotherapy.

**Table 2. Results of diagnostic accuracy studies included in the systematic review.**

Study	Patients, n	Test	Gold standard	Time period	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Meads et al, 2014 [4]	SR (9 studies, 500 pts)	PET-CT	Pathological or clinical findings	NS	95 (91 to 97)	87 (82 to 91)
Song et al, 2011 [1]	125	Hybrid Capture 2 tests for 13 types of HPV, cutoff $\geq 1$ RLU	Biopsy	3 mo	78	82
Singh et al, 2006 [26]	56	PCR (exfoliated cells)	NS	5 to 224 mo	100 (77 to 100)	29 (16 to 45)
Singh et al, 2006 [26]	56	HPV viral load in exfoliated cells	NS	5 to 224 mo	100 (77 to 100)	37 (20 to 56)
Singh et al, 2006 [26]	56	HPV DNA presence in plasma	NS	5 to 224 mo	57 (29 to 82)	93 (80 to 98)
Gupta et al, 2013 [24]*	1566	Vault cytology	Pathological or clinical findings	Up to 10 yrs after initial diagnosis (92% of recurrences occurred within 2 yrs)	NS	100
Rimel et al, 2011 [25]**	929	Liquid-based cytology	Disease recurrence detected by other methods	2.5 to 118 mo (median: 32 mo)	8	Not reported

\*Diagnosis verified by biopsy in 76% of cases determined to be malignant or inconclusive on cytology; \*\*Values calculated using figures presented in the original article. DNA= deoxyribonucleic acid, HPV=human papillomavirus, mo=months, NS=not stated, PCR=polymerase chain reaction, PET-CT=positron emission tomography-computed tomography, pts=patients, RLU=relative light unit, SR=systematic review, yrs=years

## DISCUSSION

No new comparative studies on follow-up interval were found in the literature search for this update of the PEBC's 2009 guideline for follow-up of patients with cervical cancer [6]. Therefore, this update does not recommend any alterations to the consensus-based follow-up intervals recommended in 2009. Some new information on methods of surveillance to detect asymptomatic recurrences, which, across disease stages, make up 4% to 50% of recurrences [6], was identified.

Two studies assessed the role of vaginal vault cytology in the first five years after complete response. In the past, this technique has been found to have limited sensitivity for detecting recurrences, and may be compromised by ambiguous cell morphology in the early postradiotherapy period [1]. One of the two new studies evaluated in this review corroborated these previous findings [25], while the other, which was specifically designed to assess the value of vault cytology in lower-resource populations, did not test all negative screens, and was therefore not able to calculate sensitivity [24]. The patient population in the latter study was mostly at an advanced stage at the time of initial treatment, which tends to increase the sensitivity of vault cytology [24]. In addition, patients may not have had access to the most effective treatment modalities; therefore, the applicability of this study to higher-resource locations such as Ontario is questionable. A study of cytology testing in the passive surveillance period beyond five years of recurrence-free follow-up also found a very low yield with this technique [2].

Two new studies that assessed the role of HPV DNA testing in the detection of recurrence were included in this systematic review. Both found that HPV testing had a much higher sensitivity for detection of recurrent cervical cancer, compared with previous studies that used Pap testing. The utility of HPV DNA testing appears to be highest approximately three months after completion of treatment, because HPV DNA persistence immediately after successful treatment could be a result of the presence of HPV DNA and/or HPV DNA sequence fragments in the degraded tumour cells or cell debris [29]. A potential barrier to the use of HPV DNA testing is that it is currently not funded in Ontario.

New studies on PET-CT and serum biomarkers were also included in this update. A systematic review of PET-CT found that the evidence base was of poor quality, due to the retrospective uncontrolled nature of the studies, and the bias frequently introduced by lack of verification of diagnostic test results. In addition, most studies are of patients who are being followed up for a suspected recurrence, rather than asymptomatic populations that are undergoing surveillance; e.g., the main study that contributed to the overall estimates of sensitivity and specificity in Meads et al [4] included both symptomatic and asymptomatic patients and did not distinguish between them [23]. Another study reported by Brooks et al. found that in 103 patients who had a complete metabolic response to treatment [30], 13 asymptomatic recurrences were detected by PET or PET-CT. These patients demonstrated a better cause-specific survival rate than patients who experienced symptomatic recurrences (59% versus 19%,  $p=0.09$ ); however, it is not clear whether these recurrences were also detected by other methods and, thus, the added value of PET-CT is not known. Brooks et al. conclude that prospective validation of the technology is warranted [30]. The study that assessed nine serum biomarkers found that SCC-Ag and hsCRP appear promising for detection of disease recurrence [3], but again, concluded that prospective comparative studies are needed.

## CONCLUSIONS

In conclusion, there is a gap in the evidence base for follow-up for cervical cancer; in another review of the literature, 19 randomized controlled trials of varying methodological quality were identified for colorectal and breast cancer follow-up, and none for gynecological cancer [31]. Consensus-based recommendations have largely been accepted within the gynecologic oncology community; however, the need for research that will inform evidence-based recommendations still exists. The optimal follow-up interval has still not been conclusively determined and the need remains for a prospectively designed study to validate the impact of early detection on survival rates [3], because the largest study to date has been a retrospective review [15], and lead-time and length-time biases must be taken into consideration [30]. More specific areas in need of research include the time course of HPV DNA clearance in invasive cervical carcinoma managed with radiation therapy [29], trials of the tumour marker SCC-Ag during cervical cancer follow-up [3], and prospective validation of PET-CT as a method of surveillance for asymptomatic women [30]. The idea of more personalized follow-up programs, including routine biomarker testing during follow-up [3] or more frequent intervals for individuals with higher risk levels due to, for example, HPV tumour negativity [32], could allow for more individualized surveillance programs and possibly improve the detection of asymptomatic recurrence early enough to allow for effective salvage or alternative treatment [29].

## Follow up for Cervical Cancer: Internal and External Review

### INTERNAL REVIEW

Program in Evidence-Based Care (PEBC) guidelines are reviewed by a panel of content experts, the Expert Panel, and a methodology panel, the Report Approval Panel (RAP). Both panels must approve the document. The Working Group is responsible for incorporating the feedback and changes of both of these panels. The details of these reviews and the actions taken are described below. A list of members of the Working Group, and Expert Panel and their conflict of interest declarations is provided in Appendix 2. The PEBC conflict-of-interest policy is available at: <https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=103568>

#### Expert Panel Review and Approval

The PEBC Gynecologic Cancer Disease Site Group acted as the Expert Panel for this document. The Expert Panel reviewed this document in January 2015.

For the guideline document to be approved, 75% of the Disease Site Group membership must cast a vote or abstain, and of those that vote, 75% must approve the document. Of the 10 members of the PEBC Gynecologic Cancer Disease Site Group who were not Working Group members, nine members cast votes and one abstained, for a total of 90% response. Of those that cast votes, all approved the document, with only minor wording suggestions, which were incorporated.

#### Report Approval Panel Review and Approval

Three RAP members reviewed this document in January and February 2015. The RAP approved the document with minor suggested wording changes, which were incorporated.

#### External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from several specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners. Refer to the [PEBC Handbook](#) for additional detail.

*Targeted Peer Review:* Targeted peer reviewers from Ontario, Quebec, the United States, and Italy who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three were asked and agreed to be reviewers. Two of these sent responses. Key results of the feedback survey are summarized in Table 3. The main written comments from targeted peer reviewers and the Working Group's modifications/actions taken/responses are summarized in Table 4.

**Table 3. Responses to nine items on the targeted peer reviewer questionnaire.**

Question	Reviewer Ratings (N=2)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	1
2. Rate the guideline presentation.				2	

3. Rate the guideline recommendations.			1	1	
4. Rate the completeness of reporting.				2	
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	1
6. Rate the overall quality of the guideline report.				1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	1
8. I would recommend this guideline for use in practice.				1	1
9. What are the barriers or enablers to the implementation of this guideline report?	The only barrier that I know of is the lack of knowledge of the published document on GL				

**Table 4. Modifications/actions taken/responses regarding main written comments from targeted peer reviewers.**

Main written comments	Modifications, actions, or responses
1. Summarize the conclusions in a table at the end of the document.	We are following the standard template for PEBC guidance documents.
2. I found it a bit contradictory that the guideline indicated no role of Pap testing in identifying recurrences in the first five years, but included Pap testing in the longer term follow-up.	We have clarified that vaginal vault cytology on an annual basis is appropriate in the first five years.
3. I suggest organizing the different items by ranking by grade of relevance.	We did not including grading of evidence in the study protocol.

*Professional Consultation:* Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All gynecologic oncology, radiation oncology, and family medicine experts in the PEBC database were contacted by email to inform them of the survey. Of 454 surveys sent out, 61 (13%) responses were received. In addition, 27 individuals stated that they did not have interest in this area or were unavailable to review this guideline at the time. The key results of the feedback survey from 61 people are summarized in Table 5. The main comments from the professional consultation and the Working Group's modifications/actions taken/responses are summarized in Table 6.

**Table 5. Responses to four items on the professional consultation survey.**

General Questions: Overall Guideline Assessment	Number (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the	0(0)	2(3)	2(3)	28(46)	29(48)

guideline report.					
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	3(5)	2(3)	9(15)	24(39)	23(38)
3. I would recommend this guideline for use in practice.	2(3)	2(3)	8(13)	20(33)	29(48)

4. What are the barriers or enablers to the implementation of this guideline report?
<p><i>Barriers mentioned by the respondents:</i></p> <ul style="list-style-type: none"> <li>• <i>Level of evidence</i> <ol style="list-style-type: none"> <li>1. The recommendations are based on lower level evidence which may limit uptake.</li> <li>2. It is hard to tell patients we won't do any tests because we don't know.</li> </ol> </li> <li>• <i>Lack of effective tests</i></li> <li>• <i>Stakeholder buy-in</i></li> <li>• <i>Guideline dissemination</i></li> <li>• <i>Skill/ Comfort level of primary care physicians (PCPs) with tests such as vault smears</i></li> <li>• <i>Cost and availability of tests/access to tests</i></li> <li>• <i>Patient compliance</i></li> <li>• <i>Other Barriers:</i> <ol style="list-style-type: none"> <li>1. Many women don't want to come back to their family physicians for follow up after cancer treatment even when their specialists have given them the "all clear," due to anxiety.</li> <li>2. Too few patients with treated cancer... [PCPs] often see the precancerous lesions and get them treated: "I have not seen a radiated patient for &gt;20 years."</li> <li>3. Consensus between the radiation oncologists.</li> <li>4. Overuse of surveillance imaging.</li> </ol> </li> </ul>



**Table 6. Modifications/actions taken/responses regarding main written comments from professional consultants.**

Main written comments	Modifications, actions taken, or responses
<p>1. Women with a history of cervical cancer (and high-grade squamous intraepithelial lesion [HSIL]) are at increased risk for the development of a second lower genital tract malignancy (vagina, vulva, anus). ...there does appear to be a significant discordance between management guidelines for women posttreatment for HSIL and women posttreatment for cervical cancer.</p>	<p>Follow up for women who are posttreatment for HSIL is intended to detect cervical cancer, whereas follow-up after cervical cancer is intended to detect cancer at another site.</p>
<p>2. Still not clear what we should be doing with respect to human papillomavirus (HPV) testing, Papanicolaou (Pap) smears, tumour markers, imaging - none or all?</p>	<p>There is little evidence for any of these tests, and this may be why the recommendations are difficult to interpret. The statement that these investigations <i>are not advocated</i> has been italicized for emphasis.</p>
<p>3. This guideline should state clearly that it applies specifically to cervical cancer and not to other cervical intraepithelial neoplasia (CIN) stages... some further clarification is needed. For e.g., "Symptoms elicited during the patient history should include general performance status, lower back pain (especially if it radiates down one leg), vaginal bleeding, or unexplained weight loss." Please add a statement to the effect of "focused imaging or testing appropriate to findings is warranted" and "physical examination should include a speculum examination with bimanual and pelvic/rectal examination." Again a statement about further investigation is warranted. "Routine cervical screening according to population-based guidelines is recommended for patients who have undergone surgical treatment. Cytological follow-up is not recommended for patients who have been treated with radiotherapy." Here please state specifically the frequency of so-called routine cervical screening since there really is no such thing as "routine" cervical screening after hysterectomy.</p>	<p>We have added to the target population that patients with CIN are outside of scope. The suggestions for statements about further investigations have been added. A statement about the frequency of routine cervical screening is beyond the scope of this guideline.</p>
<p>4. 1) at the very top of page 8, with 580 new cases and 140 deaths, that would suggest a case fatality rate of 24%. However, just below, the recurrence rate is listed at 13 to 17%. That would suggest that disease-specific deaths are even higher than recurrence rates. Not sure I understand that.</p>	<p>1) That would be true, as many deaths occur without recurrence. 2) We have adopted the wording suggestion for "salvage" instead of "adjuvant."</p>

<p>2) Bottom of page 18: effective adjuvant treatment. Maybe use the word "salvage" instead of "adjuvant."</p>	
<p>5. Again, this guideline needs to be clearer about whom it refers to and we need further guidance on the larger cohort of "posttreatment/postcolposcopy" patients who return to primary care once treatments are done.</p>	<p>The target population is postcervical cancer patients, not postprecancer patients. The postcolposcopy patient population is out of scope for this guideline.</p>
<p>6. ...if a woman had a "procedure" that kept her cervix intact, I presume one would still performs cervical Pap cytology. If she has no cervix, due to undergoing surgical treatment...how do we align the PEBC 4-16 with its current "no need for vault cytology" with the cervical screening guideline saying do "something," screening annually?</p>	<p>We have clarified that annual vaginal vault cytology is recommended for this specific target population. We have removed vaginal vault cytology from the list of items that are not recommended. According to the PEBC Cervical Screening Guidelines (#15-9), screening is not recommended in women who have undergone a total hysterectomy.</p>
<p>7. ...post five years ... it could be more clear what intervals and tests I should use at that point: for woman with/without full hysterectomy and no cervix do I do cytology? Do I do that yearly as these people are at somewhat higher risk or every three years? Maybe this is out of scope but not from my perspective as the family doctor: The phrase "as per usual with well woman care" is not so clear - is the idea that I then go consult a different guidance document?</p>	<p>According to the PEBC Cervical Screening Guidelines (#15-9), screening is not recommended in women who have undergone a total hysterectomy. Whatever is being done for well women in the primary care practice would apply to women who are alive five years after curative treatment for cervical cancer.</p>
<p>8. The document suggests in a few places that follow up until five years should be at a cancer centre - were impacts on rural/remote populations considered?</p>	<p>The target users for this guideline are clinicians who will conduct follow-up. This could include PCPs or nurse practitioners where access to a cancer centre is not feasible.</p>
<p>9. While still emphasizing the uncertainty of the consensus-based follow up schedule recommendations, I think it would be helpful to summarize in a table or figure as this really is the key message and I feel as though it could be better highlighted.</p>	<p>We have separated out the different time intervals and appointment frequencies with bullets in order to make them more readable.</p>
<p>10. I think family physicians should be identified for follow-up but probably require some further education.</p>	<p>Yes, this comment was made by several respondents.</p>
<p>11. Initial five-year follow up with oncologists or oncologists and family physicians together. Use of checklists may be useful.</p>	<p>Implementation aids will fall under the scope of other divisions at Cancer Care Ontario.</p>
<p>12. Well considered and explained why we should not be adopting some of the newer tests such as</p>	

biomarkers, at this time. Useful as our patients are likely to be asking.	
13. Indirect evidence hints that there may be a role for follow-up investigations. Data from Asia (Hong Kong) has shown that essentially no one who presents with symptomatic para-aortic recurrences from cervical cancer is cured whereas 50% or more patients with isolated para-aortic recurrences are long-term survivors. The only way to detect asymptomatic recurrences in the para-aortic region (which potentially can be salvaged by chemoradiation) is by periodic imaging.	This topic was outside the scope of this version of the guideline. It may be addressed in a future version of the guideline.
14. Would suggest changing the order of sections to facilitate flow of information. E.g., Sections 4, 3, 2 and 5. Thank you to all committee members for their work on this guideline.	We are currently following the PEBC template format for all documents, however we will consider this advice for future versions of the template.
15. A limitation of the biomarker paper (Hoogendam et al.) is that it is unclear how concentrations of SCC antigen (SCC-Ag) and high-sensitivity C-reactive protein (hsCRP) can be used to detect disease... the other assays that did not show promise were research assays where the quality of results and sample types may have underestimated performance.	Agree. These are limitations of the Hoogendam et al. paper.
16. In the scenario of persistent and suspicious asymptomatic palpable cervical findings and potential for central recurrence would a recommendation for further evaluation with cervical/deep stromal biopsy be appropriate to include in the guideline? This is implied in the guideline re: potential for salvage treatment, but should this qualifying statement be added?	Specific recommendations for further investigations in the situation of a suspected recurrence are beyond the scope of this guideline document.
17. ... it should be noted that the studies reported by Song et al. [1] evaluated patients with HPV deoxyribonucleic acid (DNA) positive tumours...in order to monitor HPV status post radiation therapy, tumour histotype should be taken into consideration and pretreatment HPV status of all tumours should be established.	This is a good point and would likely be relevant in a primary treatment guideline. At the present time, it was not included in the scope of this follow-up document, but may be included in a future version of the guideline.

## CONCLUSION

This Guideline report reflects the integration of feedback obtained through the external review process with final approval given by the Cervical Follow-up Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol (available at: <https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true>).

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IN REVIEW

Appendix 1. Guideline document history.

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original: April 2009	1980-2007	Full Report	Web publication. Peer-reviewed publication.	Not applicable
Version 2 2015	2007-2014	New data added to original full Report	Updated web publication.	Guideline recommendations remain the same as the 2009 version of the report. Evidence-base updated.

**Appendix 2. Working Group and Expert Panel members, their affiliations, and conflict of interest declarations.**

Guideline 4-16 Version 2 Working Group members:

<b>Name</b>	<b>Affiliation</b>	<b>Conflict of interest declaration</b>
Dr. Laurie Elit Working Group Chair Gynecologic Oncologist	Juravinski Cancer Centre and McMaster University	Dr. Elit was an author on the previous version of the Program in Evidence-Based Care's Guideline 4-16
Ms. Erin B. Kennedy Health Research Methodologist	Sunnybrook Health Sciences Centre, Toronto	None declared
Dr. Anthony Fyles Radiation Oncologist	Princess Margaret Hospital, Toronto	None declared
Dr. Ur Metser Radiologist	University of Toronto	None declared

Guideline 4-16 Version 2 Expert Panel members:

<b>Name</b>	<b>Affiliation</b>	<b>Conflict of interest declaration</b>
Dr. Allan Covens	Odette Cancer Centre, Toronto	Was an author on an editorial on PET scan after chemoradiation
Dr. Jason Dodge	Royal Victoria Hospital, Barrie	None declared
Dr. Julie Francis	Kingston General Hospital	None declared
Dr. Michael Fung-Kee-Fung	Ottawa General Hospital	None declared
Dr. Hal Hirte	Juravinski Cancer Centre, Hamilton	None declared
Dr. Tien Le	Ottawa General Hospital	None declared
Dr. Helen Mackay	Princess Margaret Hospital, Toronto	None declared
Dr. Joan Murphy	University Health Network, Toronto	None declared
Dr. Michel Prefontaine	London Health Sciences Centre	None declared



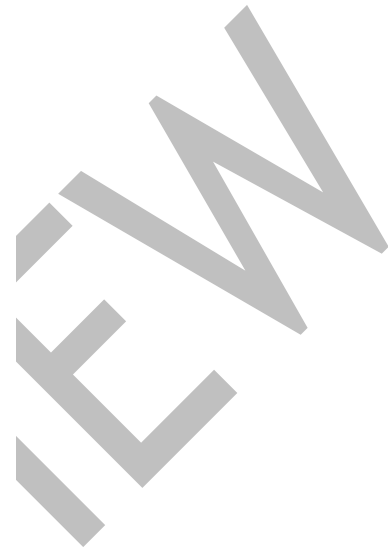
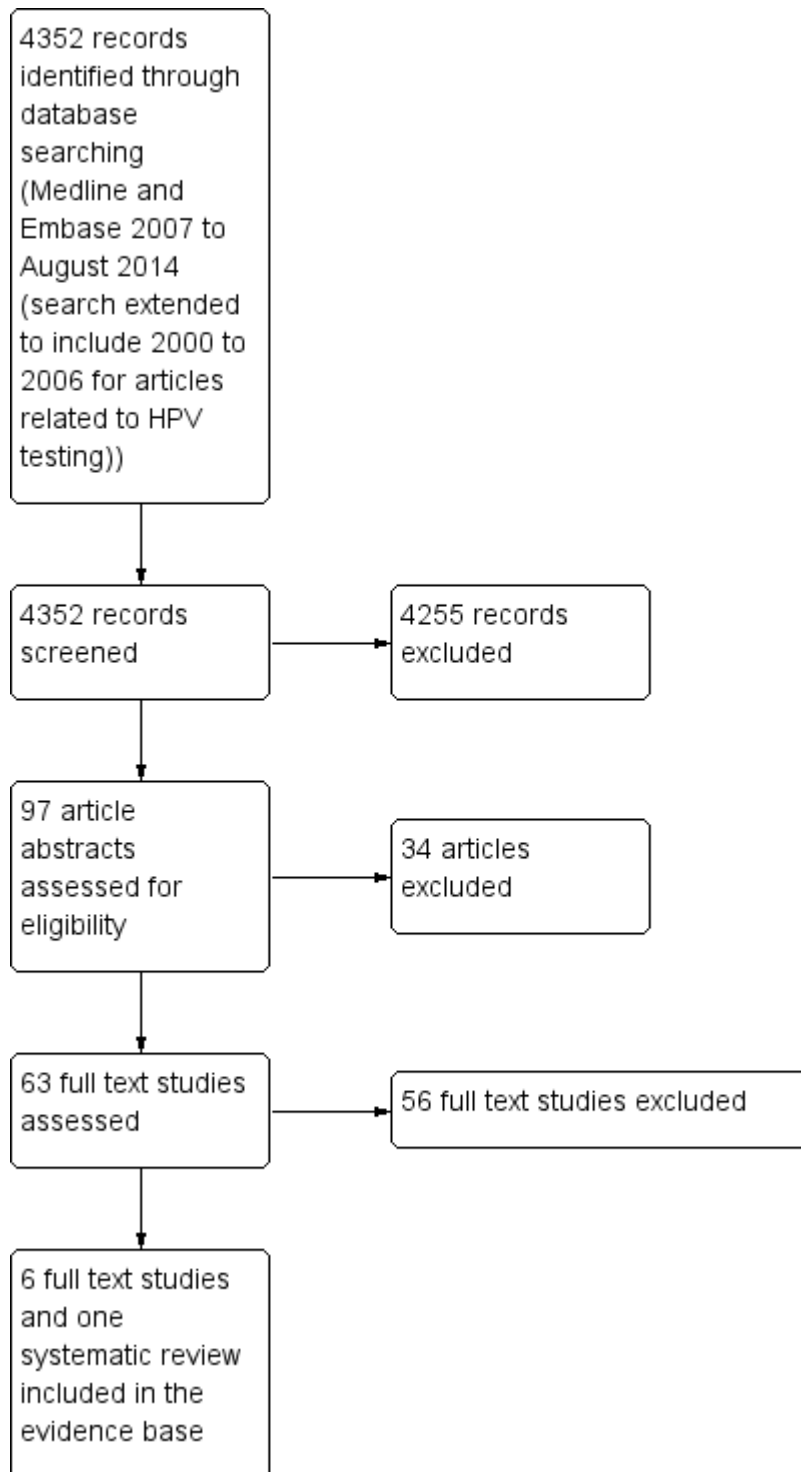
### Appendix 3. Search strategy.

1. exp cervix neoplasms/
2. (cerv\$ and (neoplasm\$ or cancer\$ or carcin\$ or tumo\$ or malig\$)).ti,tw.
3. 1 or 2
4. Neoplasm recurrence, local/
5. Cerv\$.ti,tw.
6. 4 and 5
7. 3 or 6
8. Follow up.ti,tw.
9. Follow-up.ti,tw.
10. Follow\$.ti,tw.
11. Recur\$.ti,tw.
12. Surveillance.ti,tw.
13. or/8-12
14. 7 and 13
15. exp randomized controlled trials/
16. Randomized controlled trial.pt.
17. Clinical trial/
18. Random\$.ti,tw.
19. Random allocation/
20. Follow-up studies/
21. exp cohort studies/
22. Prospective\$.ti,tw.
23. Retrospective\$.ti,tw.
24. Comparative study/
25. (systematic review? or systematic overview?).ti,tw.
26. Practice guidelines/
27. Practice guideline?.ti,tw.
28. Practice guideline.pt.
29. or/15-28
30. 14 and 29
31. limit 30 to yr="2000 - 2006"
32. HPV.mp.
33. human papillomavirus.mp.
34. 31 and (32 or 33)

#### Appendix 4. AMSTAR questions and responses for Meads et al [20].

1. Was an *a priori* design provided? Yes
2. Was there duplicate study selection and data extraction? Yes
3. Was a comprehensive literature search performed? Yes
4. Was the status of publication (e.g., grey literature) used as an inclusion criterion? Grey literature was not mentioned for inclusion.
5. Was a list of studies (included and excluded) provided? Excluded studies were not listed.
6. Were the characteristics of the included studies provided? Yes
7. Was the scientific quality of the included studies assessed and documented? The QUADAS tool was used to assess study quality. Study quality overall was found to be poor.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? Yes
9. Were the methods used to combine the findings of studies appropriate? Yes
10. Was the likelihood of publication bias assessed? Yes

**Appendix 5. Study results flow diagram.**



IN REVIEW