Guideline 4-16 Version 2

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

Follow-up for Cervical Cancer

L. Elit, E.B. Kennedy, A. Fyles, U. Metser, and the PEBC Gynecologic Cancer Disease Site Group

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An assessment conducted in November 2016 deferred the review of Evidence-based series (EBS) 4-16 Version 2, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The Complete Guideline 4-16 comprises five sections:

Section 1: Recommendations Summary
Section 2: Guideline
Section 3: Guideline Methods Overview
Section 4: Evidence Review
Section 5: Internal and External Review

For information about this document, please contact Dr. Laurie Elit, via the PEBC:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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


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Guideline 4-16 Version 2: 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.

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

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

Follow-up to Five Years
• A reasonable follow-up strategy involves visits at the following intervals:
  o every three to four months within the first two years,
  o 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.
  o 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.
  o 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.
  o If vaginal vault cytology examination is used to detect new precancerous conditions of
the vagina it should be performed no more frequently than once a year. An abnormal cytology result that suggests the possibility of neoplasia warrants colposcopic evaluation and directed biopsy for histological confirmation.

- Because their role has not been evaluated in a definitive manner, the following investigations are not advocated:
  - Positron emission tomography (PET) with computed tomography (PET-CT),
  - Other imaging or biomarker tests in asymptomatic patients.

- Although there is evidence showing that HPV DNA testing has promise as a method of detection of recurrence after radiotherapy, data are preliminary and need verification in higher quality studies with larger sample sizes, and HPV DNA testing is currently unfunded at this time in the province of Ontario.

Follow-up Beyond Five Years

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

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RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

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    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.

### Key Evidence

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

**HPV Testing**

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

**Cervicovaginal Cytology**

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

**Serum Biomarkers**

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

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

Cytology Follow-up After Radiotherapy

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

Summary of 2009 Evidence Base [6]:

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

Qualifying Statement:

The National Advisory Committee on Immunization issued a statement in 2012 recommending the use of a quadrivalent human papillomavirus vaccine (Gardasil, Merck Canada, Inc.) or bivalent vaccine (Cervarix™, GalaxoSmithKline, Inc.) in girls and women to protect against dysplastic lesions caused by HPV 16/18. The quadrivalent vaccine is available for females 9 to 45 years and males 9 to 26 years of age. The bivalent quadrivalent 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.
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.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=122178. Guideline history is presented in Appendix 1.

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

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