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Guideline 4-16 Version 3

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

Follow-up for Cervical Cancer

Members of the Follow-up for Cervical Cancer Expert Panel

Report Date: May 23, 2025

Guideline 4-16 Version 2 was reviewed in 2025 and ENDORSED by the Follow-up for Cervical Cancer Expert Panel.
(See Section 6: Document Assessment and Review for details)

Guideline 4-16 Version 3 comprises 6 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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Section 4:	**Evidence Review**
Section 5:	**Internal and External Review**
Section 6:	**Document Assessment and Review**

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Elit L, Fyles AW, Devries MC, Oliver TK, Fung-Kee-Fung M; Gynecology Cancer Disease Site Group. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 2009 Sep;114(3):528-35.

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.
Version 3 May 2025	2014 - 2024	New data found in Section 6: Document Assessment and Review	Updated web publication.	2015 recommendations are **ENDORSED** with some modifications.

Guideline 4-16 Version 3: Section 1

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.

May 2025: Some recommendations have been modified to align with guidance from the Ontario Cervical Screening Program (OCSP) https://www.cancercareontario.ca/en/types-of-cancer/cervical/screening. Also, some other minor wording changes were made that are explained in Section 6.

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.

Added May 2025 (See Section 6 for details):

1. **Patients who had stage 1A1 cervical cancer and retained their cervix.** These patients should be followed with HPV testing according to the OCSP guideline and use the follow-up strategy below. https://www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/resources-healthcare-providers/cervical-screening-recommendations-summary. Hysterectomy can be considered once childbearing is complete or cervix cannot be adequately followed.

2. **Patients who had a hysterectomy.** These patients should be considered for vaginal vault testing according to the OCSP guidance for vaginal vault testing and use the follow-up strategy below. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43336.

3. **Patients who had 1A2 and beyond cervical cancer and retained their cervix.** These patients are not covered in the OCSP. Hysterectomy can be considered once childbearing is complete or cervix cannot be adequately followed.

4. **<u>Patients who had radiation with or without chemotherapy.</u>** Follow-up with HPV/cytology is not recommended for these patients. It is fairly standard to order MRI after three months post radiation/chemotherapy. Patients should receive a physical exam or an MRI when a physical exam is difficult to perform, incomplete, or challenging to interpret.

Follow-up for Groups 1 to 3:

Follow-up to Five Years

- A reasonable follow-up strategy involves visits at the following intervals in either a colposcopy or cancer clinic:
    - every four to six 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.
    - For patients with a cervix, HPV and cytology testing (co-test) at each visit.
    - For patients without a cervix, a single test vault at 6 to 12 months post-hysterectomy is recommended. For those patients with a negative vault HPV test, there is no evidence available suggesting that ongoing vault testing is beneficial. For those with positive HPV test, colposcopy of the vaginal vault is recommended to rule out a vaginal lesion. Ongoing surveillance is up to the discretion of the treating physician.
- 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.

Follow-up Beyond Five Years

- After five years of recurrence-free follow-up:
    - Patients with 1A2 and beyond with a cervix may return to primary care follow-up at the discretion of the treating physician.
    - Primary care follow-up should include a history and general physical, including pelvic examination performed by the primary care physician that is consistent with standards for well-woman care; however, some patients with treatment complications may require more prolonged follow-up at the cancer centre.

Follow-up for Group 4:

Follow-up to Five Years

- A reasonable follow-up strategy involves visits at the following intervals at a cancer clinic:
    - every four to six 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.

- After three months post-treatment, 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), or biomarker tests.

Follow-up Beyond Five Years

- After five years of recurrence-free follow-up:
  Primary care follow-up should include a history and general physical, including pelvic examination 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.

Guideline 4-16 Version 3: Section 2

Follow-up for Cervical Cancer: Guideline

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.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

May 2025: Some recommendations have been modified to align with guidance from the Ontario Cervical Screening Program (OCSP) https://www.cancercareontario.ca/en/types-of-cancer/cervical/screening. Also, some other minor wording changes were made that are explained in Section 6.

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.

Added May 2025 (See Section 6 for details):

1. **Patients who had stage 1A1 cervical cancer and retained their cervix.** These patients should be followed with HPV testing according to the OCSP guideline and use the follow-up strategy below. https://www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/resources-healthcare-providers/cervical-screening-recommendations-summary. Hysterectomy can be considered once childbearing is complete or cervix cannot be adequately followed.

2. **Patients who had hysterectomy.** These patients should be considered for vaginal vault testing according to the OCSP guidance for vaginal vault testing and use the follow-up strategy below. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43336

3. **Patients who had 1A2 and beyond cervical cancer and retained their cervix.** These patients are not covered in the OCSP. Hysterectomy can be considered once childbearing is complete or cervix cannot be adequately followed.

4. **Patients who had radiation with or without chemotherapy.** Follow-up with HPV/cytology is not recommended for these patients. It is fairly standard to order an MRI after three months post radiation/chemotherapy. Patients should receive a physical exam or an MRI when a physical exam is difficult to perform, incomplete, or challenging to interpret.

Follow-up for Groups 1 to 3:

Follow-up to Five Years

- A reasonable follow-up strategy involves visits at the following intervals in either a colposcopy or cancer clinic:
    - every four to six 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.
    - For patients with a cervix, HPV and cytology testing (co-test) at each visit.
    - For patients without a cervix, a single test vault at 6 to 12 months post-hysterectomy is recommended. For those patients with a negative vault HPV test, there is no evidence available suggesting that ongoing vault testing is beneficial. For those with positive HPV test, colposcopy of the vaginal vault is recommended to rule out a vaginal lesion. Ongoing surveillance is up to the discretion of the treating physician.
- 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.

Follow-up Beyond Five Years

- After five years of recurrence-free follow-up:
    - Patients with 1A2 and beyond with cervix may return to primary care follow-up at the discretion of the treating physician.
    - Primary care follow-up should include a history and general physical, including pelvic examination performed by the primary care physician that is consistent with standards for well-woman care; however, some patients with treatment complications may require more prolonged follow-up at the cancer centre.

Follow-up for Group 4:

Follow-up to Five Years

- A reasonable follow-up strategy involves visits at the following intervals at a cancer clinic:
    - every four to six 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.

- After three months post-treatment, 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), or biomarker tests.

Follow-up Beyond Five Years

- After five years of recurrence-free follow-up:

Primary care follow-up should include a history and general physical, including pelvic examination 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.

Key Evidence – Evidence below is from the 2015 update. For evidence up to 2024, see Section 6

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.

Section 3

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.

Guideline 4-16 Version 2: Section 4

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.

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-α, 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-α=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 (≥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 ≥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].

Section 5

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.

	Reviewer Ratings (N=2)				
Question	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.

	Number (%)				
General Questions: Overall Guideline Assessment	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?

Barriers mentioned by the respondents:

- *Level of evidence*
    1. The recommendations are based on lower level evidence which may limit uptake.
    2. It is hard to tell patients we won't do any tests because we don't know.
- *Lack of effective tests*
- *Stakeholder buy-in*
- *Guideline dissemination*
- *Skill/ Comfort level of primary care physicians (PCPs) with tests such as vault smears*
- *Cost and availability of tests/access to tests*
- *Patient compliance*
- *Other Barriers:*
    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.
    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 >20 years.”
    3. Consensus between the radiation oncologists.
    4. Overuse of surveillance imaging.

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

Main written comments	Modifications, actions taken, or responses
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.	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.
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?	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 *are not advocated* has been italicized for emphasis.
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.	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.
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.	1) That would be true, as many deaths occur without recurrence. 2) We have adopted the wording suggestion for “salvage” instead of “adjuvant.”

2) Bottom of page 18: effective adjuvant treatment. Maybe use the word "salvage" instead of "adjuvant."	
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.	The target population is postcervical cancer patients, not postprecancer patients. The postcolposcopy patient population is out of scope for this guideline.
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?	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.
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?	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.
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?	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.
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.	We have separated out the different time intervals and appointment frequencies with bullets in order to make them more readable.
10. I think family physicians should be identified for follow-up but probably require some further education.	Yes, this comment was made by several respondents.
11. Initial five-year follow up with oncologists or oncologists and family physicians together. Use of checklists may be useful.	Implementation aids will fall under the scope of other divisions at Cancer Care Ontario.
12. Well considered and explained why we should not be adopting some of the newer tests such as	

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

Guideline 4-16 Version 2 Working Group members:

Name	Affiliation	Conflict of interest declaration
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:

Name	Affiliation	Conflict of interest declaration
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

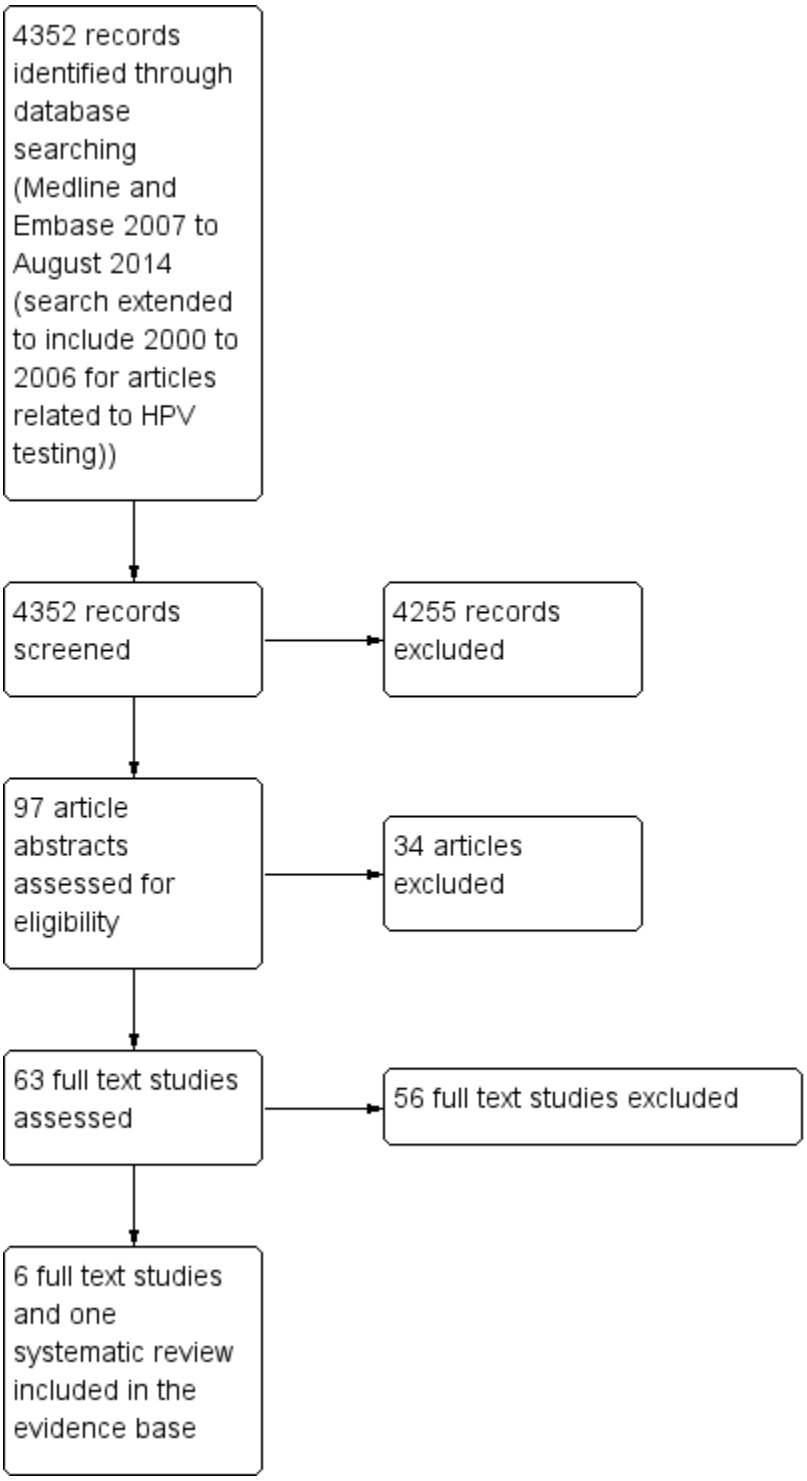
Appendix 3. Search strategy.

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.



Ontario Health
Cancer Care Ontario

Evidence-Based Series 4-16 Version 3: Section 6

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

Follow-up for Cervical Cancer

Document Assessment and Review

R. Kupets, C. Zwaal, and the Follow-up for Cervical Cancer Expert Panel

May 23, 2025

The 2015 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2009 and updated in 2015.

In November 2022, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CZ) conducted an updated search of the literature. A clinical expert (RK) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Follow-up for Cervical Cancer Expert Panel endorsed the recommendations found in Section 1 (Recommendations Summary) in May 2025.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

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

Literature Search and New Evidence

The new search (January 2014 to June 2024) yielded 2 practice guidelines, 2 systematic reviews and 12 cohort studies. Brief results of these publications are shown in the Document Review Tool.

Impact on the Guideline and Its Recommendations

The new data support existing recommendations. The recommendations involving cytology and imaging are still relevant and appropriate. However, the recent release of Ontario Cervical Screening Program (OCSP) guidance pertaining to HPV testing and vaginal vault testing must be highlighted in this guideline on cervical cancer follow-up.

Discussions with the Expert Panel led to a reorganization of the patient population into four groups:

1. **Patients who had stage 1A1 cervical cancer and retained their cervix.** These patients should be followed with HPV testing according to the OCSP guideline and use the follow-up strategy below. https://www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/resources-healthcare-providers/cervical-screening-recommendations-summary. Hysterectomy can be considered once childbearing is complete or the cervix cannot be adequately followed.

2. **Patients who had hysterectomy.** These patients should be considered for vaginal vault testing according to the OCSP guidance for vaginal vault testing and use the follow-up strategy below. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43336

3. **Patients who had 1A2 and beyond cervical cancer and retained their cervix.** These patients are not covered in the OCSP. Hysterectomy can be considered once childbearing is complete or the cervix cannot be adequately followed.

4. **Patients who had radiation with or without chemotherapy**. Follow-up with HPV/cytology is not recommended for these patients. It is fairly standard to order an MRI after three months post radiation/chemotherapy. Patients should receive a physical exam or an MRI when a physical exam is difficult to perform, incomplete, or challenging to interpret.

The follow-up of up to 5 years and beyond 5 years was adjusted for these 4 groups:

For groups 1 to 3:

Follow-up to Five Years

- A reasonable follow-up strategy involves visits at the following intervals in either colposcopy or cancer clinic:
    - every four to six 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.
    - For patients with a cervix, HPV and cytology testing (co-test) at each visit.
    - For patients without a cervix, a single test vault at 6 to 12 months post hysterectomy is recommended. For those patients with a negative vault HPV test, there is no evidence available suggesting that ongoing vault testing is beneficial. For those with positive HPV test, colposcopy of the vaginal vault is recommended to rule out a vaginal lesion. Ongoing surveillance is up to the discretion of the treating physician.
- 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.

Follow-up Beyond Five Years

- After five years of recurrence-free follow-up:
    - Patients with 1A2 and beyond with cervix may return to primary care follow-up at the discretion of the treating physician.
    - Primary care follow-up should include a history, general physical, including pelvic examination 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.

For group 4:

Follow-up to Five Years

- A reasonable follow-up strategy involves visits at the following intervals at a cancer clinic:
    - every four to six 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.

- After three months post-treatment, 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), or biomarker tests.

Follow-up Beyond Five Years

- After five years of recurrence-free follow-up:
    - Primary care follow-up should include a history, general physical, including pelvic examination performed by the primary care physician that is consistent with standards for well-woman care; however, some patients with treatment complications may require more prolonged follow-up at the cancer centre.

The Follow-up for Cervical Cancer Expert Panel ENDORSED the 2015 recommendations on the follow-up of cervical cancer.

Ontario Health
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Document Review Tool

Number and Title of Document under Review	4-16 Version 2 Follow-up for Cervical Cancer
Original Report Date	May 12, 2015
Date Assessed (by DSG or Clinical Program Chairs)	November 18, 2022
Health Research Methodologist	Caroline Zwaal
Clinical Expert	Rachel Kupets
Approval Date and Review Outcome (once completed)	May 23, 2025 ENDORSE

Original Question(s):
What is the most appropriate follow-up strategy for patients with cervical cancer who are clinically disease free after receiving primary treatment?

Target Population:
Women who are clinically disease free and asymptomatic after receiving potentially curative primary treatment for cervical cancer. This does not include women who have been treated for cervical precancer.

Study Selection Criteria:
No changes to the inclusion or exclusion criteria.

Inclusion criteria:

- Follow-up strategies or methods reported in systematic reviews, 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, only prospective or retrospective studies that compared two or more distinct study groups were included.
- Outcomes of interest included comparisons of overall or progression-free survival rates for different follow-up strategies and patient quality of life. For diagnostic accuracy studies, the outcomes of interest were sensitivity, specificity, positive predictive value, negative predictive value, and hazard ratios for disease recurrence.

Exclusion criteria:

- 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.

Search Details:
Search ran on June 4, 2024
EMBASE 1996 to 2024 June 4
MEDLINE 1996 to 2024 June 4
Limited to English only
Search strategy identical to that used for original 2015 guideline.

Summary of new evidence:
Retrieval:
Search results: 4050 citations
Title and abstract review: 91
Guidelines: 51 relevant citations
Systematic reviews: 7 relevant citations
Cohort studies: 109 relevant citations
Full text review:43
Guidelines: 2
Systematic reviews: 6 relevant
Cohort studies: 40 relevant
Included:
Guidelines: 2
Systematic reviews: 1
Cohort studies: 12

No studies from Clinical Trials.gov or Cochrane Library.
Details from the included trials are summarized in the tables below.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	Yes
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes, the recommendations involving cytology and imaging are similar. However, OSCP guidance documents have been added into the recommendations requiring the delineation of follow-up for different populations.
Review Outcome as recommended by the Clinical Expert	Endorse

If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/Expert Panel Commentary	

Evidence Tables: Guideline 4-16 Follow-up for Cervical Cancer -Updated Article Summary

Table 1.0 Summary of Relevant Guidelines -2

Citation	Implementation dates	Recommendations

Cibula, 2023	ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer – Update 2023
	
	Levels of Evidence I-V
	
	I- Evidence from at least one large RCT with low risk of bias or meta-analysis of well-conducted RCTs
	II- Small or large RCTs or meta-analysis with some risk of bias
	III- Prospective cohort studies
	IV- Retrospective cohort studies
	V- Studies without a controls group, case reports, expert opinions
	
	Grades of Recommendations A-E
	
	A- Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
	B- Strong or moderate evidence for efficacy but with limited clinical benefit, generally recommended
	C- Insufficient evidence for efficacy or benefit does not outweigh the risk or disadvantages, optional
	D- Moderate evidence against efficacy for adverse outcome, generally not recommended
		Follow-up During and After Treatment/Long-term Survivorship
		
		General Recommendations
		
		• Patients should be informed and educated at the time of diagnosis and throughout follow-up about signs/symptoms of recurrence. They should be informed about possible side effects (by physicians, nurses, brochures, videos, etc.) [V, A].
		• A network of healthcare providers including all care providers should be involved in the care of survivors (e.g., primary care physicians, gynecologists, psychologists, sexologists, physiotherapists, dieticians, social workers) for the follow-up [V, A].
		• Follow-up strategy should be individualized in terms of intensity, duration and procedures, taking into account individual risk assessment [V, A]. Available prognostic models, such as the Annual Risk Recurrence Calculator available on the ESGO website can be used to tailor surveillance strategy in an individual patient [IV, B].
		• Follow-up should be centralized/coordinated in a center specialized in the treatment and follow-up of gynecological cancer patients [IV, A].
		• Follow-up is designed to monitor disease response, to detect recurrence and to screen for subsequent primary tumors [V, B].
		• Regular and systematic monitoring of side effects and quality of life should be performed to improve the quality of care [V, A].
		• Prevention and early detection of immediate and persistent symptoms and side effects of the different cancer treatments and the individual patient supportive care needs should be identified and established at diagnosis and monitored throughout the follow-up [V, A].
		• All side effects should be identified and treated, if possible, namely physical and psychosocial [V, A].
		• The development of an individual survivorship monitoring and care plan is recommended [V, B].
		• Recommendations for a healthy lifestyle should include smoking cessation, regular exercise, healthy diet and weight management [V, B].
		• Clinical trials should address long-term cancer survivorship and should include patient related outcomes [V, B].
		• Quality control of care should be established [V, B].
		• Each visit should be composed of the following [V, A]:
		  ○ Patient history (including identification of relevant symptoms and side effects)
		  ○ Physical examination (including a speculum and bimanual pelvic examination)
		  ○ Imaging and laboratory tests should be performed only based on risk of recurrence, symptoms or findings suggestive of recurrence and/or side effects.

	E- Strong evidence against efficacy or for adverse outcome, never recommended	○ Regular review of an ongoing survivorship plan that can be shared with other healthcare providers. • Oncological follow-up ○ Patients should be educated about symptoms and signs of potential recurrence [V, A]. ○ Appropriate imaging test (MRI, ultrasound for pelvic assessment, CT scan or PET-CT for systemic assessment) should be used in symptomatic women [IV, A]. ○ In case of suspected tumor persistence, recurrence or second primary cancer, histological verification is strongly recommended [V, A]. ○ Vaginal vault cytology is not recommended [IV, D]. ○ After fertility sparing treatment, follow-up should include HPV testing (at 6–12 and 24 months) [V, A]. • Monitoring of quality of life and side effects ○ Quality of life and side effects should be regularly assessed at least by the physicians/clinical care nurses and if possible, by patients (using patient related outcomes). Patient self-reporting of side effects should be encouraged during and after treatment with the same frequency as medical visits [IV, B]. ○ A checklist of potential main side effects should be included in the patient survivorship monitoring and care plan (e.g., sexual dysfunction, lymphedema, menopausal symptoms and osteoporosis, genitourinary and gastrointestinal disorders, chronic pain, fatigue) [IV, A]. ○ After CTRT and BT, patients should be counseled about sexual rehabilitation measures including the use of vaginal dilators. Topical estrogens are indicated [IV, B]. ○ Hormone replacement therapy is indicated to cervical cancer survivors with premature menopause and should be consistent with standard menopausal recommendation [IV, B]. Physical and lifestyle changes may also help [V, C]. ○ Bone status should be assessed regularly in patients with early menopause [V, B]. ***Follow-up After Definitive CTRT and BT*** • Follow-up should be performed/coordinated by a physician experienced with follow-up care after radiotherapy and BT including monitoring of early, and late treatment-related side effects [V, A]. • The same imaging method used at the start of treatment should be used to assess tumor response [V, B]. • Routine biopsy to assess complete remission should not be performed [IV, D]. • Cytology is not recommended in detecting disease recurrence after radiotherapy [IV, D]. • Imaging (pelvic MRI±CT scan or PET-CT) should be performed not earlier than 3 months after the end of treatment [IV, B]. • In patients with uncertain complete remission at 3 months post-radiotherapy, the assessment should be repeated after an additional 2–3 months with biopsy if indicated [IV, B].

Hillemanns, 2020	Statement of the AGO and AG-CPC on the Aftercare/Follow-up for Surgical Procedures of the Lower Genital Tract after the Introduction of a New Cancer Screening Guideline The new guideline on organized cancer screening programs has been in force in Germany since January 1st, 2020	**Section on: Follow-up after Hysterectomy for Cervical Cancer** • The S3 guideline on the diagnosis, treatment and follow-up of patients with cervical cancer states the following with regard to the issue of screening women who had cervical cancer and a hysterectomy (p. 158; consensus-based recommendation no. 17.2): "A mandatory examination should be carried out every 3 months for a period of 3 years, then every 6 months for a further period of 2 years. The examination should include taking the patient's medical history, a rectovaginal (sic!) examination, speculum examination and cytology." • The guideline also references HPV-testing (p. 158; consensus-based recommendation no. 17.3): "Optional examinations can be carried out if findings are clinically unremarkable (the patient is asymptomatic). These can include colposcopy, HPV-testing, vaginal ultrasound scan of the lesser pelvis and ultrasound scan of the urinary system." • Follow-up examinations must be carried out for 5 years. Co-testing with HPV-testing and cytology is particularly indicated for patients who had a trachelectomy, primary radio-chemotherapy and associated multifocal (intra-)epithelial neoplasia. The intervals between cytology examinations of the vaginal stump performed as part of follow-up after treatment for cervical cancer (p. 159; Table 19) are every 3 months for the first 3 years, then every 6 months for a further 2 years. The total follow-up time is 5 years. This guideline does not specify the intervals between HPV-tests nor how long serial HPV-testing should be carried out, and the decision should therefore be taken on an individual basis (p. 160; Table 20). Annual screening or follow-up is recommended after 5 years. • During the curative follow-up period, the recommendations of the annual general screening guideline (KFE-RL) without screening for cervical cancer apply.

Table 2.0 Summary of Relevant Systematic Reviews -1

Citation	Search details	Inclusion criteria	Intervention/ comparison	Results	Included studies
Sabeena, 2019	A comprehensive electronic literature search was performed to assess all the published literature in English between 1984 and 2018 regarding the persistence of HPV in cervical cancer cases after radiotherapy. The electronic databases included were PubMed/Medline, Scopus, and Google Scholar. Relevant articles in English were retrieved combining search terms of "human papillomavirus OR HPV AND cervical cancer AND radiotherapy NOT head and neck cancer." A manual library search for articles published in the peer-reviewed journals was performed. The search was last updated on September 30th, 2018.	Cohort studies in which histologically confirmed cervical cancer cases treated by radiotherapy, screened by HPV molecular assays and followed up for at least 1-year post-radiation were included. Studies with no molecular testing for HPV, no data on relapses/ recurrences, no histological correlation with outcome, carried out in immunocompromised individuals and not followed up for 1 year were excluded.	The objective of the present systematic review and meta-analysis was to assess the role of HPV DNA testing in early detection of recurrence among cervical cancer survivors after radiotherapy	A total of 1,055 cervical cancer cases who had received pelvic radiation with or without chemotherapy from ten cohort studies were evaluated. The overall pooled sensitivity and specificity of HPV DNA testing was 0.84 (95% CI=0.66–0.94) and 0.35 (95% CI=0.20–0.54) respectively. The positive likelihood ratio was 1.3 (95% CI=1.0–1.7) and the negative likelihood ratio was 0.45 (95% CI=0.18–1.10). The estimated diagnostic odds ratio was 3 (95% CI=1–9) denoting that a cervical cancer case with positive HPV DNA test after radiation has 3 times the odds of developing the recurrence in comparison to cervical cancer tested negative for HPV DNA after radiation.	Kaliff et al. Okonogi et al. Mahantshetty et al. Intharaburan et al. Song et al. Badaracco et al. Singh et al. Nagai et al. Harima et al. Bachtiary et al.

Table 3.0 Summary of Relevant Cohort Studies -12 studies

Citation (ref)	**Population**	**Test** (hpv/pap/pet)	**Follow-up** Time	**Objective and Outcomes**	**Results**
Wang Q, 2024 Retrospective	607 (all) patients with cervical cancer who underwent surgery between January 1, 2018, and June 30, 2019, were identified. The inclusion criterion was pathologically confirmed diagnosis of patients who underwent surgery for cervical cancer with HPV infection.	Clinical examination, a liquid-based cytology test, and HPV DNA genotyping and quantitative detection.	Follow-up visits were scheduled every 3 months during the first 2 years. Only data from 6, 12, and 24 months were included in the analysis.	The study objectives included controlling factors of HPV persistent infection and viral load to reduce the occurrence of vaginal intraepithelial lesions and cancer. The study aimed to guide a precise HPV follow-up schedule after cervical cancer surgery and mitigate the patient's psychological anxiety. The main outcome was the HPV rate.	Altogether, 607 women were eligible for the final analysis. The persistence rates of HPV at 6 months, 1 year, and 2 years after surgery were 17.3, 13.7, and 10.2%, respectively. In univariate analysis, the factors that were predictive of the persistence of HPV infection were old age, postmenopausal status, and positive vaginal incision margin with cancer. In multivariate analysis, the significant independent predictive factors were postmenopausal status and positive vaginal incision margin with cancer ($p < 0.05$, OR = 2.289, 95 % CI: 1.262–4.150 and OR = 3.271, 95 % CI: 1.253–8.537, respectively). A vaginal lesion with cancer or squamous intraepithelial lesion (SIL) and positive vaginal incision margin influenced HPV viral load at 6 months after surgery ($p < 0.05$).
Giannella, 2024 Retrospective	Multi-institutional study. 127 women treated conservatively with a histological diagnosis of adenocarcinoma in situ (AIS) or microinvasive adenocarcinoma (AC) (stage 1A) on cone specimens between January 2012 and	HPV, Pap test and colposcopy.	HPV and Pap test (co-testing) + colposcopy every six months for three years and then co-testing + colposcopy annually for two years.	The present study aimed to assess long-term follow-up outcomes in women with in situ/ microinvasive adenocarcinoma of the uterine cervix, treated conservatively.	127 participants underwent conservative treatment. During follow-up, recurrences were found in nine women (7.1%). The only factor associated with recurrence during follow-up was positive hr-HPV testing (odds ratio 6.21, 95% CI 1.47–26.08, $p = 0.012$). HPV positivity in follow-up showed a recurrence rate of 21.7% vs. 3.8% in patients who were HPV negative ($p = 0.002$, Log rank test).

	December 2017, with a total follow-up of 5 years. All patients with previous conizations, ongoing pregnancy, immunological disease, or undergoing hysterectomy were excluded.			Outcomes included recurrence rate, HPV DNA test results.	Among women with negative high-risk HPV tests in follow-up, recurrences occurred in 20.0% of non-usual-type histology vs. 2.1% of usual-type cases (p = 0.005). Conclusion: HPV testing in follow-up is of pivotal importance in women with early glandular lesions undergoing conservative treatment, given its recurrence predictive value. However, women who are high-risk HPV-negative in follow-up with non-usual-type histopathology may represent a sub-population at increased risk of recurrences.
Schuurman, 2023 Retrospective	1462 patients aged 18–40 years with cervical cancer of any histology who received fertility-sparing surgery (i.e., large loop excision of the transformation zone, conisation, or trachelectomy) between Jan 1, 2000, and Dec 31, 2020, were included.	Cervical cytology and hr-HPV testing.	After a median follow-up of 6.1 years (IQR 3.3–10.8), a median of seven cervical smears (IQR 4–10) were performed per patient. During the first 2 years after primary treatment, cervical smears were done in 1415 patients. Of these 1415 patients, 413 (29·2%) had one or two smears, 842 (59·5%) had three to five smears, and 160 (11·3%) had six or more smears.	The aim was to establish the predictive value of cervical cytology and hr-HPV testing to detect recurrent CIN2+ or worse; including recurrent cervical cancer, after fertility-sparing surgery. The primary and secondary outcomes were the cumulative incidence of recurrent CIN2+ and recurrence-free survival, overall and stratified by results for cytology and hr-risk HPV.	Of these included patients, 19568 pathology reports were available. The median age at diagnosis was 31 years (IQR 30–35). After a median follow-up of 6.1 years (IQR 3.3–10.8), recurrent CIN2+ was diagnosed in 128 patients (cumulative incidence 15.0%, 95% CI 11.5–18.2), including 52 patients (cumulative incidence 5.4%, 95% CI 3.7–7.0) with recurrent cervical cancer. The overall 10-year recurrence-free survival for CIN2+ was 89.3% (95% CI 87.4–91.3). By cytology at first follow-up visit within 12 months after fertility-sparing surgery, 10-year recurrence-free survival for CIN2+ was 92.1% (90.2–94.1) in patients with normal cytology, 84.6% (77.4–92.3) in those with low-grade cytology, and 43.1% (26.4–70.2) in those with high-grade cytology. By hr-HPV status at first follow-up visit within 12 months after surgery, 10-year recurrence-free survival for CIN2+ was 91.1% (85.3–97.3) in patients who were negative for

			In total, 3654 hr-HPV tests were performed on cervical smears and cervicovaginal self-samples during follow-up with a median of two per patient (IQR 1–4).		high-risk HPV and 73.6% (58.4–92.8) in those who were positive for high-risk HPV. Cumulative incidence of recurrent CIN2+ within 6 months after any follow-up visit (6–24 months) in patients negative for high-risk HPV with normal or low-grade cytology was 0.0–0.7% and with high-grade cytology was 0.0–33.3%. Cumulative incidence of recurrence in patients positive for hr-HPV with normal or low-grade cytology were 0.0–15.4% and with high-grade cytology were 50.0–100.0%. None of the patients who were negative for hr-HPV without high-grade cytology, at 6 months and 12 months, developed recurrence. Results suggest that co-testing seems to be the best follow-up strategy, but even separate test results are highly predictive. Patients who are negative for hr-HPV with normal or low-grade cytology at 6–24 months after fertility-sparing surgery, could be offered a prolonged follow-up interval of 6 months. This group comprises 80% of all patients receiving fertility-sparing surgery. An interval of 12 months seems to be safe after two consecutive negative tests for hr-HPV with an absence of high-grade cytology, which accounts for nearly 75% of all patients who receive fertility-sparing surgery.
Aryasomayajula, 2022 Retrospective	262 patients with a cervical cancer diagnosis. Squamous cell, adenocarcinoma,	hr-HPV	Median follow-up was 3.8 years (IQR: 2.4, 6.2).	The association of high-risk HPV in the posttreatment surveillance setting and	58 (22%) recurrences were diagnosed, and recurrence was most commonly detected by a surveillance imaging study (71%)

	adenosquamous, and neuroendocrine histologies were included. Those with cancer progression within 3 months of treatment or <1 year of documented surveillance were excluded.			cervical cancer recurrence. The secondary outcome was to determine which surveillance modalities were most commonly utilized, and which were most likely to lead to a diagnosis of recurrent disease.	169 patients that were tested for hr-HPV during the surveillance period, 41 (24%) had at least one positive hr-HPV test. Of those, 24 patients (14%) had recurrent disease. Five (21%) of those patients had a positive hr-HPV test documented during surveillance compared to 36 (25%) of the 145 patients without cancer recurrence, suggesting no association between hr-HPV status and disease recurrence (p = 0.67). No recurrences were detected by hr-HPV testing.
Jeannot, 2021 Prospective	419 patients with stage IB2–IV disease (2018 FIGO staging system); all histologic subtypes (excluding neuro-endocrine type); no prior treatment for cervical cancer. Serum samples from 94 patients, selected for HPV16- or HPV18-positive CC.	Circulating HPV DNA (HPV ctDNA)	Samples were collected before and after treatment and during an 18-month follow-up period.	The main objective was to investigate whether HPV ctDNA may be used for the early prediction of relapse after primary treatment in cervical cancer, similarly to other HPV-related cancers. Outcomes included HPV DNA testing, and progression-free survival.	HPV E7 gene was the most sensitive tumor marker, superior to both HPV integration sites and PIK3CA mutations in serum. Circulating HPV DNA (HPV ctDNA) was detected in 63% (59/94) of patients, before treatment. HPV ctDNA detection in serum sample was associated with high FIGO stage (p= 0.02) and para-aortic lymph node involvement (p= 0.01). The level of HPV ctDNA was positively correlated with HPV copy number in the tumor (r= 0.39, p< 0.001). Complete clearance of HPV ctDNA by the end of treatment was significantly associated with a longer PFS (p < 0.0001). Patients with persistent HPV ctDNA in serum relapsed with a median time of 10 months (range, 2–15) from HPV ctDNA detection.

Thomas, 2020 Retrospective	101 patients treated for cervical cancers and precancers (CIN 2 or CIN 3) between 1 January 2014 and 31 December 2015 and had post-treatment HPV DNA testing.	HPV DNA test	Patients treated for cancer were advised to have check-ups every 3-months for the initial two years, 6-month reviews for another three years and subsequently annual check-up. The patients were followed up till 31 June 2018. Average follow-up time of 9.3 months.	The primary objective was to determine the prevalence of HPV DNA in patients treated for cervical neoplasia. The secondary objective was to find any association between HPV positivity and local recurrence.	Of 101 patients, 26 had CIN 2 or 3 and 75 had cervical cancer. Post-treatment HPV was done in precancers and cancers after a mean duration of 14.9 and 8.2 months, respectively. Positive HPV detection occurred in 46.2% of precancers. At an average follow-up time of 9.3 months, HPV was positive in 14 cancer patients (18.7%). Among 14 cancer patients with positive post-treatment HPV, three (21.4%) had recurrence, and the RR was 3.3 (0.8- 13.9), with p = 0.09 with a positive HPV test after treatment compared to a negative HPV result. The average time between detection of positive HPV and recurrence in cancers was 3.3 ± 3.8 months.
Chao, 2020 Retrospective	264 recurrent cervical cancer patients. The inclusion criteria consisted of the following (1): confirmed recurrence during the study period, March 2012-April 2018 (2); histopathology of squamous cell carcinoma (SCC), endocervical adenocarcinoma, or adenosquamous carcinoma; and (3) acceptance of primary treatment	A comprehensive physical examination, cervical/vaginal cytology testing with or without high-risk human papillomavirus (hr-HPV) testing, a serum biomarker analysis (CA-125 for all patients and SCCAg for patients with SCC), abdominal and pelvic sonography and chest X-ray	Within the first year after the last treatment, the patient visited an outpatient clinic every 3 months. For the next year, the outpatient visit frequency was changed to every 4 months if no abnormal findings appeared.	The primary objective of the study was to provide a landscape of recurrence sites and relevant diagnostic methods in patients with cervical cancer. The secondary objective was to compare the efficiency of different diagnostic methods in detecting recurrence.	Recurrence occurred in the first three years after the last primary treatment in 214 patients (81.06%). Half of the recurrence events (50.76%) occurred only within the pelvic cavity, and most lesions (78.41%) were multiple in nature. Among all recurrent cases, approximately half were diagnosed based on clinical manifestations (n=117, 44.32%), followed by imaging examinations (n=76, 28.79%), serum tumor markers (n=34, 12.88%), physical examinations (n=33, 12.50%) and cervical cytology with or without high-risk human papillomavirus (hr-HPV) testing (n=4, 1.52%).

	and customized follow-up at the study center.	imaging were also performed. In addition, every 12 months, a secondary imaging assessment, including CT, MRI or PET-CT, was performed according to the preference of the patient and the potential necessity for disease evaluation.	In the third to fifth years, the visit frequency was changed to every 6 months, and for the subsequent period, it was reduced to every 12 months.	Outcomes included progression free and overall survival.	The reliability of the diagnostic methods was affected by the stage (p<0.001), primary treatment regimen (p=0.001), disease-free survival (p=0.022), recurrence site (p=0.002) and number of recurrence sites (p=0.001). Primary imaging methods (sonography and chest X-ray) were not inferior to secondary imaging methods (CT, MRI PET-CT) in the detection of recurrence. The chest X-ray examination only detected three cases (1.14%) of recurrence. Patients assessed with various diagnostic strategies had similar progression-free and overall survival outcomes.
Fuglsang, 2019 Case-control	282 women who had been surgically treated (i.e. radical hysterectomy and full PLN excision) for early-stage cervical cancer. January 1, 2003, to December 31, 2015. Cases were eligible if the primary tumor was HPV-DNA positive and if they had been diagnosed with cervical cancer recurrence in the period from cervical cancer diagnosis until August 24,2016, death, or emigration. Controls were randomly selected	Analysis of the tissue from the primary tumour, PLN and recurrent tissue for DNA extraction and HPV DNA genotyping.	-	To investigate HPV DNA genotyping in primary tumor, pelvic lymph nodes (PLN) and recurrence in early-stage cervical cancer patients. The outcome was HPV DNA genotype.	Recurrence happened in: Cases =25 Primary tumour HPV-DNA negative n=7 Primary tumour HPV-DNA positive n=18 Controls=18 Primary tumour HPV-DNA negative n=3 Primary tumour HPV-DNA positive n=15 HPV DNA-positive PLN was significantly associated with recurrence, 83% (95%CI: 52–98%), compared to patients with HPV-negative PLN, 38% (95%CI: 18–62%) (p < 0.05). HPV DNA genotyping was positive in eight of 12(67%) patients with recurrent disease. The genotype was identical in all three tissue types. The positive predictive value for recurrence was the same for detection of HPV-DNA and metastases in the PLN, with reasonable sensitivity (83%). The negative predictive

	from the study population and had to have no record of cervical cancer recurrence in the same time period.				value for recurrence, however, was best for HPV-DNA, 62% (95%CI: 38–98%). The median interval from surgery to recurrence was 22 months (IQR 8–35). The distribution of HPV DNA strains detected in the primary tumor was HPV16 (17/51%), HPV18 (8/24%), HPV31 (3/9%), HPV39 (4/12%), and HPV45 (1/3%)
Mahantshetty, 2018 Prospective	150 cervical cancer patients treated with radio (chemo) therapy were accrued between May 2010 and April 2012.	Cervical biopsies/ brushings were collected at pre-treatment, end of treatment and at 3 monthly intervals up to 24 months. Quantitative estimation of HPV 16/18 was done using real-time polymerase chain reaction and correlated with various clinical endpoints.	All patients were followed up regularly at three monthly intervals till two years after treatment completion, followed by 6 monthly check-ups for next 3 years and thereafter annually.	To investigate the impact of HPV 16/18 infection on clinical outcomes in locally advanced cervical cancers treated with radical radio (chemo) therapy. Outcomes included: HPV infection status, recurrence free survival, overall survival and loco-regional control.	135 patients were considered for final analysis. Pre-treatment HPV16/18 DNA was detected in 126 (93%) patients, with HPV-16 present in 91%. The mean log (±SD) HPV-16 and HPV-18 viral load at pre-treatment was 4.76 (±2.5) and 0.14 (±2.1) copies/10 ng of DNA, respectively. Significant decline in viral load was observed on follow-ups ($p < 0.0001$); by 9-month follow-up, 89 (66%) patients had persistence of HPV infection. Patients with persistent HPV 16/18 infection had significantly higher overall and loco-regional relapses (44/89 (49%) and 29/89 (32%)) as compared to HPV clearance by 9 months (12/43 (28%) and 5/43 (11%)) with $p = 0.024$ and $p = 0.02$, respectively. Relapses were higher with persistence HPV 70% (n = 19/27) vs. clearance 38% (n = 22/58) Vs. re-infection 30% (15/50), by 24-month post-treatment period.
Hallowell, 2018 Retrospective	693 participants were selected from seven central, population-	Initial HPV genotyping was performed on all samples using the	The Kaplan-Meier method was used to estimate five-	The objective of the present study was to overcome some of the limitations of previous	Five-year all-cause survival rates varied by HPV status (HPV 16: 66.9%, HPV 18: 65.7%, HPV 31/33/45/52/58: 70.8%, other oncogenic HPV genotypes: 79.0%, non-

	based cancer registries. Study eligibility included cases diagnosed between 1994 and 2005 with histologically HPV-typed confirmed ICC.	Linear Array HPV Genotyping Test, followed by INNO-LiPA HPV Genotyping Assay (Innogenetics) for negative or inadequate results.	year all-cause survival.	investigations to better characterize the impact of HPV genotype on ICC survival with follow-up data from a large sample of ICC patients from population-based cancer registries in the United States. Outcomes included HPV genotypes of tumours and survival.	oncogenic HPV: 69.3%, HPV-negative: 54.0%). Following multivariable adjustment, no statistically significant survival differences were found for ICC patients with HPV 16-positive tumors compared with women with tumors positive for HPV 18, other oncogenic HPV types, or HPV-negative tumors. Women with detectable HPV 31/33/33/45/52/58 had a statistically significant 40% reduced hazard of death at five years (95% CI= 0.38-0.95), and women who tested positive for non-oncogenic HPV genotypes had a statistically significant 57% reduced hazard of death at five years (95% CI =0.19-0.96) compared with women with HPV 16 tumors. Few statistically significant differences in HPV positivity, tumor characteristics, treatment, or survival were found by race/ethnicity. HPV genotype statistically significantly influenced five-year survival rates among women with ICC.
Song, 2017 Retrospective	173 (all) patients with cervical cancer who were treated at Beijing Obstetrics and Gynecology Hospital, Beijing, China, between January 2011 and December 2012 were identified. The inclusion criteria were as followed: a pathologically confirmed diagnosis	hr-HPV test Cervical or vaginal vault cytology	Patients were followed up from the completion of treatment to December 2015. Follow-up consisted of visits every 3 months for the first 2 years and then every 6 months during the third year. All patients were	To determine the negative conversion regularity of high-risk human papillomavirus (HR-HPV) and to evaluate the prognostic implications of HR-HPV testing in patients with cervical cancer after treatment	The negative conversion rate of hr-HPV reached 68.9 % within half a year and increased most rapidly within the first 2 years after treatment. Univariate and multivariate analyses suggested that the negative conversion rate of HR-HPV was significantly correlated with clinical stage, treatment regimens, and hr-HPV type ($p<0.05$). Among the 35 patients who experienced recurrences, 26 patients (74.29 %) relapsed

	of untreated squamous cervical cancer with HR-HPV infection. Patients with other malignant tumors, a history of HPV vaccination, and negative HR-HPV testing results, as well as patients receiving irregular treatments, were excluded.		followed up for at least 3 years. Cervical or vaginal vault cytology and HPV testing were performed every 6 months.	Primary outcomes included hr-HPV negative conversion and 3-year survival. Secondary outcomes included the sites and times of recurrence and/or metastasis.	within 2 years, and 9 patients (25.71 %) relapsed during the third year. hr-HPV status was predictive of 3-year survival rate and disease recurrence ($p<0.05$). Pelvic recurrence, but not distant metastasis, was influenced by HR-HPV status ($p<0.05$). Through 2x2 table analysis, it was found that hr-HPV was more sensitive (71.43 %) and specific (94.20 %) than cervical cytology (sensitivity 62.86 % and specificity 78.26 %). Negative conversion of hr-HPV can increase 3-year survival rates ($p<0.05$) and reduce the risk of recurrence ($p<0.05$). Persistent hr-HPV infection is associated with a poor prognosis.
Yu, 2015 Retrospective	Identified all patients who were given a diagnosis of and treated for cervical cancer at the institution from January 1, 2005, to December 31, 2012. Patients who underwent hr-HPV testing as part of their routine surveillance for cervical cancer.	Hr-HPV DNA testing was ordered by clinicians according to several ordering options: reflex testing triggered by atypical squamous cell ThinPrep cytology; co-testing with ThinPrep tests for women 30 years and older; and co-testing regardless of either age or ThinPrep test results. Hybrid Capture II with a	The average number of follow-up cytology tests was 4.3 with a range of 1 to 11. The average number of follow-up hr-HPV tests was 1.8 with a range of 1 to 7. Patients were followed up for an average of 26.6 months.	To identify the role of cervicovaginal high risk human papilloma virus (hr-HPV) testing in predicting cervical cancer recurrence. Outcomes included: hr-HPV status and recurrence.	A total of 133 patients were identified, of whom 107 (80%) had squamous cell carcinoma. 90 patients (68%) had bulky disease and were treated primarily with chemoradiation and brachytherapy. Recurrent disease was diagnosed in 12 patients. Five patients (42%) had tested positive for hr-HPV during their surveillance period, compared to 13 patients (11%) for whom disease did not recur (RR: 3.88, p= 0.002). On multivariate logistic regression, hr-HPV status remained significantly predictive of disease recurrence (OR: 12.3, p = 0.02, 95% CI: 1.5–99.6). Using 2x2 table analysis, it was found that while cervicovaginal cytology has limited specificity (5.7%) in predicting

	133 patients were identified, of whom 107 (80%) had squamous cell carcinoma.	cutoff point of 1pg/mL.			recurrence, the combination of cytology with hr-HPV testing increases the specificity of testing to 89.3%.

AIS: Adenocarcinoma in situ; AC: Adenocarcinoma; CI: Confidence Interval; CIN: Cervical intraepithelial neoplasia; CT: Computed Tomography; DNA: Deoxyribonucleic Acid; HPV: Human Papillomavirus; hr-HPV; high-risk HPV; MRI: Magnetic Resonance Imaging; ICC: Invasive Cervical Cancer; ICD: International Classification of Diseases; IQR: Interquartile Range; OR: Odds Ratio; PET-CT: Positron emission tomography-computed tomography; SCC: Squamous Cell Carcinoma; RR: Relative Risk; SIL: Squamous Intraepithelial Lesion

Appendix 1.0 Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Authors		
Rachel Kupets	Gynecologic Oncologist, Odette Cancer Centre - Sunnybrook Health Sciences Centre; Scientific Lead, Ontario Cervical Screening Program	None
Caroline Zwaal	Health Research Methodologist, Program in Evidence-based Care McMaster University	None
Expert Panel		
George Gray	Gynecologic Oncologist, Queens University and Kingston Health Sciences Centre	None
Eric Leung	Radiation Oncologist, Odette Cancer Centre - Sunnybrook Health Sciences Centre	None
Lina Salman	Gynecologic Oncologist, London Health Sciences Centre	None
Tiffany Zigras	Gynecologic Oncologist, Trillium Health Partners - Credit Valley Hospital	Other financial or material support of $500 or more in a single year: Roche & Merck provided sponsorship for Colposcopy Day 2023 for which I was the chair. Published an editorial, commentary, or other clear opinion regarding any of the objects of study: Zigras T, Mayrand MH, Bouchard C, Salvador S, Eiriksson L, Almadin C, Kean S, Dean E, Malhotra U, Todd N, Fontaine D, Bentley J. Canadian Guideline on the Management of a Positive Human Papillomavirus Test and Guidance for Specific Populations. Curr Oncol. 2023 Jun 9;30(6):5652-5679. Had managerial responsibility for an organization or department that has received $5,000 or more in a single year from a relevant business entity: MHCW regional cancer program hosted colpo day in 2023; we recieved sponsorship from ROCHE and MERCK

		Any other interests: I am a board member of the Society of Colposcopist of Canada and also Co-Chair the Community of Practice in HPV for the Society of Gynecologic Oncologists of Canada

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DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary, but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.