Follow-up for women after treatment for cervical cancer

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ABSTRACT

Question

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

Perspectives

For women with cervical cancer who have been treated with curative intent, follow-up includes identification of complications related to treatment and intervention in the event of recurrent disease. Most women who recur with cervical cancer are not curable; however, early identification of recurrence can alter disease management or treatment-planning options, and for those with a central pelvic recurrence and no evidence of distant disease, there is a potential for cure with additional therapy. Follow-up protocols in this population are variable, using a number of tests at a variety of intervals with questionable outcomes.

Outcomes

Outcomes of interest included recurrence, survival, and quality of life.

Methodology

The Gynecology Cancer Disease Site Group (DSG) conducted a systematic review of the literature and a narrative review of emerging clinical issues to inform the most appropriate follow-up strategy for patients with cervical cancer. The evidence was insufficient to specify a clinically useful recommended follow-up schedule, and therefore, the expert consensus opinion of the Gynecology Cancer DSG was used to develop recommendations on patient surveillance. The resulting recommendations were reviewed and approved by the Gynecology Cancer DSG and by the Program in Evidence-Based Care Report Approval Panel. An external review by Ontario practitioners completed the final phase of the review process. Feedback from all parties was incorporated to create the final practice guideline.

Results

The systematic review of the literature identified seventeen retrospective studies. The Gynecology Cancer DSG used a consensus process to develop recommendations based on the available evidence from the systematic review, the narrative review, and the collective clinical experience and judgment of the DSG members.

Practice Guideline

The recommendations in this practice guideline are based on the expert consensus opinion of the

Cancer Care Ontario's Program in Evidence-Based Care is sponsored by Cancer Care Ontario and the Ministry of Health and Long-Term Care.

Gynecology Cancer DSG, informed by evidence from retrospective studies. These are some general features of an appropriate follow-up strategy:

1. At a minimum, follow-up visits with a complete physical examination, including a pelvic–rectal exam and a patient history, should be conducted by a physician experienced in the surveillance of cancer patients.
2. There is little evidence to suggest that vaginal vault cytology adds significantly to the clinical exam in detecting early disease recurrence.
3. Routine use of various other radiologic or biologic follow-up investigations in asymptomatic patients is not advocated, because the role of those investigations has yet to be evaluated in a definitive manner.
4. A reasonable follow-up schedule involves follow-up visits every 3–4 months in the first 2 years and every 6–12 months in years 3–5. Patients should return to annual population-based general physical and pelvic examinations after 5 years of recurrence-free follow-up.

KEY WORDS

Cervical cancer, follow-up, schedule, recurrence, practice guideline, surveillance

1. QUESTIONS

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

Of clinical interest, do differences in follow-up strategy influence patient outcomes related to recurrence, survival, or quality of life?

2. CHOICE OF TOPIC AND RATIONALE

Cervical cancer is the second most common cancer worldwide, resulting in approximately 275,000 deaths annually [1]. Despite cervical screening programs that have dramatically reduced the incidence of cervical cancer in Canada, approximately 1300 Canadian women are diagnosed annually, and approximately 390 women die of the disease [2].

The concept of long-term surveillance of patients treated with curative intent is based on the premise that early detection will result in decreased morbidity and mortality. The assumptions are that screening has adequate sensitivity and specificity and is resource-effective, that the natural history of both the anatomic pattern and the timing of disease recurrence is known, and that effective low-morbidity salvage therapy is available and applied. Follow-up protocols in this population are variable, using a number of tests at a variety of intervals with questionable outcomes.

The primary objective of the present practice guideline is to provide an optimal recommended program for the follow-up of patients who are disease-free after completed therapy for cervical cancer. The specific components of such a program that need to be addressed include optimal intervals for follow-up, clinical utility of the surveillance tests currently available [history, physical exam, vaginal cytology, ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), positron-emission tomography (PET), or tumour markers], and modification of follow-up programs based on an individual patient's risk of recurrence and complications related to primary therapy.

3. METHODS

3.1 Guideline Development

This practice guideline report was developed by the Gynecology Cancer Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) using the methods of the practice guidelines development cycle [3,4]. The guideline is a convenient and up-to-date source of the best available evidence on the follow-up of patients with cervical cancer who are clinically disease-free after receiving primary treatment. It was developed through systematic review of the evidentiary base, evidence synthesis, and input from internal and external review participants in Ontario.

For this project, the core methodology used by the DSG to develop the evidentiary base was the systematic review [5]. Evidence was selected and reviewed by one member of the PEBC Gynecology Cancer DSG (LE) and one methodologist (TKO). External review was obtained for the practice guideline report through a mailed survey of Ontario practitioners. The survey consisted of items that addressed the quality of the draft practice guideline report and the recommendations, and that asked whether the recommendations should serve as a practice guideline. Final approval of the original practice guideline report was obtained from the PEBC Report Approval Panel.

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

3.2 Literature Search Strategy

A systematic search of the MEDLINE (OVID: 1980 through November 2007), EMBASE (OVID: 1980 through November 2007), Cochrane Library (OVID: Issue 3, 2007), Canadian Medical Association Infobase (mdm.ca/cpgsnew/cpgs/index.asp), and the National Guideline Clearinghouse (www.guideline.gov/search/detailedsearch.aspx) databases was conducted. In addition, proceedings of the meetings of

the American Society of Clinical Oncology (1999–2007) were searched for relevant abstracts. Reference lists of studies deemed eligible for inclusion in the systematic review were scanned for additional citations. Articles were selected for inclusion if they reported data on follow-up strategies for patients who received potentially curative treatment for cervical cancer and who were clinically disease-free at the study point.

4. RESULTS

The Gynecology DSG places particular emphasis on a high-quality evidentiary base, but the paucity of evidence in the present case necessitated consideration of other sources. Data from studies of lesser quality design are considered in the absence of evidence from randomized controlled trials, particularly where such studies provide information that is consistent in direction of effect. The search of the literature on patient outcomes related to follow-up strategies after primary treatment for cervical cancer found seventeen retrospective studies [6–22].

Sixteen of the seventeen retrospective studies outlined the timing for follow-up visits [6–15,17–22]. Most studies used similar intervals: follow-up visits every 3–4 months within the first 2 years, every 6 months for the next 3 years, and annually thereafter or until year 10 or discharge at the discretion of the treating physician. All seventeen studies also reported that physical examinations with or without patient histories were performed at each follow-up visit [6–22].

Recurrence rates in most of the studies ranged from 8% to 26% of patients [6–16,18,20,21]. Overall, the median time to recurrence ranged from 7 months to 36 months after primary treatment [6–22]. Recurrences that were distant or detected at multiple sites occurred in 15%–61% of patients [10–12,14,16,17,20–22]. The timing of recurrences was inconsistently reported, and no observed differences in survival were reported by the timing of recurrence detection.

Thirteen of the seventeen studies reported mean or median survival after recurrence [6–15,19,20,22]. Five studies reported median overall survival after recurrence—a finding that ranged between 7 months and 12 months for the total patient population [6,8–10,20]. Eight studies reported results separately for patients who were symptomatic compared with those who were asymptomatic at the time of recurrence detection [7,11–15,19,22]. For patients who were symptomatic at the time of recurrence detection, median overall survival after recurrence ranged from 8 months to 38 months; for asymptomatic patients, the range was 8 months to unreached after 53 months of follow-up.

No quality-of-life data were provided in any of the retrospective reviews identified in the literature search.

5. DSG CONSENSUS PROCESS

The Gynecology Cancer DSG agreed that, considering the lack of prospective data comparing one follow-up strategy with another, or of data comparing the effect of various follow-up intervals on the clinical outcomes of interest, the recommendations put forth in this clinical practice guideline would be based on the expert consensus opinion of the group, informed by evidence from the retrospective studies and a narrative review of emerging clinical issues (such as the role of PET–CT or tumour markers in this patient population). The draft recommendations were approved by the Gynecology Cancer DSG in June 2008.

6. INTERNAL REVIEW

6.1 Results

Before submission of the practice guideline for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members: the director of the PEBC, and an oncologist with expertise in clinical and methodologic issues. Key issues raised by the Report Approval Panel included the quality of the key evidence and a need to discuss the limitations (with regard to sensitivity and specificity) of the use of biomarkers for early detection of recurrence. The Gynecology DSG agreed with the concerns of the Report Approval Panel and, in response, made changes to better reflect the quality of the evidence. The discussion on biomarkers and early detection of recurrent disease was also expanded. Additional editorial changes suggested by the panel were made as well.

7. EXTERNAL REVIEW

7.1 Methods

The practice guideline underwent a two-pronged external review process:

- A targeted peer review aimed to obtain direct feedback on the draft report from a small number of specified content experts (4 oncologists)
- A professional consultation aimed to facilitate dissemination of the final guidance report to Ontario practitioners

The survey sent to the 4 targeted physicians (3 radiation oncologists, 1 gynecologic oncologist) consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and the overall quality and use of the practice guideline in clinical decision-making. Written comments were invited.

Individuals who chose to take part in the informal professional consultation were asked to rate the

overall quality and use of the practice guideline in clinical decision-making.

7.2 Results

Three responses were received from the 4 targeted peer reviewers. All 3 responders rated the guideline development, presentation, recommendations, and completeness of reporting to be high. Two reviewers strongly believed that the document provided sufficient information to inform their decisions, and all three strongly felt they would make use of this guideline in their professional decisions and would recommend this guideline for use in practice.

The professional consultation process produced 7 responses. Responders considered the guidelines easy to adopt and adhere to. Some concern was expressed about the limited evidence upon which the guidelines were based.

8. PRACTICE GUIDELINE

This practice guideline integrates the feedback obtained through the external review process, with final approval given by the Gynecology Cancer DSG and the Report Approval Panel of the PEBC. It applies to women who are clinically disease-free after receiving potentially curative primary treatment for cervical cancer. It is directed to clinicians involved in the care and follow-up of women who have received potentially curative treatment for cervical cancer.

8.1 Recommendations

Patients need to be informed about symptoms of recurrence, because most women have signs or symptoms of recurrence that occur outside of scheduled follow-up visits.

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 may well enhance and facilitate early detection of cancer recurrence and help to avoid duplication of surveillance testing and effort.

A reasonable follow-up strategy involves follow-up visits every 3–4 months in the first 2 years, and every 6–12 months in years 3–5.

After 5 years of recurrence-free follow-up, the patient should return to annual assessment with a history, general physical, and pelvic examination with cervical or vaginal cytology (or both) performed by the primary care physician.

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.

A physical examination should attempt to identify abnormal findings related to general health or those that suggest vaginal, pelvic sidewall, or distant recurrence. Because central pelvic recurrences are potentially curable, the physical examination should include a speculum exam with bimanual, pelvic, and rectal examination.

The routine use of other investigations in asymptomatic patients is not advocated, because the roles of those investigations have yet to be evaluated in a definitive manner.

There is little evidence to suggest that vaginal vault cytology adds significantly to the clinical exam in detecting early disease recurrence. If cytology is performed as part of routine follow-up after surgery for cervical cancer, its role would be to detect new precancerous conditions of the vagina, and 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.

The role of abdominal or pelvic CT, MRI, PET, or ultrasonography as part of routine follow-up has not been fully evaluated in prospective studies.

Use of serum markers such as squamous cell carcinoma antigen or cancer antigen 125 has shown promise in predicting surgical findings or the post-radiotherapy course when disease is present; however, the role of such markers in the follow-up of patients post treatment has yet to be determined.

9. PRACTICE GUIDELINE DATE

This clinical practice guideline is based on work completed in May 2009. Practice guidelines developed by the PEBC of Cancer Care Ontario are reviewed and updated regularly. Please visit the Cancer Care Ontario Web site (www.cancercare.on.ca) for a complete list of current projects and subsequent updates.

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Please see the page for the Gynecology Cancer Disease Site Group (www.cancercare.on.ca/cms/one.aspx?pageId=10245 at March 2010) in the Program in Evidence-Based Care section of the Cancer Care Ontario Web site for a complete list of current group members.