CURRENT ONCOLOGY
A Canadian Cancer Research Journal

PRACTICE GUIDELINE

Follow-up for cervical cancer: a Program in Evidence-Based Care systematic review and clinical practice guideline update

L. Elit MD,* E.B. Kennedy MHSc,† A. Fyles MD,‡ and U. Metser MD‡

ABSTRACT

Background In 2009, the Program in Evidence-based Care (PEBC) of Cancer Care Ontario published a guideline on the follow-up of cervical cancer. In 2014, the PEBC undertook an update of the systematic review and clinical practice guideline for women in this target population.

Methods The literature from 2007 to August 2014 was searched using MEDLINE and EMBASE [extended to 2000 for studies of human papillomavirus (HPV) DNA testing]. Outcomes of interest were measures of survival, diagnostic accuracy, and quality of life. A working group evaluated the need for changes to the earlier guidelines and incorporated comments and feedback from internal and external reviewers.

Results One systematic review and six individual studies were included. The working group concluded that the new evidence did not warrant changes to the 2009 recommendations, although HPV DNA testing was added as a potentially more sensitive method of detecting recurrence in patients treated with radiotherapy. Comments from internal and external reviewers were incorporated.

Recommendations Summary Follow-up care after primary treatment should be conducted and coordinated by a physician experienced in the surveillance of cancer patients. A reasonable follow-up strategy involves visits every 3–4 months within the first 2 years, and every 6–12 months during years 3–5. Visits should include a patient history and complete physical examination, with elicitation of relevant symptoms. Vaginal vault cytology examination should not be performed more frequently than annually. Combined positron-emission tomography and computed tomography, other imaging, and biomarker evaluation are not advocated; HPV DNA testing could be useful as a method of detection of recurrence after radiotherapy. General recommendations for follow-up after 5 years are also provided.

Key Words Cervical cancer, systematic reviews, clinical practice guidelines, follow-up, surveillance

Curr Oncol. **2016 Apr;23(2):109-118** **www.current-oncology.com**

INTRODUCTION

Approximately 580 new cases of, and 140 deaths from, cervical cancer occur in the province of Ontario each year[1]. Most cervical cancers are squamous cell carcinomas (SCCS); adenocarcinoma accounts for 10%–15% of cases[2]. Depending on disease stage, treatment consists of surgery, radiation therapy, or a combination of radiation and chemotherapy[2], and the risk of recurrence ranges from 13% to 17%[3]. Most cases are diagnosed at International Federation of Gynecology and Obstetrics stage I or II[3], and the 5-year survival rate for those women is high—that is, 80%–85% for stage IB disease treated with radical hysterectomy and pelvic lymphadenectomy[4].

In 2009, the Program in Evidence-Based Care (PEBC) published a guideline for the follow-up of cervical cancer patients who had experienced complete response to treatment[5]. The evidence base for that guideline was developed using a systematic review of follow-up methods and follow-up appointment frequency. Outcomes of interest included survival, recurrences detected during screening, and quality of life. The evidence base contained no prospective studies with direct comparisons of follow-up regimens and was therefore deemed to be of lower quality.

Correspondence to: Laurie Elit, McMaster University, Juravinski Hospital, G Wing, 2nd Floor, Room 226, 1280 Main Street West, Hamilton, Ontario L85 4L8. E-mail: ccopgi@mcmaster.ca ■ **DOI:** http://dx.doi.org/10.3747/co.23.2742

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 noted that areas for future research included the roles of positron-emission tomography combined with computed tomography (PET-CT) and of tumour markers in detecting recurrence. In the course of the regular guideline review process in 2014, the PEBC Gynecologic Cancer Disease Site Group became aware that new evidence concerning those methods of detection had been published, as had new information on the potential for human papillomavirus (HPV) DNA testing in this patient population. On that basis, the members of the PEBC Gynecologic Cancer Disease Site Group decided to undertake a full update of the PEBC guideline for the follow-up of cervical cancer.

The goal of the present 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 for cervical cancer. This practice guideline is for clinicians involved in the care and follow-up of women who have received treatment for cervical cancer and is intended to promote evidence-based practice in Ontario.

METHODS

This evidence base was developed by Cancer Care Ontario's PEBC, using the methods of the practice guidelines development cycle[6]. Evidence was selected and reviewed by members of the Cervical Cancer Follow-up Guideline Working Group, which included individuals with expertise in gynecologic oncology, health research methodology, and oncology-related imaging.

Literature Search Strategy

A search of the literature from 1980 to 2007 had been conducted for the previous version of the guideline. For this update, the literature was searched using MEDLINE and EMBASE (OVID: November 2007 through 18 August 2014; Table I). The search for articles related to HPV DNA testing was extended to also include the years 2000–2006, because that term had not been captured in the earlier version of the guideline. The Cochrane Library, the Canadian Medical Association Infobase, and ClinicalTrials.gov were searched for 2007–2014. Reference lists of studies deemed eligible for inclusion in the systematic review were scanned for additional citations.

TABLE I Literature 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)

Study Selection Criteria and Outcomes of Interest

Inclusion Criteria

Studies were included if they reported follow-up strategies for patients who were clinically disease-free after potentially curative treatment for cervical cancer. Eligible study types were systematic reviews, randomized controlled trials, or nonrandomized studies.

For studies of follow-up interval, the working group chose to include only prospective or retrospective studies that compared two or more distinct study groups. The working group was 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 for various follow-up strategies. For diagnostic-accuracy studies, the outcomes of interest were sensitivity, specificity, positive predictive value, negative predictive value, and hazard ratios for recurrence. Patient quality of life was an additional outcome of interest.

Exclusion Criteria

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 for fewer than 25 patients.

Data Extraction and Quality Assessment

Systematic reviews identified in the search of electronic databases were assessed for methodologic quality using the 11-item AMSTAR tool[7] (Table II).

For primary studies, important characteristics of the study populations were extracted, including primary treatment type, histologic type of cervical cancer, and disease stage. The intervention and comparator under study were extracted where applicable. Determination of study quality was based on an assessment of study design and risk of bias. Data extraction was conducted by the project methodologist and was verified by a project research assistant. All authors 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.

Internal Review

The draft document underwent review by the PEBC Gynecologic Cancer Disease Site Group, which acted as the Expert Panel for this report, and by the PEBC Report Approval Panel, a 3-person panel with methodologic and clinical expertise. Formal approval by the panels was required, and the members were also invited to provide comments. The working group was responsible for incorporating the feedback and changes that were suggested.

External Review by Ontario Clinicians and Other Experts

The PEBC's external review process includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to practitioners.

Several weeks before completion of the draft report, targeted peer review nominees were contacted by e-mail and asked to serve as reviewers. Two nominees agreed, and the draft report and a questionnaire were sent to them by e-mail. The questionnaire consisted of items evaluating the methods, presentation, and clinical soundness of the recommendations and the completeness of reporting. Written comments were invited. The questionnaire and draft document were distributed 26 February 2015.

Professional consultation feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline and whether they would use or recommend it. Written comments were invited. Participants were contacted by e-mail and directed to the survey Web site, where they were provided with access to the survey, the guideline recommendations, and the evidentiary base. The e-mail notification was sent 27 February 2015. The consultation period ended 4 April 2015.

LITERATURE SEARCH RESULTS

Figure 1 presents a detailed flow diagram of the literature search results.

Systematic Reviews

Three systematic reviews that met the inclusion criteria were located in the search. One review[8] limited inclusion of studies to randomized controlled trials. No studies met the inclusion criteria, and that systematic review was therefore eliminated from further consideration. Two systematic reviews authored by Meads *et al.*[9,10] covered the role of PET-CT in detecting recurrence after complete response to treatment for cervical cancer. The more up-to-date version, which scored highly on the AMSTAR tool for methodologic quality (Table II), was retained; the older review was excluded from further consideration. Using QUADAS to assess the quality of included diagnostic accuracy studies, Meads *et al.*[9] found that overall study quality was poor because very little information about the characteristics of the study participants was provided and because studies were frequently subject to verification bias.

TABLE II AMSTAR questions and responses

Question	Response
Was an *a priori* design provided?	Yes
Was there duplicate study selection and data extraction?	Yes
Was a comprehensive literature search performed?	Yes
Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Grey literature not mentioned for inclusion
Was a list of studies (included and excluded) provided?	Excluded not provided
Were the characteristics of the included studies provided?	Yes
Was the scientific quality of the included studies assessed and documented?	QUADAS tool was used to assess study quality; study quality overall was found to be poor
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
Were the methods used to combine the findings of studies appropriate?	Yes
Was the likelihood of publication bias assessed?	Yes

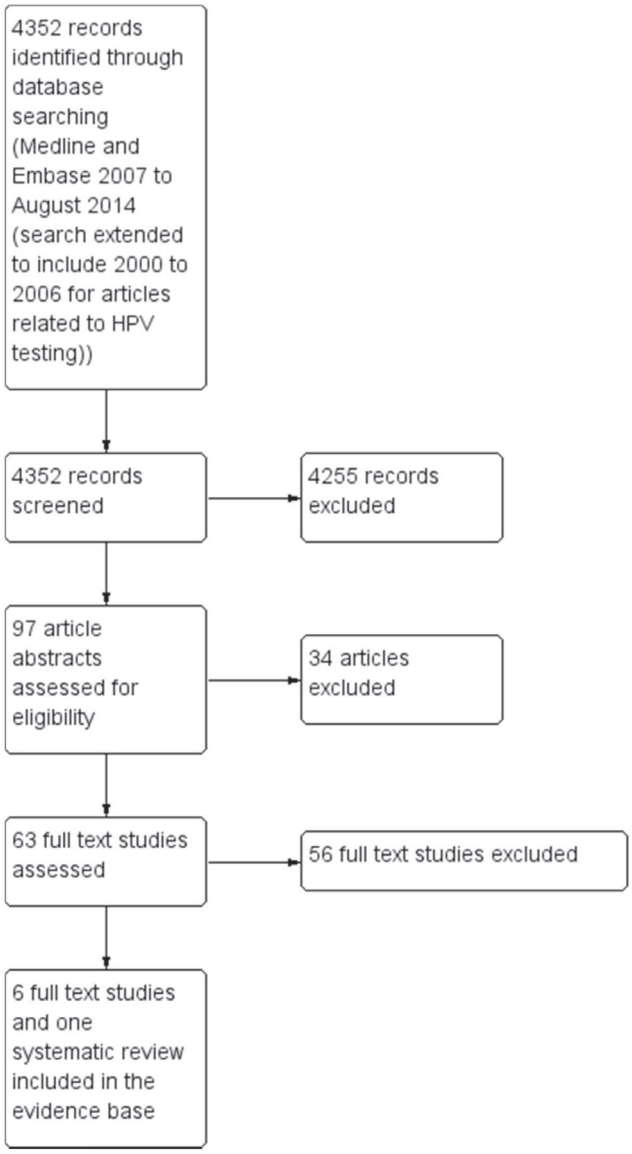

FIGURE 1 Flow diagram of study results.

Primary Literature

Study Characteristics

No studies that compared one regimen of follow-up frequency with another were found. Six individual studies that assessed various methods of follow-up[11–16] were included; two of them looked at HPV DNA testing[15,16], one addressed the role of serum biomarkers in detecting recurrence[11], and three addressed the role of vaginal vault cytology[12–14]. No studies were found that addressed the following methods of detection that were considered in the previous version of the guideline: chest radiography, ultrasonography, PET or magnetic resonance imaging as stand-alone modalities, or intravenous pyelography.

Studies included in this update were conducted in India[12,15], Korea[16], the United States[13,14], and the Netherlands[11] (Table III). Study sample size ranged from 56[15] to more than 1500 patients[12]. Most studies were retrospective; two looked at prospective cohorts[15,16]. A variety of data sources, including hospital records, cancer registries, patient databases, and a biobank (for the tumour marker study[11]) were used. Follow-up timelines ranged from a few days[11] to more than 5 years[13]. Funding, where reported, was provided by government sources[15,16]. Outcomes of interest included measures of diagnostic accuracy, and hazard ratios for recurrence. The predominant histologic type considered in the studies was SCC; a small number addressed adenocarcinoma or other histologic types. The studies varied widely with respect to the types of treatment and the initial stage of the patient population (Table IV). Institutional review board approval was sought and obtained in all studies.

Quality Assessment of Individual Studies

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

Internal Review

The Expert Panel reviewed the document in January 2015. Of the 10 members, 9 cast votes, and 1 abstained, for a 90% response. Of members that voted, all approved the document with only minor rewording suggestions, which were incorporated.

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

External Review

The 2 reviewers who provided targeted peer review responses were located in the Canadian province of Ontario and in Italy. The professional consultation resulted in 61 replies from the province of Ontario.

The participants in both processes rated the guideline highly on methods, presentation, recommendations, completeness of reporting, information included, and quality. Many of the respondents to the professional consultation were primary care practitioners, and they commonly expressed concerns about barriers to implementation of the recommendations within in their professional group. Those concerns included potential difficulty in justifying the recommendations to patients given the lower level of evidence, concerns about skill and comfort level with tests such as vault smears, concerns about the cost and availability of tests, and concerns about patient compliance.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

After review and analysis of the new evidence, the working group determined that no changes to the existing recommended screening intervals or screening methods were warranted. Additionally, the new studies that were added to the evidence base concerning PET-CT and serum

TABLE III Study characteristics

Reference	Country	Study cohort	Sample	Comparison	Data source	Years of treatment	Follow-up (months)	Funding source	Outcomes of interest
Singh *et al.*, 2006[15]	India	Prospective	56 Post-RT cervical cancer patients	HPV vs. no HPV, high vs. low viral load	Samples taken after final RT fraction	1988 and 2004	Range: 5–224	Government	Prevalence of HPV in exfoliated cells and plasma
Orr *et al.*, 2011[13]	U.S.A.	Retrospective	61 Post-surgical or post-RT patients	Single group	Tumour registry database	1990 to 2003	Median: 143 (after 5 years recurrence-free follow-up)	Not stated	Yield from cytology screening
Rimel *et al.*, 2011[14]	U.S.A.	Retrospective	929 Patients	Cytology-positive vs. cytology-negative	Cancer registries and patient databases	2000 to Nov 2009	2.5–118.2 (median: 32)	Not stated	Percentages of recurrences detected by liquid-based cytology
Song *et al.*, 2011[16]	Korea	Prospective	156 Patients with HPV-positive cervical cancer	HPV cleared vs. HPV persistent	Hospital records	Jul 2003 to Dec 2006	Range: 6–66 (median: 41)	National Cancer Centre Korea	Diagnostic accuracy of HPV test, local relapse-free survival
Gupta *et al.*, 2013[12]	India	Retrospective	1566 Women who underwent hysterectomy	Cytology-positive vs. cytology-negative	Samples from a tertiary care hospital	2001 to 2010	24–120	Not stated	Diagnostic accuracy of vault cytology, with "gold standard" biopsy
Hoogendam *et al.*, 2013[11]	Netherlands	Retrospective	75 Patients	9 serum biomarkers: CA 15-3, CA 125, CEA, CYFRA 21-1, hsCRP, IL-6, SCC-Ag, TNF-α, VEGF	Biobanked samples from cervical cancer patients	Jan 1988 to Jan 2000	7 Days to 5 years	Not stated	Diagnostic accuracy of 9 serum biomarkers; odds ratio for recurrence

RT = radiation therapy; HPV = human papillomavirus; CA = cancer antigen; CEA = carcinoembryonic antigen; CYFRA 21-1 = cytokeratin 19 fragment; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; SCC-Ag = squamous cell carcinoma antigen; TNF-α = tumour necrosis factor α; VEGF = vascular endothelial growth factor.

TABLE IV Study data

Reference	Pts (*n*)	Primary treatment (%)					Histology (%)			Stage (%)					
		Surgery	Radiotherapy	Chemoradiation	Surgery plus radiotherapy	Surgery plus chemoradiation	Squamous	Adenosquamous	Adenocarcinoma	IA	IB	IIA	IIB	III	IV
Singh *et al.,* 2006[15]	56	—	100	—	—	—	"Carcinoma"			—	11	2	36	IIIB: 46	IVB: 5
Orr *et al.,* 2011[13]	61	69	10	18	—	2	77	20			80			20	
Rimel *et al.,* 2011[14]	929	40	3	42	4	11	74	26		13	55	19		11	2
Song *et al.,* 2011[16]	156	—	13	81	—	—	91.3	8.7		—	21	56		IIIA, IIIB, IVA: 18	IVB: 6
Gupta *et al.,* 2013[12]	1566	All had surgery combined with unspecified other treatment					"Carcinoma"			Early: 34; advanced: 66					
Hoogendam *et al.,* 2013[11]	75	51	—	47	—	3	84	16		5	47	11	17	15	5

biomarkers lacked sufficient evidence to warrant a recommendation for the use of those tests. Testing for HPV DNA is noted as a new option that has the potential to detect risk of recurrence in patients treated with radiotherapy.

The full recommendations follow.

Recommendations

General Guidance for Follow-Up

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

Follow-Up to Five Years—Intervals and Methods

A reasonable follow-up strategy involves visits at these intervals:

- Every 3–4 months within the first 2 years
- Every 6–12 months during years 3–5

At a minimum, follow-up visits should include a patient history and 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 or findings 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 or rectal examination. Focused imaging or testing appropriate to findings is warranted.

If vaginal vault cytology is used to detect new precancerous conditions of the vagina, it should be performed no more frequently than once annually. An abnormal cytology result that suggests the possibility of neoplasia warrants colposcopic evaluation and directed biopsy for histologic confirmation.

Because their role has not been evaluated in a definitive manner, these investigations *are not advocated*:

- PET-CT
- Other imaging or biomarkers in asymptomatic patients

HPV DNA testing

Smaller preliminary studies indicate that HPV DNA testing holds promise as a method of detection of recurrence after radiotherapy, with potential for highest utility at 3 months after completion of treatment, rather than immediately after treatment has been completed. However, HPV DNA testing is currently unfunded in the province of Ontario. The available evidence does not warrant serial testing with Pap and HPV DNA testing.

Follow-Up Beyond Five Years

After 5 years of recurrence-free follow-up,

- patients can return to annual assessment, with history, general physical examination, and pelvic examination with cervical or 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 might require more prolonged follow-up at the cancer centre.

- routine lower genital tract screening according to population-based guidelines is recommended for patients who have undergone surgical treatment. Cytology follow-up is not recommended for patients who have been treated with radiotherapy because, after treatment with radiotherapy, the accuracy of cervicovaginal cytology for cervical cancer is compromised by the anatomic and tissue changes resulting from irradiation[17].

Summary of Key Evidence and Justification for Recommendations

HPV DNA testing

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

In Singh *et al.*[15], HPV DNA was detected in samples taken from 44 of 56 patients immediately after their last radiation treatment. Recurrences were detected in 14 patients. Significant association (correlation) with recurrence was seen in women with HPV-positive exfoliated cells ($p = 0.01$) and a high viral load (≥100 pg/mL, $p = 0.007$). Presence of HPV DNA in plasma was significantly associated with its presence in exfoliated cells, with viral load, and with recurrence. Table v presents sensitivity and specificity data. Disease-free survival was significantly higher in patients who tested negative for plasma HPV DNA than in those who tested positive ($p = 0.04$). The authors concluded that in post-radiotherapy cervical cancer patients, high viral load in exfoliated cells and HPV DNA in plasma samples could be used to identify patients at increased risk for disease recurrence and progression.

In Song *et al.*[16], HPV DNA test results at 1, 3, 6, and 12 months after radiotherapy were evaluated for an association with local recurrence. Results of HPV DNA testing at 3 months had the highest sensitivity, specificity (Table v), and overall accuracy and were more accurate than the results of testing at 1 month after radiotherapy, possibly as a result of the presence of cellular debris after radiotherapy. A patient's HPV status at 24 months was significantly associated with local relapse after radiotherapy.

Cervicovaginal Cytology

Two studies[12,14] found during the update addressed the value of vaginal vault cytology during follow-up within 5 years after treatment. The first[12] was a retrospective examination of the value of vaginal vault or cervical smears that was designed to address the utility of that method of detection in a lower-resource location managing a population of women who presented mostly with advanced-stage disease. Confirmatory biopsies were conducted for smears that were indicative of malignancy or were inconclusive. In 1972 women who had previously been treated for gynecologic malignancies, 140 recurrences were detected. In all cases in which a biopsy was conducted based on a smear malignancy, the diagnosis was confirmed (specificity of 100%); however, a confirmatory biopsy was conducted in only 72% of positive smears. Sensitivity and false-negative rates could not be calculated because negative smears were not followed up with biopsy. Of the 140 women who tested positive for recurrence with cytology, 65.7% presented with advanced disease, most within 2 years (92.1%) of initial treatment. In nearly 24% of cases, cytology testing was the method of detection; the other 76% of the women either presented with symptoms or had vaults that were "clinically unhealthy" on examination.

Rimel *et al.*[14] evaluated the utility of liquid-based cytology in detecting recurrent cervical cancer. No data on recurrences detected by other methods were provided. Cancer recurrence was documented in 147 of the women in the study population (15.8%), with 12 recurrences (8.1%) being detected by Pap test. Compared with patients treated using surgery alone, those who had been treated with radiation therapy had more abnormal Pap test results (8.7% vs. 14.8% respectively). In the study, Pap surveillance appears to have led to salvage for recurrence in 3 of 929 cervical cancer survivors (0.3%). In that study population, 810 Pap tests would be required to detect at least 1 cancer with 90% probability.

Orr *et al.*[13] found a very low yield with continued cytology surveillance among women who had completed 5 years of post-treatment surveillance without recurrence. No cases of cancer were diagnosed in the 61 women included in the study population. The authors considered their results to be evidence of the futility of Pap testing in the passive surveillance period (beyond 5 years without recurrence). The 17 abnormal Pap tests reported led to the performance of 3 diagnostic procedures, and the diagnosis and treatment of 1 case of vaginal dysplasia.

Serum Biomarkers

The results of one study[11] with a sample size of 75 indicated that elevated serum levels of SCC antigen and high-sensitivity C-reactive protein were associated with increased odds of experiencing a disease recurrence ($p = 0.003$ and $p < 0.001$ respectively). The diagnostic accuracy of both those 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. The former 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

A meta-analysis[9] evaluated the diagnostic accuracy of PET-CT as surveillance in women with suspected recurrent or persistent cervical cancer and in asymptomatic women. The overall estimate of sensitivity was 94.8% (95% CI: 91.2% to 96.9%), and the specificity, 86.9% (95% CI: 82.2% to 90.5%); however, only two of nine studies in the analysis included asymptomatic patients.

Summary of the Evidence Base for the 2009 Guideline

The basis for the 2009 version of this PEBC guideline is a systematic review that included seventeen studies published between 1980 and November 2007[5]. Those studies reported

TABLE V Results of diagnostic accuracy studies included in the systematic review

Reference	Patients (*n*)	Test	Comparator ("gold standard")	Time period	Sensitivity (%)	Sensitivity (95% CI)	Specificity (%)	Specificity (95% CI)
Singh *et al.*, 2006[15]	56	PCR (exfoliated cells)	Not stated	5–224 Months	100	77–100	29	16–45
	56	HPV viral load in exfoliated cells		5–224 Months	100	77–100	37	20–56
	56	HPV DNA presence in plasma		5–224 Months	57	29–82	93	80–98
Rimel *et al.*, 2011[14,a]	929	Liquid-based cytology	Disease recurrence detected by other methods	2.5–118 Months (median: 32 months)	8		Not reported	
Song *et al.*, 2011[16]	125	Hybrid Capture 2[b] tests for 13 types of HPV; cut-off: ≥1 RLU	Biopsy	3 Months	78		82	
Gupta *et al.*, 2013[12,c]	1566	Vault cytology	Pathology or clinical findings	Up to 10 years after initial diagnosis (92% of recurrences detected within 2 years)	Not stated		100	
Meads *et al.*, 2014[9]	Systematic review (9 studies, 500 patients)	PET-CT	Pathology or clinical findings	Not stated	95	91–97	87	82–91

a Values calculated using figures presented in the original article.
b Qiagen, Hilden, Germany.
c Diagnosis verified by biopsy in 76% of cases determined to be malignant or inconclusive on cytology.
CI = confidence interval; PCR = polymerase chain reaction; HPV = human papillomavirus; RLU = relative light unit; PET-CT = positron-emission tomography–computed tomography.

follow-up strategies for women who were disease-free after primary treatment for cervical cancer.

- In nine studies that reported data, 62%–89% of cervical cancer recurrences were detected within 2 years of primary treatment. In six studies that reported data, a minimum of 89% of recurrences were detected by 5 years.
- Fifteen of the seventeen retrospective studies reported whether recurrences were symptomatic or asymptomatic. Approximately two thirds of patients presented with symptoms (range: 46%–87%), and approximately one third of patients were asymptomatic (range: 4%–54%).
- Scheduled follow-up visits varied from a low of 9 to a potential high of 28 over 5 years. Most studies described similar intervals: follow-up visits every 3–4 months within the first 2 years, every 6 months during the next 3 years, and 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 seventeen retrospective studies. Across those studies, a median 52% of recurrences were detected by physical examination, and a median 6% were detected by vaginal vault cytology.
- Of the studies that reported on the routine use of chest radiography, abdominal and pelvic ultrasonography, PET, CT, magnetic resonance imaging, intravenous pyelography, or tumour markers, the reporting was generally inconsistent, and the impact of asymptomatic recurrence detection on survival was not known.

DISCUSSION

No new comparative studies on follow-up interval were found during the literature search for this update of the PEBC's 2009 guideline on the follow-up of cervical cancer[5]. Some new information was identified about methods of surveillance to detect asymptomatic recurrences, which, across disease stages, constitute 4%–50% of recurrences[5].

Two studies assessed the role of vaginal vault cytology in the first 5 years after complete response. In the past, that technique was found to have limited sensitivity for detecting recurrences, and might be compromised by ambiguous cell morphology in the early post-radiotherapy period[16]. One of the two new studies located for the present systematic review corroborated those earlier findings[14]; 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[12]. 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[12]. In addition, patients might not have had access to the most effective treatment modalities, and so the applicability of the study to higher-resource locations is therefore questionable. A study of cytology testing in the passive surveillance period beyond 5 years of recurrence-free follow-up was also found to have a very low yield with the technique[13].

Two new studies that assessed the role of HPV DNA testing in the detection of recurrence were included in the present systematic review. Both showed that, compared with Pap testing as reported in earlier studies, HPV DNA testing had a much higher sensitivity for detection of recurrent cervical cancer after radiotherapy. The utility of such testing appears to be highest approximately 3 months after completion of treatment, because HPV DNA persistence immediately after successful treatment could be a result of the presence of HPV DNA or HPV DNA sequence fragments (or both) in the degraded tumour cells or cell debris[18]. Although the results of these new studies are promising, the data are preliminary and require verification in higher-quality studies with larger sample sizes. In addition, HPV DNA testing is not currently funded in Ontario.

New studies on PET-CT and serum biomarkers were also included in the update. A systematic review of PET-CT found that the evidence base was of poor quality because of the retrospective and uncontrolled nature of the studies and because of the bias frequently introduced by lack of verification of diagnostic test results. In addition, most studies involved patients with a suspected recurrence rather than asymptomatic populations undergoing surveillance. For example, the study that made the main contribution to the overall estimates of sensitivity and specificity in Meads *et al.*[9] included both symptomatic and asymptomatic patients and did not distinguish between them[19]. Another study found that, in 103 patients who had a complete metabolic response to treatment[20], 13 asymptomatic recurrences were detected by PET or PET-CT. Those patients demonstrated better cause-specific survival than did patients who experienced symptomatic recurrences (59% vs. 19%, $p = 0.09$); however, it is not clear whether the recurrences were also detected by other methods, and thus the added value of PET-CT is not known. The authors concluded that prospective validation of the technology is warranted[20]. The study that assessed 9 serum biomarkers found that SCC antigen and high-sensitivity C-reactive protein appear promising for the detection of disease recurrence[11]; but again, the authors concluded that prospective comparative studies are needed.

CONCLUSIONS

The evidence base for the follow-up of cervical cancer contains a gap; in another review of the literature, nineteen randomized controlled trials of varying methodologic quality were identified for colorectal and breast cancer follow-up, but none for gynecologic cancer[21]. 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 still has not been conclusively determined, and a prospectively designed study to validate the effect of early detection on survival rates is needed[11] because the largest study to date has been a retrospective review[22], and lead-time and length-time biases must be taken into consideration[20]. More specific topics in need of research include the time course of HPV DNA clearance in invasive cervical carcinoma managed with radiation therapy[18], trials of the tumour marker SCC antigen during cervical cancer follow-up[11], and prospective validation of PET-CT as a method of surveillance for asymptomatic women[20]. The idea of more-personalized follow-up programs, including routine biomarker testing during follow-up[11] or more frequent intervals for individuals at higher risk could allow for more individualized surveillance programs and could possibly improve the detection of asymptomatic recurrence early enough to allow for effective salvage or alternative treatment[18].

ACKNOWLEDGMENTS

The PEBC Gynecologic Cancer Disease Site Group thanks the following individuals for providing feedback on draft versions of this guideline: Chika Agbassi, Fulvia Baldasarre, Melissa Brouwers, Bill Evans, Sheila McNair, Hans Messersmith, Rebecca Wong, and Kristy Yiu (for conducting a data audit).

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

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: LE was coauthor on the previous version of this PEBC systematic review and clinical practice guideline. The remaining authors have no conflicts of interest to declare.

AUTHOR AFFILIATIONS

*Juravinski Cancer Centre, Hamilton, ON; †Program in Evidence-Based Care, Cancer Care Ontario and McMaster University, Hamilton, ON; ‡University Health Network, Toronto, ON.

REFERENCES

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. *Canadian Cancer Statistics 2014*. Toronto, ON: Canadian Cancer Society; 2014. [Available online at: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2014-EN.pdf; cited 2 December 2014]
2. Colombo N, Carinelli S, Colombo A, *et al.* Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23(suppl 7):vii27–32.
3. Sartori E, Pasinetti B, Carrara L, Gambino A, Odicino F, Pecorelli S. Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients. *Gynecol Oncol* 2007;107(suppl 1):S241–7.
4. Zola P, Fuso L, Mazzola S, *et al.* Could follow-up different modalities play a role in asymptomatic cervical cancer relapses diagnosis? An Italian multicenter retrospective analysis. *Gynecol Oncol* 2007;107(suppl 1):S150–4.
5. Elit L, Fyles AW, Devries MC, Oliver TK, Fung-Kee-Fung M on behalf of the Gynecology Cancer Disease Site Group. Follow-up for women after treatment for cervical cancer: a systematic review. *Gynecol Oncol* 2009;114:528–35.
6. Browman GP, Levine MN, Mohide EA, *et al.* The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502–12.
7. Shea BJ, Grimshaw JM, Wells GA, *et al.* Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.
8. Lanceley A, Fiander A, McCormack M, Bryant A. Follow-up protocols for women with cervical cancer after primary treatment. *Cochrane Database Syst Rev* 2013;11:CD008767.

9. Meads C, Davenport C, Malysiak S, *et al.* Evaluating PET-CT in the detection and management of recurrent cervical cancer: systematic reviews of diagnostic accuracy and subjective elicitation. *BJOG* 2014;121:398–407.
10. Meads C, Auguste P, Davenport C, *et al.* Positron emission tomography/computerised tomography imaging in detecting and managing recurrent cervical cancer: systematic review of evidence, elicitation of subjective probabilities and economic modelling. *Health Technol Assess* 2013;17:1–323.
11. Hoogendam JP, Zaal A, Rutten EG, *et al.* Detection of cervical cancer recurrence during follow-up: a multivariable comparison of 9 frequently investigated serum biomarkers. *Gynecol Oncol* 2013;131:655–60.
12. Gupta S, Sodhani P, Singh V, Sehgal A. Role of vault cytology in follow-up of hysterectomized women: results and inferences from a low resource setting. *Diagn Cytopathol* 2013;41:762–6.
13. Orr JM, Barnett JC, Leath CA 3rd. Incidence of subsequent abnormal cytology in cervical cancer patients completing five-years of post treatment surveillance without evidence of recurrence. *Gynecol Oncol* 2011;122:501–4.
14. Rimel BJ, Ferda A, Erwin J, *et al.* Cervicovaginal cytology in the detection of recurrence after cervical cancer treatment. *Obstet Gynecol* 2011;118:548–53.
15. Singh RK, Maulik S, Mitra S, *et al.* Human papillomavirus prevalence in postradiotherapy uterine cervical carcinoma patients: correlation with recurrence of the disease. *Int J Gynecol Cancer* 2006;16:1048–54.
16. Song YJ, Kim JY, Lee SK, *et al.* Persistent human papillomavirus DNA is associated with local recurrence after radiotherapy of uterine cervical cancer. *Int J Cancer* 2011;129:896–902.
17. Shield PW, Daunter B, Wright RG. Post-irradiation cytology of cervical cancer patients. *Cytopathology* 1992;3:167–82.
18. Nagai Y, Toma T, Moromizato H, *et al.* Persistence of human papillomavirus infection as a predictor for recurrence in carcinoma of the cervix after radiotherapy. *Am J Obstet Gynecol* 2004;191:1907–13.
19. Chung HH, Kim JW, Kang KW, *et al.* Predictive role of post-treatment ^{18F}FDG PET/CT in patients with uterine cervical cancer. *Eur J Radiol* 2012;81:e817–22.
20. Brooks RA, Rader JS, Dehdashti F, *et al.* Surveillance FDG-PET detection of asymptomatic recurrences in patients with cervical cancer. *Gynecol Oncol* 2009;112:104–9.
21. Vistad I, Moy BW, Salvesen HB, Liavaag AH. Follow-up routines in gynecological cancer—time for a change? *Acta Obstet Gynecol Scand* 2011;90:707–18.
22. Bodurka-Bevers D, Morris M, Eifel PJ, *et al.* Posttherapy surveillance of women with cervical cancer: an outcomes analysis. *Gynecol Oncol* 2000;78:187–93.