Guideline 4-22

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

Follow-up of Patients who are Clinically Disease-free After Primary Treatment for Fallopian Tube, Primary Peritoneal, and Epithelial Ovarian Cancer

T. Le, E.B. Kennedy, J. Dodge, L. Elit, and the Ovarian Follow-up Guideline Expert Panel

Report Date: November 11, 2015

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PEBC Report Citation (Vancouver Style): Le T, Kennedy EB, Dodge J, Elit L. Follow-up of patients who are clinically disease-free after treatment for fallopian tube, primary peritoneal, and epithelial ovarian cancer. Toronto (ON): Cancer Care Ontario; 2015 November 11. Program in Evidence-Based Care Guideline No.: 4-22.

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GUIDELINE OBJECTIVE

The objective of this guideline is to make recommendations for appropriate follow-up of women with confirmation of remission, after surgery and first-line chemotherapy, for fallopian tube, primary peritoneal, or epithelial ovarian cancer. Of interest are appropriate intervals and methods, as well as who should conduct the follow-up examinations.

TARGET POPULATION

Women who have received confirmation of clinical complete remission (i.e., are disease-free) after surgery and first-line chemotherapy for fallopian tube, primary peritoneal, or epithelial ovarian cancer. Disease-free status is determined according to the standard procedure at the unit where treatment was provided and may include negative clinical examinations, negative imaging investigations, and/or negative tumour marker results.

INTENDED USERS

The intended users of this guideline are clinicians who provide follow-up examinations to the target population, and may include gynecologic oncologists, medical oncologists, specialist nurses, gynecologists, family physicians, or other clinicians who deliver follow-up cancer care in the province of Ontario.

ENDORSEMENT OF CANCER AUSTRALIA RECOMMENDATIONS

After a systematic review found no new studies meeting the inclusion criteria, the authors of this guideline agreed to endorse recommendations from the Cancer Australia guidance document entitled Follow-up of Women with Epithelial Ovarian Cancer: A Systematic Review [1]. A general strength of these recommendations, and a reason that they were chosen for endorsement, is that they include recommendations for clinician-patient discussion regarding the harms and benefits of surveillance, a discussion of the limitations of recurrence detection, and consideration of patient preferences. The Working Group members identified key recommendations from that document, which are reproduced verbatim below with Program in Evidence-Based Care (PEBC) qualifying statements presented in italics. While the members of the Working Group chose to endorse the wording of the recommendations, the format and organization of the recommendations was altered to align with the PEBC guideline template. Recommendations are organized under the following headings:
RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

1. Recommendations for Follow-up Post-treatment
   a. While the optimal method of follow-up is not yet established, possible options for follow-up and the implications and possible consequences of these options should be discussed with the woman at the completion of primary treatment.
   b. Consideration should be given as to how anxiety might be lessened, such as scheduling tests before the visit so that test results are available for discussion at the time of the follow-up visit.

   **PEBC Qualifying Statement:** Based on feedback received in the PEBC review process, the members of the Working Group for this guideline would like to emphasize that women should clearly be given the option of no follow-up, as there is no evidence for the impact of this practice on outcomes, and follow-up appointments may be associated with stress, inconvenience, and cost. A further recommendation is to provide survivors with written information, potentially in the form of a fact sheet, outlining symptoms of concern (as described under recommendation #4), follow-up suggestions, and when and how to contact the appropriate specialist.

2. Recommendations for CA-125 in Follow-up
   a. Women should be informed that there is no evidence that monitoring cancer antigen 125 (CA-125) improves survival outcome, and that it may worsen quality of life. There should be a time provided for the woman and her clinician to discuss the implications of monitoring progress and initiating treatment based on CA-125 levels. Women can be advised that they have the option to have CA-125 levels tested at agreed intervals, or not at all. Women who choose to have CA-125 levels measured should be informed that CA-125 levels may fluctuate due to individual and laboratory assay variations, and the implications of stable, fluctuating, and rising levels should be discussed.
   b. Women should be fully informed of the limitations and potential harms of routine measurement of CA-125 during follow-up and supported to make an informed decision, considering the findings of the randomized controlled trial on follow-up after ovarian cancer [2].
   c. The decision to initiate re-treatment requires careful consideration based on the individual woman’s situation, and factors including the nature of the recurrence and the wishes of the woman.

   **PEBC Qualifying Statement:** Treatment based on a rising CA-125 result alone is not recommended. Clinical or radiologic confirmation of disease progression should be obtained prior to reinitiation of treatment.

   **PEBC Qualifying Statement:** In the text of the Cancer Australia guidance document, it was recommended that women be advised of the pros and cons of routine measurement of CA-125 during follow-up. The members of the Working Group for this guideline have chosen to reword this recommendation to stress that the limitations and potential harms of routine measurement of CA-125 should be made explicit to patients, and to emphasize that monitoring with CA-125 has not been associated with improvements in survival rate, and may be associated with a decrease in quality of life.
3. Recommendation for Timing of Follow-up Consultations
   a. Women should be offered the opportunity to have regular follow-up. Discussion with the woman about follow-up could incorporate a schedule of follow-up appointments, including the possibility of no formal follow-up schedule, based on the identified needs and wishes of the individual.
   b. There is no recommended frequency of follow-up consultations, but a clear and mutually agreed arrangement should be negotiated with the women, tailored according to risk and to individual patient characteristics, which acknowledges the benefits of an ongoing relationship and the opportunity to deal with issues as they arise.
   c. Women residing in rural and regional areas face additional challenges of access to specialist clinicians for follow-up appointments. Individual circumstances should be considered when establishing a follow-up schedule.

   PEBC Qualifying Statement: No specific frequency of follow-up appointments is endorsed; however, if desired, follow-up visits may occur more frequently immediately following the completion of active treatment, and may occur less frequently after more time has passed since the completion of active treatment.

4. Recommendations for Format for Follow-up Consultations
   a. The basic format of consultation is to update the patient history, assess psychosocial and supportive care needs, and undertake physical examination, which may include pelvic examination.
   b. Women should be encouraged to report a range of symptoms, including nausea, vomiting, abdominal distension, cramping, pain, and shortness of breath, and any other concerning symptoms.
   c. Radiological imaging should not be done routinely, but should be performed if there is clinical or CA-125 evidence of recurrence. The rationale for not undertaking routine imaging should be discussed with the woman.

   PEBC Qualifying Statement: Patients should be informed that physical examination has a low level of sensitivity for detecting early cancer recurrences, particularly if the patient is also undergoing regular monitoring for CA-125.

   PEBC Qualifying Statement: In the case of transfer of care from the patient’s oncologist to a clinician such as a gynecologist, family physician, or nurse practitioner, a written, individualized plan should be developed by the oncologist in consultation with the patient and provided to the clinician to whom care has been transferred. This should include plans for patient care in the event of delayed or long-term treatment sequelae.

5. Recommendation for Models of Follow-up Care
   a. A woman may be reviewed by either a gynecologic oncologist or a medical oncologist. Communication with a woman’s primary care physician should be maintained throughout follow-up.
   b. The use of alternate models of care for women with ovarian cancer, such as primary care physician or nurse-led follow-up, telephone follow-up and patient-initiated care is an area for future research. Some of the issues that would need to be addressed in any future studies include patient and clinician preferences, the effectiveness and cost effectiveness of the alternative models, and the ability of health services to support them.
FURTHER QUALIFYING STATEMENTS

- The Working Group members stress that if women opt not to engage in routine follow-up, they must be fully informed about signs and symptoms of recurrence, and be instructed to contact their oncologist or primary care provider if signs and symptoms suggestive of recurrence appear.

- In some remote areas of Ontario, follow-up has been delivered via TeleHealth. This model of follow-up care for patients with ovarian cancer has not been studied; however, it may be a viable model for patients who live in geographically remote areas and who are not able to travel to a Cancer Centre.

- There are currently two ongoing randomized trials of secondary debulking surgery, DESKTOP III [3] and GOG-0213 (www.cancer.gov). This guideline should be reviewed for currency when the results of these trials have been published.
Follow-up of Patients who are Clinically Disease-free After Primary Treatment for Fallopian Tube, Primary Peritoneal, and Epithelial Ovarian Cancer: Guideline

GUIDELINE OBJECTIVE

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TARGET POPULATION

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Key Evidence for CA-125 in Follow-up

- The hazard ratio (HR) for overall survival rate did not differ between asymptomatic women who had earlier treatment based on elevated CA-125 levels alone compared with those who waited for clinical symptoms before initiating treatment (HR, 0.98; 95% confidence interval [CI], 0.80 to 1.20; p=0.85) [2].
- Quality of life results showed that patients in the delayed treatment group reported good global health scores for longer than those in the early treatment arm (9.2 months [95% CI, 6.4 to 10.5] versus 7.2 months [95% CI, 5.3 to 9.3], respectively) [2].

3. Recommendation for Timing of Follow-up Consultations
   a. Discussion with the woman about follow-up could incorporate a schedule of follow-up appointments, including the possibility of no formal follow-up schedule, based on the identified needs and wishes of the individual.
   b. There is no recommended frequency of follow-up consultations, but a clear and mutually agreed arrangement should be negotiated with the women, tailored according to risk and to individual patient characteristics, which acknowledges the benefits of an ongoing relationship and the opportunity to deal with issues as they arise.
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Key Evidence: Physical Examination

- In the study reported by Menczer et al., physical examination had a low sensitivity for diagnosing recurrent disease (34.9%) [4]. They found that in 95.3% of patients with recurrence, other diagnostic criteria such as symptoms or elevated CA-125 levels were
present. Physical examination was the only criterion for recurrence in two of 69 (4.6%) patients. In these two patients, other diagnostic criteria appeared within two months. In the study reported by Chan et al. [5], women with abnormal findings on physical examination also had either suspicious symptoms, elevated CA-125 levels, or both. No patient presented with physical findings alone.

**Key Evidence: Ultrasound**
- Ultrasound has not been shown to detect a higher percentage of recurrences compared with a combination of CA-125 testing and clinical examination [6].

**Key Evidence: Symptoms of Recurrence**
- Signs and symptoms of recurrent ovarian cancer are based on the findings of Chan et al. [5].

**Key Evidence: Radiological Imaging**
- The recommendation for radiological imaging to detect recurrence is based on evidence from Fehm et al. [7]. This study found that imaging techniques did not add clinically relevant information during follow-up and should therefore only be performed prior to planned surgical or therapeutic intervention [7].

**Key Evidence: Role of Other Imaging Modalities**
- Computed tomography (CT) and magnetic resonance imaging (MRI) have a role in treatment planning when a recurrence has been diagnosed [6]. When macroscopic disease recurrence has been identified, CT, or, where that is inconclusive, MRI, is more useful than ultrasound for assessment.
- Positron emission tomography and Doppler ultrasound may have some role, but this is still under investigation [6].

5. Recommendation for Models of Follow-up Care
   a. A woman may be reviewed by either a gynecologic oncologist or a medical oncologist. Communication with a woman's primary care physician should be maintained throughout follow-up.
   b. The use of alternate models of care for women with ovarian cancer, such as primary care physician or nurse-led follow-up, telephone follow-up, and patient-initiated care is an area for future research. Some of the issues that would need to be addressed in any future studies include patient and clinician preferences, the effectiveness and cost effectiveness of the alternative models, and the ability of health services to support them.

**Key Evidence: Models of Follow-up Care**
- A previous guideline by the PEBC recommended discharge from specialist care to community-based family physician-led care or nurse-led care within an institution as a reasonable option for breast, colorectal, or prostate cancer patients [8]. At the time of that report, evidence for other disease sites was not available.
- A pilot study of ovarian cancer patients agreeing to participate in a telephone follow-up study found that 73% of women preferred telephone follow-up, 18% preferred doctor/consultant appointments, and 9% were “not sure” [9].
- Ovarian cancer patients who agreed to participate in the pilot trial of nurse-led follow-up reported significant improvements in well-being post-treatment with nurse-led telephone follow-up (p=0.016) [9].
INTERPRETATION OF EVIDENCE

The single randomized controlled trial included in the evidence review detected no impact on overall survival rate associated with earlier initiation of chemotherapy based on CA-125 elevation pattern alone. Despite these findings, it is the consensus of the members of the Working Group that the benefits of surveillance may outweigh the harms for some women in this patient population and, thus, the option of regular follow-up may be offered. The Working Group members identified several harms that are associated with routine surveillance, including a potentially shorter time living in a progression-free status with no corresponding increase in overall survival time and a decrease in quality of life due to earlier initiation of treatment, anxiety associated with follow-up, inconvenience and cost of attending follow-up appointments, and potential for unnecessary and costly follow-up testing in the case of falsely elevated CA-125 levels. In the Working Group’s opinion, the greatest benefit of ongoing follow-up is the maintenance of a relationship with the oncologist and the reassurance associated with continued involvement in the cancer care system, given the high likelihood of recurrence. Other potential benefits include the opportunity to discuss ongoing psychosocial concerns and referral to appropriate providers, such as psychologists, psychiatrists, or social workers, reassurance or alleviation of anxiety after negative results at follow-up appointments, prompt identification of women who may be candidates for open clinical trials, and the opportunity to discuss importance of genetic testing and familial counselling.

FURTHER QUALIFYING STATEMENTS

- The Working Group members stress that if women opt not to engage in routine follow-up, they must be fully informed about signs and symptoms of recurrence, and be instructed to contact their oncologist or primary care provider if signs and symptoms suggestive of recurrence appear.
- In some remote areas of Ontario, follow-up has been delivered via TeleHealth. This model of follow-up care for patients with ovarian cancer has not been studied; however, it may be a viable model for patients who live in geographically remote areas and who are not able to travel to a Cancer Centre.
- There are currently two ongoing randomized trials of secondary debulking surgery, DESKTOP III [3] and GOG-0213 (www.cancer.gov). This guideline should be reviewed for currency when the results of these trials have been published.

IMPLEMENTATION CONSIDERATIONS

The members of the Working Group report no specific implementation considerations.

RELATED GUIDELINES

Follow-up of Patients who are Clinically Disease-free After Primary Treatment for Fallopian Tube, Primary Peritoneal, and Epithelial Ovarian 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 (CCO). The PEBC 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 (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

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

JUSTIFICATION FOR THE GUIDELINE

This guideline development project was undertaken because the members of the PEBC Gynecologic Cancer Disease Site Group (Gyne DSG) identified a need to provide evidence-based guidance in order to fill a gap in the disease management pathway for ovarian cancer.

GUIDELINE DEVELOPERS

This guideline was developed by the Ovarian Follow-up Guideline GDG (Appendix 1), which was convened at the request of the PEBC Gyne DSG.

The project was led by a small Working Group of the Ovarian Follow-up Guideline GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The members of the Working Group had expertise in gynecologic oncology and health research methodology. Other members of the GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the PEBC Conflict of Interest Policy.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle ([10]. This process includes a systematic review, interpretation of the evidence, creation of draft recommendations by the members of the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [11] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.
The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the PEBC Document Assessment and Review Protocol. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook.

SEARCH FOR EXISTING GUIDELINES
A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. Only guidelines that are based on a systematic review of evidence are considered for inclusion; consensus-based guidelines are generally not considered.

For this project, the following sources were searched for existing guidelines that addressed the research questions:
- National Guidelines Clearinghouse
- Guideline developer websites (Scottish Intercollegiate Guidelines Network, UK National Institute for Health and Clinical Excellence, American Society of Clinical Oncology)

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the seven-item Rigour of Development Domain of the AGREE II instrument [11]. A search for existing guidelines yielded an appropriate source document for endorsement (see Section 4, Evidence Review).

GUIDELINE REVIEW AND APPROVAL

Internal Review
For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by the RAP and the GDG Expert Panel.

External Review
Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.
ACKNOWLEDGEMENTS

The Ovarian Follow-up Guideline GDG would like to thank the following individuals for their assistance in developing this report:

- Alon Altman, Melissa Brouwers, Craig Earle, Paul Hoskins, Monique Lefebvre, Jake McGee, Sheila McNair, Hans Messersmith, Fulvia Baldassarre, Raymond Poon, and Rebecca Wong for providing feedback on draft versions.
- Crystal Su for conducting a data audit.
- Janet Rowe and Sara Miller for copy editing.
Follow-up of Patients who are Clinically Disease-free After Primary Treatment for Fallopian Tube, Primary Peritoneal, and Epithelial Ovarian Cancer: Evidence Review

INTRODUCTION

In 2014, there were an estimated 2700 new cases of ovarian cancer in Canada, and 1750 deaths. The proportion of people with cancer who were still alive five years after the initiation of treatment was between 41% and 43% [12]. Ovarian cancer patients have a lower rate of survival relative to many other cancer disease sites because ovarian cancer is often diagnosed at an advanced stage. An estimated 70% to 75% of patients will experience a recurrence [13].

Structured follow-up of patients who have been classified as disease-free after primary treatment, also known as surveillance, is conducted in order to identify disease recurrence and deliver therapeutic interventions that lead to improved outcomes [14]. Managing side effects of primary treatment, facilitating clinical trials recruitment, or building a relationship with the patient and oncology team in anticipation of a subsequent recurrence have been mentioned as additional reasons for follow-up. Recently, there has been some controversy regarding frequent, structured follow-up for patients who are disease-free after treatment of ovarian and other cancers [15]. Evidence from follow-up of vulvar, cervical, and endometrial cancers has called into question the value of detecting asymptomatic recurrences, and follow-up has even been shown to delay detection, as some women will not report symptoms until their next scheduled appointment [16]. In the case of cancer in other disease sites, such as the bowel, intensive follow-up does appear to provide a benefit over little or no follow-up [6].

Cancer Care Ontario’s Program in Evidence-Based Care (PEBC) has published guidelines on follow-up of cancer at other gynecologic cancer disease sites, including cervical and endometrial cancers, but a gap exists in recommendations for ovarian cancer. In the experience of the members of the Working Group for this guideline, many women who have received treatment for epithelial ovarian cancer in Ontario are followed up with regular appointments that include history and physical examination in the Cancer Centre where they received treatment. Methods to detect recurrence, such as cancer antigen 125 (CA-125) testing, examinations, and imaging tests vary across the province. There is controversy regarding the regular use of CA-125 testing; it is used mainly to identify women who may be candidates for clinical trials. Imaging is usually done based on clinical indications or follow-up of prior abnormalities. Follow-up appointments tend to occur every three to four months for the first three to four years, every six months for year 4 to 5, and annually after five years have elapsed since initial treatment. Currently, in Ontario, the most common standard practice for follow-up survivorship care involves specialist-coordinated care within an institution [8]. This systematic review will inform a new PEBC guideline that will provide evidence-based guidance to fill this gap in the disease management pathway.

At the outset of this project, an environmental scan for existing guidelines yielded a guideline document that closely aligned with the intended objectives of this project, as outlined in our publically available protocol [17]: i.e., to gather evidence on variations in overall survival rate and quality of life (QOL) with differing interventions, and comparisons of follow-up intervals and methods for patients who were in remission after primary treatment for epithelial ovarian cancer. The guideline, called Follow-up of Women with Epithelial Ovarian Cancer [1], was produced by Cancer Australia, and scored highly on the AGREE II [11]
rigour of development domain (Appendix 2). It was based on a systematic review that received high scores for quality on the AMSTAR tool [18], and was current to January 2010. The members of the Working Group agreed that the Australian document would be suitable for endorsement, with potential modifications to suit the Ontario context, provided that no more recent evidence was available of a contradictory nature. Thus, the members of the Working Group decided to systematically search the literature from February 2010 onwards for any more current systematic reviews, and, if necessary, primary studies.

RESEARCH QUESTION

In women with confirmation of remission after surgery and first-line chemotherapy for epithelial ovarian cancer, what are the differences in survival rate, QOL, and level of anxiety associated with different follow-up intervals and methods for detection of recurrence?

METHODS

Search for Systematic Reviews

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for existing systematic reviews that had been published after the final search date (January 2010) of Cancer Australia’s Follow-up of Women with Epithelial Ovarian Cancer: A Systematic Review [1]. The search terms, which were adopted from Cancer Australia’s systematic review, related to ovarian cancer and asymptomatic detection of recurrence and follow-up (Appendix 3). This portion of the search was limited to review articles. Systematic reviews that were found to be directly relevant to this guideline were assessed using the AMSTAR tool [18].

Search for Primary Literature

If a relevant systematic review was found, the Working Group would include the results of that review in the evidence base and conduct a search for primary literature from that review’s final search date to the present. If no relevant systematic reviews were found, then the primary literature would be searched from the Cancer Australia guideline’s search date (January 2010) to the present. MEDLINE and EMBASE were searched with the same terms related to ovarian neoplasms and follow-up used in the search for systematic reviews described previously (Appendix 3). Clinicaltrials.gov was searched for in-progress randomized controlled trials (RCTs).

Study Selection Criteria and Process

In order to limit the review to the highest possible level of evidence, and in view of the fact that this literature search was intended to update an existing source of primary literature, publication types other than RCTs were not considered eligible for inclusion. There was no size limit specified for RCTs. Studies of follow-up of a suspected recurrence are not included in the scope of this report.

Articles were limited to those reported in the English language because resources for translation were not available.

A review of the titles and abstracts that resulted from the search was conducted by the study methodologist (EK).

Synthesizing the Evidence

As the members of the Working Group were aware prior to the initiation of the search that the number of studies in this field is very limited, a meta-analysis was not planned.
RESULTS

Two systematic reviews and no primary studies met the inclusion criteria. A flow diagram outlining the literature search is included in Appendix 4, and the results of the two reviews are described in detail below.

Systematic Reviews

1. Follow-up of Women with Epithelial Ovarian cancer: A Systematic Review (Cancer Australia, July 2010) [1]

The systematic review reported by Cancer Australia included a search of OVID MEDLINE and EMBASE, PubMed, and the Cochrane Library that was current to January 2010. The search strategy included terms related to follow-up of ovarian neoplasms after completion of active treatment. The goal was to answer questions related to optimal method of detection, and to interval, sequence, and duration of follow-up care, to patient and healthcare provider preferences, to psychosocial outcomes, to subpopulations with specific needs, and to different models of conducting follow-up. Randomized and nonrandomized study designs were included. Twelve full-text studies met their inclusion criteria: one RCT, five retrospective cohort studies on method of detection, two pilot studies, and four qualitative/observational papers. Psychosocial concerns, healthcare provider and patient preferences/satisfaction, and patterns of care were addressed.

In some studies, patients and providers were unsure whether general practitioners and/or nurses could manage patients’ follow-up care; however, in a pilot study of nurse-led telephone-based follow-up care, 73% of patients preferred this method of follow-up. Women reported significant improvement in emotional well-being after participating in this pilot study, and received referrals for psychological counselling or social support programs as needed. There was considerable variability in anxiety level associated with the time period before and after follow-up visits; some patients reported more anxiety before the visit (54%), some less (44%), and some were the same (2%). Similar results were found regarding anxiety levels after the follow-up appointment. In one study, patient experience of follow-up was enhanced by having their CA-125 test results available at the time of the clinic appointment. No studies were found that compared one model of follow-up care with another.

The findings of this review with respect to methods of follow-up, such as physical examination and CA-125 testing, are similar to those of Clarke et al. [6]; therefore, they are discussed in the subsequent section.

2. Evaluation of Follow-up Strategies for Patients with Epithelial Ovarian Cancer Following Completion of Primary Treatment (Review) (Clarke et al. 2014 [6])

This review was found in search for systematic reviews published after the Cancer Australia review, i.e., from January 2010 onwards. This systematic review limited its inclusion criteria to RCTs; therefore, Rustin et al. [2] was the only study to meet the inclusion criteria. This RCT, which was at low risk of bias, randomly assigned women with elevated CA-125 to immediate treatment, or delayed treatment until symptoms appeared. The authors found that in women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA-125 concentration, there was no evidence of a difference in overall survival rate between early and delayed treatment (hazard ratio, 0.98; 95% confidence interval [CI], 0.80 to 1.20; p=0.85). Median survival time for those patients with elevated CA-125 who were randomized to immediate treatment was 25.7 months (95% CI, 23.0 to 27.9) compared with 27.1 months (95% CI, 22.8 to 30.9) for those with elevated CA-
125 who delayed treatment until symptomatic relapse occurred. QOL results showed that patients in the delayed-treatment group reported good global health scores for longer than those in the early-treatment arm (9.2 months [95% CI, 6.4 to 10.5] versus 7.2 months [95% CI, 5.3 to 9.3], respectively).

Other methods of detection that have been evaluated in nonrandomized studies include physical examination, measuring other tumour markers, imaging (including ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]), and peritoneal cytology. Although studies of these methods did not meet the inclusion criteria of Clarke et al. [6], they were addressed in the discussion of the systematic review. In summary:

- Physical examination has a low sensitivity (34.9%) [4]. In the trial reported by Chan et al. [5], women with abnormal findings on physical examination also had either suspicious symptoms, elevated CA-125 levels, or both. No patient presented with physical findings alone.
- Ultrasound has not been shown to detect a higher percentage of recurrences compared with a combination of CA-125 testing and clinical examination.
- CT, or, where that is inconclusive, MRI, is more useful than ultrasound for proving macroscopic disease recurrence. CT and MRI have a role for treatment planning when a recurrence has been diagnosed.
- The roles of positron emission tomography (PET) and Doppler ultrasound are still under investigation.

**Primary Studies**
A search was conducted from the final search date for Clarke et al. to the present (August 2013 to March 2015). There were no items located that met the inclusion criteria.

**DISCUSSION**

**Follow-up Methods**
It is known that elevated CA-125 levels can accurately predict recurrence approximately 4.5 months before symptoms become apparent [19]; however, the only RCT to compare early versus delayed chemotherapy for treatment of recurrence found that early treatment based on elevated levels of CA-125 did not translate into a survival rate advantage. Early treatment also had a detrimental effect on QOL [2], although the difference was not significant. It is possible that the advantage gained by treating smaller tumour sizes in the early-treatment arm was balanced by the advantage of a longer platinum-free interval in the delayed-treatment arm [19]. Another potential explanation is that chemotherapy delivered upon relapse will be equally effective for platinum-sensitive disease, independent of tumour size, and be ineffective for any truly refractory disease [14]. The decline in QOL scores could be related to the adverse effects associated with chemotherapy treatments.

The European Society of Gynaecological Oncology urges clinicians to continue to conduct follow-up with CA-125 testing [20]; while they agreed that routine use of CA-125 results does not provide patient benefit in terms of survival rate or QOL, they recommended continuation of its use in epithelial ovarian cancer survivors who are currently, or will be, participating in a study, who will not have frequent (every three months) follow-up, or for whom secondary surgery will be considered upon recurrence. Women with better performance scores, which may be more likely if recurrence is detected earlier, are better candidates for secondary surgery. This issue will be better understood when the results of the DESKTOP III study described under *Ongoing, Unpublished, or Incomplete Studies* have been published [3]. It is felt by some that if CA-125 monitoring is stopped, then reintroduction at a
time when it has proven value could be confusing and difficult (i.e., if the results of DESKTOP III confirm the value of surgery plus chemotherapy at recurrence) [20].

It is unclear what other methods of detection can be recommended. Physical examination has a low sensitivity and may not add information that could not be gleaned by CA-125 testing and monitoring for suspicious symptoms [4,5,19]. Likewise, ultrasound has not been shown to be more useful than a combination of CA-125 testing and clinical examination. CT and MRI have a role in treatment planning when a recurrence has been diagnosed, and the roles of PET and Doppler ultrasound are currently unclear.

Follow-up Schedule

No studies have been published that compare one follow-up schedule with another. Several guidelines recommend a frequent schedule of follow-up; e.g., the European Society of Medical Oncology [20] recommends history and physical examination, including pelvic examination, every three months for two years, every four months during the third year, and every six months during years 4 and 5 or until progression is documented. Working Group members for this guideline report a similar follow-up schedule currently in use in Ontario.

Potential Benefits and Harms of Frequent Surveillance

Unmet psychological needs may be more prevalent than unmet physical needs in this patient population [21]. A study found that 45% of patients with cancer cite the emotional effects of cancer as the most difficult to cope with [9]. A possible benefit of follow-up is the potential opportunity to identify women who may need referral for counselling for psychological needs or for social support services [9]. In addition, some patients may view appointments as reassuring [22].

There is some disagreement about whether management of residual side effects should be a goal of follow-up [14,23], as these may resolve independently over time [14].

There are potential harms to frequent surveillance. A recent systematic review examined the fear of recurrence (FCR), which can be defined as “fear that the cancer will return or progress in the same place or a different part of the body” [13]. FCR has been identified as one of the greatest concerns expressed by survivors. It is possible that frequent follow-up testing for ovarian cancer may elevate FCR [24]. Testing for CA-125 has been associated with depression and anxiety [21]; however, normal CA-125 results may provide patients with reassurance that their disease has not recurred. Thirty-three percent of respondents in the pilot study reported by Cox et al. discussed FCR with the nurse during telephone-based follow-up [9]. This study was associated with improvements in emotional well-being among patients.

A further potential harm of frequent follow-up is the deterioration of QOL that may occur with the earlier initiation of treatment when asymptomatic disease is detected by CA-125 testing at routine follow-up appointments [2]. In addition, there is some evidence to show that patients may delay reporting of symptoms until a routine scheduled follow-up appointment, which could result in a possible delay in the diagnosis of recurrent disease [16].

CONCLUSIONS

No studies have been published that compare different follow-up intervals, sequences, or durations. Furthermore, the value of earlier detection has been called into question with the results of Rustin et al. [2], who detected no improvement in overall survival rate with early detection using CA-125 monitoring. Only one model of follow-up care has been evaluated in ovarian cancer, i.e., a pilot study of nurse-led telephone follow-up [9].

Survivors of epithelial ovarian cancer should be made fully aware of the potential harms and benefits of surveillance, including a thorough discussion of the limitations of CA-
125 testing. Women may be offered the option of no formal follow-up, or a follow-up schedule that the woman and the healthcare provider have mutually agreed upon.

Delivery of follow-up by providers other than the primary treating specialists may be feasible, provided that prompt access to specialized services is available. A previous guideline published by the PEBC recommended discharge from specialist care to community-based family physician-led care or nurse-led care within an institution as a reasonable option for patients with breast, colorectal, or prostate cancer [8]. Further recommendations specific to gynecologic oncology patients or other models of care, such as shared-care, or nurse-led care in a community setting, could not be made in that guideline due to lack of published evidence [8]. Since then, the nurse-led telephone-based intervention study mentioned above was published; its results show that this method of follow-up is likely to be feasible in the ovarian cancer survivor population. The high satisfaction rating of patients in this study indicates that nurses may be better equipped to address the psychosocial concerns of patients, which are among the highest needs of ovarian cancer patients, and that this type of follow-up could be an area for further research. We are also awaiting the findings of an RCT reported by Lanceley, which has been completed and investigates a similar model of care [25].

Given the lack of evidence for any particular follow-up schedule or method of detection of recurrence, follow-up for ovarian cancer requires a critical appraisal [14]. With very little high-quality evidence available to underpin recommendations, the values and preferences of patients and providers that lead to consensus-based recommendations must be clearly described. Regardless of the follow-up schedule that is adopted, women should be educated regarding the most common symptoms of recurrence, which include abdominal pain, abdominal discomfort/distension, nausea/vomiting, and shortness of breath [5], with abdominal pain being the most common reported symptom [26]. They should also be provided with clear information on how to contact appropriate healthcare professionals when and if potential symptoms are detected. A further recommendation is to provide survivors of ovarian cancer with written information, potentially in the form of a fact sheet, outlining symptoms of concern, follow-up suggestions, and when and how to contact the appropriate specialist.

**ONGOING, UNPUBLISHED, OR INCOMPLETE STUDIES**

Currently there is no evidence that early treatment of recurrence prolongs survival time. Ongoing studies that are attempting to identify a treatment that provides a survival rate benefit at the time of recurrent disease include an RCT of debulking surgery plus chemotherapy versus chemotherapy alone for treatment of recurrent ovarian cancer. This study, DESKTOP III, is recruiting patients until August 2015 [3]. A previous DESKTOP study demonstrated that complete resection was possible at first relapse in experienced hands, predicted for by an Eastern Cooperative Oncology Group Scale of Performance Status of 0 at relapse, complete resection at the original surgery, and no ascites at relapse (DESKTOP II, [27]). Earlier detection by CA-125 testing may increase the likelihood of patients meeting these criteria and thus being candidates for debulking [14]. Another relevant clinical trial that is actively recruiting patients is *Phase III Randomized Study of Adjuvant Chemotherapy Comprising Carboplatin and Paclitaxel with Versus without Bevacizumab and/or Secondary Cytoreduction Surgery in Patients with Platinum-Sensitive Recurrent Ovarian Epithelial Cancer, Primary Peritoneal Cavity Cancer, or Fallopian Tube Cancer* (GOG-0213) ([www.cancer.gov](http://www.cancer.gov)).

Another RCT of interest compares patient satisfaction with follow-up led by a trained cancer nurse versus conventional medical follow-up after primary treatment for ovarian cancer. Recruitment for this study has been completed and results are awaited [25].

The PEBC is currently developing a guideline for Sexual Health for Patients with Cancer that will include patients with ovarian cancer.
INTERNAL REVIEW

The guideline was evaluated by the Guideline Development Group (GDG) Expert Panel and the Program in Evidence-Based Care (PEBC) Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group’s responses are described below.

Expert Panel Review and Approval

Of the nine members of the GDG Expert Panel, all members cast votes and none abstained, for a total of 100% response in June 2015. Of those that cast votes, all approved the document (100%); however, some modifications to the document were required before approval could be granted. The main comments from the Expert Panel and the Working Group’s responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group’s responses to comments from the Expert Panel.

<table>
<thead>
<tr>
<th>Comments</th>
<th>Responses</th>
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<tbody>
<tr>
<td>1. An Expert Panel member expressed concerns that we were not making it clear enough that routine monitoring of cancer antigen 125 (CA-125) is not recommended.</td>
<td>We have modified the language of the recommendations to more clearly emphasis that the evidence shows no role for the routine monitoring of CA-125.</td>
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<tr>
<td>2. An Expert Panel member commented that it would be appropriate for us to acknowledge that CA-125 is often monitored in order to identify women who are candidates for clinical trials and that this should be added as a qualifying statement.</td>
<td>We have added a qualifying statement.</td>
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</table>

RAP Review and Approval

After approval was obtained from the Expert Panel, three RAP members, including the PEBC Director, reviewed this document in July 2015. The RAP conditionally approved the document. The main comments from the RAP and the Working Group’s responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group’s responses to comments from the RAP.

<table>
<thead>
<tr>
<th>Comments</th>
<th>Responses</th>
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<tbody>
<tr>
<td>1. There was conditional approval of the document from two RAP members who questioned the need for any type of routine surveillance, given the lack of evidence for its impact on outcomes.</td>
<td>The members of the Working Group for this guideline agree that the evidence for routine surveillance is not strong; however, there are, in the opinion of the Working Group members, many reasons to offer women the option of follow-up, while giving</td>
</tr>
</tbody>
</table>
them the option of no follow-up, and clearly stating the harms and benefits associated with follow-up. Examples of reasons to conduct follow-up include management of monitoring for recurrence given the high risk for recurrence among this population, monitoring for adverse effects, identification of appropriate genetic testing, and identification of symptom-management and supportive-care needs.

<table>
<thead>
<tr>
<th>2.</th>
<th>A reviewer commented on the relevance of the qualifying statement indicating that CA-125 may be monitored to identify women for clinical trials.</th>
<th>The members of the Working Group agreed to delete this qualifying statement.</th>
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<tr>
<td>3.</td>
<td>A reviewer noted that our title indicates that the guideline is for fallopian tube, primary peritoneal, and epithelial ovarian cancer; however, the evidence only covers epithelial ovarian cancer.</td>
<td>The consensus of the Working Group’s members is that the evidence for epithelial ovarian cancer also applies to these related disease sites.</td>
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<tr>
<td>4.</td>
<td>A reviewer recommended that the more evidence-based recommendation (i.e., regarding CA-125) be placed further up in the list of recommendations.</td>
<td>We have moved the CA-125 recommendation up to the first page of the recommendations.</td>
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<tr>
<td>5.</td>
<td>There was a suggestion to remove mention of a future guideline on sexual health from the qualifying statements and add it to the discussion.</td>
<td>This suggestion was incorporated.</td>
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<tr>
<td>6.</td>
<td>Quote: The guideline talks about key evidence for radiological imaging and key evidence for the role of other imaging modalities. The two sentences seem incongruent. The first section on page 4 says “this study found that imaging techniques did not add clinically relevant information.” The second section goes on to suggest magnetic resonance imaging (MRI) instead of ultrasound. Recommend consider rewording to reconcile the two statements.</td>
<td>We reworded this recommendation to clarify that in the former situation, recurrence has not yet been identified, whereas in the latter situation recurrence has already been identified.</td>
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<tr>
<td>7.</td>
<td>A reviewer questioned why we did not consider consensus-based guidelines.</td>
<td>We clarified in Section 3 that only guidelines based on a systematic review, and not consensus-based guidelines were eligible for consideration as possible guidelines to endorse.</td>
</tr>
<tr>
<td>8.</td>
<td>A reviewer stated that the recommendations seem mostly to be based on the reported practice of the</td>
<td>This is true. As the evidence base is very poor, the members of the Working Group relied on consensus opinion for many of the</td>
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</table>
recommendations, stressing that a range of options are acceptable and that a follow-up plan should be developed on an individual patient basis, with discussion between the oncologist and patient.

9. A reviewer questioned the rationale for more frequent monitoring earlier on.

This recommendation is the opinion of the Working Group’s members, based on the experience that the needs of women (e.g., with respect to anxiety or adverse effects) may be greater immediately following treatment.

10. A reviewer commented that the recommendations were vague and that it would be difficult for a nurse practitioner or family physician to know what to do.

The members of the Working Group agreed with this statement and added a qualifying statement to the recommendations to indicate that an individualized plan should be completed by the oncology team upon transferring follow-up care to another clinician.

### EXTERNAL REVIEW

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

*Targeted Peer Review*

Three targeted peer reviewers from Ontario, one from British Columbia and one from Manitoba who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. All five completed a review of the document (Appendix 1). Results of the nine questions included in the feedback survey are summarized below.

<table>
<thead>
<tr>
<th>Question</th>
<th>Lowest Quality (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>Highest Quality (5)</th>
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<tbody>
<tr>
<td>1. Rate the guideline development methods.</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>4</td>
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<tr>
<td>2. Rate the guideline presentation.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
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**Reviewer comment:** Since this document is essentially a consensus statement of committee members, I do not understand why consensus guidelines would not be considered part of the evidence base.

**Authors’ response:** A systematic review was conducted as part of the guideline development methodology. The committee members came to consensus on their interpretation of this evidence. Consensus statements that were not based on a systematic review of evidence were not included in the evidence base.
Reviewer Comment: A concise summary at the start is key, as this is what will be reviewed/used by the end users. 
Authors’ response: A summary of the recommendations only will be provided in a separate section at the beginning of the final report.

Reviewer comment: The only comment in this section is that it remains unclear for family doctors and nurse practitioners as to what follow-up they should do. I think the list of symptoms is crucial, and while the main ones have been listed, there are still many other concerning symptoms that can exist. You may consider forming an appendix of further signs and symptoms that should initiate a follow-up visit with a physician for those patients that do not want routine follow up.
Authors’ response: We have added to the recommendation that patients should be encouraged to report any concerning symptoms (recommendation #4). Under recommendation #4, we have provided a qualifying statement that in the case of transfer of care from the patient’s oncologist to a clinician such as a gynecologist, family physician, or nurse practitioner, a written, individualized plan should be developed by the oncologist in consultation with the patient and provided to the clinician to whom care has been transferred.

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<th>Question</th>
<th>Reviewer Ratings (N=5)</th>
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<td>3. Rate the guideline recommendations.</td>
<td>Lowest Quality (1) 0</td>
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Reviewer comment: An alternative strategy would have been to adopt a more stringently defined follow-up, particularly in light of the fact that the majority of patients will be followed in tertiary care settings.
Authors’ response: In order to allow for variations in patient values and preferences and due to the limited nature of the evidence, the Working Group believed that it was not possible to recommend a more stringently defined follow-up schedule.

Reviewer comment: I would have liked to see a (re) mention of the importance of patients' psychosocial needs in the conclusion section because such needs (notably around sexual dysfunction and clinical fear of recurrence) are among the highest that patients report, and for the purpose of these guidelines, continue to be important even for patients who may not need regular oncologist follow-ups.
Authors’ response: In response to this reviewer comment, the guideline authors have added a mention of psychosocial needs to the conclusion.

Reviewer comment: I would have liked to see a bit more on patient care for delayed or long-term treatment sequelae, because while some symptoms do remit on their own, some do not; many patients report that family physicians do not feel it is their responsibility to manage these. Could this be touched on somewhere, if only under development of an individualized plan?
Authors’ response: The guideline authors have added this consideration to the qualifying statement that describes the development of an individualized treatment plan in the event of transfer of care.
**Reviewer comment:** Recommendation 2: perhaps the first qualifying statement could be modified to indicate treatment based on rising CA-125 alone is not recommended outside of a clinical trial. This way, clinicians would be protected when starting patients on clinical trials that allow for CA-125 rise as an entry criterion.

**Author’s response:** The authors have chosen to leave the statement as it is because treatment in the context of a clinical trial is outside the scope of this guideline.

**Reviewer comment:** For the second qualifying statement under recommendation 2, could there be a statement to indicate this guideline should be reviewed and possibly modified after the two ongoing randomized trials including secondary debulking surgery report results? Especially if one of these trials is a positive trial?

**Authors’ response:** This information has been added as suggested to the Further Qualifying Statements section after the recommendations and key evidence. It also appears in Section 4 after the Discussion.

**Reviewer comment:** Recommendation 4: The first qualifying statement is very strongly worded, stating physical examination may be of limited value. However, this statement comes from a single small retrospective study.

**Authors’ response:** The limited evidence suggests that physical examination has limited value; however, to enhance clarity, the wording for this recommendation was modified to specify that patients should be informed that physical examination has a low level of sensitivity. As well, the key evidence for this recommendation (Menczer et al. [4] and Chan et al. [5]) was moved to appear directly below the recommendation and qualifying statement, making the evidence base (limited as it is) more transparent. The authors did not feel that the absence of evidence warranted a recommendation to routinely conduct physical examination.

**Reviewer comment:** The second qualifying statement should perhaps also include the general gynecologist as someone who may follow patients after being transferred out of oncology care.

**Authors’ response:** We have added general gynecologist to the list.

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<th>Question</th>
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<td>4. Rate the completeness of reporting.</td>
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<td>Lowest Quality</td>
<td>Highest Quality</td>
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<td>(1) (2) (3) (4) (5)</td>
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<td>4. Rate the completeness of reporting.</td>
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<tr>
<th>Question</th>
<th>Reviewer Ratings (N=5)</th>
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<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
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<tr>
<td>Lowest Quality</td>
<td>Highest Quality</td>
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<tr>
<td>(1) (2) (3) (4) (5)</td>
<td>(1) (2) (3) (4) (5)</td>
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<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
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**Reviewer comment:** This document allows for almost any follow-up provided that it is established between the physician and the patient. It does not go far enough to make clear recommendations. This guideline provides very little information, because there is very little evidence to guide follow-up practices.

**Authors’ response:** The authors agree with these statements; however, because there is very little evidence to support recommendations for follow-up, a discussion with the patient is needed to determine an individualized follow-up plan.

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<th>Question</th>
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<tr>
<td>6. Rate the overall quality of the guideline report.</td>
<td>Lowest Quality (1) (2) (3) (4) Highest Quality (5)</td>
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<td>0 0 1 2 2</td>
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<th>Question</th>
<th>Reviewer Ratings (N=5)</th>
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<td>7. I would make use of this guideline in my professional decisions.</td>
<td>Lowest Quality (1) (2) (3) (4) Highest Quality (5)</td>
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<td>0 1 1 2 1</td>
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<th>Question</th>
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<td>8. I would recommend this guideline for use in practice.</td>
<td>Lowest Quality (1) (2) (3) (4) Highest Quality (5)</td>
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<td>0 0 2 1 2</td>
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</table>

9. What are the barriers or enablers to the implementation of this guideline report?

- Changing physicians’ philosophy and patterns of pattern.
- They are vague, and do not provide any clear direction in an area where there is clearly a void in terms of evidence. In this scenario, a strong consensus of expert opinion is (in my opinion) preferable to the heterogeneity of follow-up that will continue for this patient population.
- I was impressed with the manner in which the emotional needs of the patient were considered in recommendations around the frequency of follow-ups, i.e., not only looking at the non-significant differences in survival rates.
- Barriers to implementation of this guideline include time pressures in oncology clinics to be able to thoroughly discuss the goals of follow-up and the lack of evidence to support follow-up, as well as to explain the CA-125 literature. Also, patients frequently want more follow-up care (visits, CA-125) than is supported by the evidence, and it can be difficult to persuade them that ‘less is more’.
- Patients demanding CA-125 testing, computed tomography
scanning, positron emission tomography scanning, etc. The difficulty will not be with patients that do not want monitoring, it will be much more difficult for the patient that wants ongoing monitoring.

Additional comments:
- An important document that underscores areas where more research data are needed.
- Excellent work. I think it is a very clear and concise document.

Professional Consultation
Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Gynecologic oncologists, family physicians, and advanced practice nurses with contact information in the PEBC database were contacted. Fourteen responses were received of 108 surveys distributed. Nine individuals stated that they did not have interest in this area or were unavailable to review the guideline at this time. The results of the feedback survey are summarized in Table 5-3.

Table 5-3. Responses to four items on the professional consultation survey.

<table>
<thead>
<tr>
<th>General Questions: Overall Guideline Assessment</th>
<th>Number (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate the overall quality of the guideline report.</td>
<td>Lowest Quality: (1) (2) (3) (4) Highest Quality: (5)</td>
</tr>
<tr>
<td></td>
<td>0 (0) 0 (0) 1 11 2</td>
</tr>
<tr>
<td>Rate the overall quality of the guideline report.</td>
<td>Strongly Disagree: (1) (2) (3) (4) Strongly Agree: (5)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>I would make use of this guideline in my professional decisions.</td>
<td>0 (0) 0 (0) 1 7 6</td>
</tr>
<tr>
<td>I would recommend this guideline for use in practice.</td>
<td>0 (0) 0 (0) 1 10 3</td>
</tr>
</tbody>
</table>

What are the barriers or enablers to the implementation of this guideline report?

Barriers
1. Lack of evidence/lack of guidance:
   - This is a strange guideline in that it is saying there is no evidence to guide the use of much post cancer monitoring, so we need to discuss pros and cons and individualize decisions. We do that anyways. So now I have a guideline that says there is no guidance...
   - Incomplete instructions from oncology to family physician on follow-up of discharged patients. The family physician should be given this guideline as part of the oncology discharge report.
   - Following the guideline report still leaves many issues at discretion of attending physician and/or patient, e.g., follow-up visits: nil versus regular; carcinoembryonic antigen monitoring: yes versus no; follow-up (if done): oncologist versus family doctor versus nurse; visits versus telephone contact; emphasis on anxiety with monitoring as opposed to anxiety of apparently doing nothing in follow-up (difficult to assess)
   - Lack of evidence for this follow-up care - many primary care providers may lack confidence providing follow-up care
   - "Despite these findings, it is the consensus of the members of the Working Group that the benefits of surveillance may outweigh the harms for many women in this patient population and, thus, the option of regular follow-up should be offered." This consensus will lead to confusion. Primary care providers will be left in the position of trying to explain to patients that this is what the experts...
say despite what the trials say. The harms of following this opinion are well noted and until better trial evidence is available, I think the advice needs to be stronger toward no routine follow-up if the woman is well. This is in keeping with the colorectal cancer and breast guidelines being based on evidence. Patients need to know that close follow-up will most likely have a negative effect. I think this is the same for breast cancer patients needing to know that close post-curative-intent treatment will not affect time of death due to a recurrence but may reduce risk of death from a new breast cancer found. Having patients in this group returning to cancer centres long term for examinations and tests that have been shown to have negative effects is not sustainable as the general population ages, with cancer survivor numbers growing many times faster than specialist supply.

- The guideline is rather vague for clinical utility. Although I agree that there is no good evidence in terms of timing of follow-up, it would be helpful to clinicians to have a range cited for accepted periods of follow-up if that is decided between the clinical and patient (i.e., three to six months for the first five years and annually thereafter). The symptom list, however, is useful and it is this kind of specific recommendation that will allow clinicians to apply the guideline to practice.
- Because it (appropriately) identifies the lack of evidence for monitoring it may well be difficult for primary care physicians and specialists to agree on what is the best approach; I suspect many patients will find this disconcerting. Routines are comforting.

2. **Strongly held patient beliefs:**
   
   - Overcoming strongly held beliefs of patients in remission that early detection of recurrence not beneficial to improving outcomes. Many patients also want to maintain contact with oncology team so that they will benefit from any advances in detection and treatment. They need to know that if they choose “no follow-up” they will not miss out on any advances in disease management.
   
   - Implementation may be hampered by online material and patient resistance.
   
   - Changing the way of doing things! In many respect, the decision to perform routine CA-125 in the follow-up of patients versus wait for symptoms has traditionally been based on a ‘philosophical’ approach to treatment with the belief that if a recurrence is discovered and treated earlier, the results will be better. Unfortunately, this does not seem to be the case with ovarian cancer. This belief is hard to change. This is why we need solid data and evidence-based decisions. It is also difficult to handle the issue within a group if some colleagues perform routine CA-125 every three months, and other colleagues do not. Patients speak a lot to one another in the waiting room...!

3. **Referral to specialists for implementation**

   - Definitely too detailed for family doctors. Most will only have a small number of patients for follow-up so a condensed cheat sheet approach should be considered. Clearly, more detailed guidelines like this one should be available for review if wanted.
   
   - Oncology and surgery would be more likely users because primary care probably would defer to them; however, primary care would assist in counseling patients if they were uncertain.
   
   - As a general practitioner, these guidelines make me want to refer to the specialist to implement.

**Enablers:**

- Leaves quite a bit of flexibility to follow-up.
- CA-125 is not covered by the Ontario Health Insurance Plan.

Additional comments from Practitioner Feedback:

- Family physicians need to be educated on the role of CA-125 with more information on its appropriate use in Continuing Medical Education. The report should more clearly state that although it discusses epithelial ovarian cancer its recommendations are valid to the other cancers.
- Survivorship Plan of Management should be available to the patient at time of completion of treatment, clearly outlining all potentially relevant signs and symptoms
that may indicate recurrence (again, this may be anxiety provoking, even to the physician).

- Perhaps mention nurse practitioners explicitly for primary care follow-up?
- The guideline pertains to “clinically disease-free after primary treatment”; however, the definition of what this implies is very vague. In addition, although I agree that for high-grade serous cancers and high-grade endometrioid cancers, earlier diagnosis of recurrence and treatment will not translate into a longer disease-free period, I am not sure that this is true for low-grade serous or low-grade endometrioid or mucinous cancers. Is there evidence to suggest this? Are there exceptions to the rule? That is, is there value in detecting first recurrences shortly after the two-year mark to find those who would benefit from surgical re-exploration?
- Doing less is often the right thing. Thanks.
- I agree that results of the DESKTOP III trial are important and that the issue of participating in clinical trials is also important to take into consideration. It would also be nice to factor in the increasing trend of maintenance treatment following completion of first-line chemotherapy. This was not addressed.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.
REFERENCES


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<table>
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<tr>
<td>Dr. Paul Hoskins</td>
<td>Medical Oncologist, British Columbia Cancer Agency, University of British Columbia</td>
<td>Published an editorial, commentary or clear opinion regarding any of the objects of study: <em>Current Oncology Reports</em> 15: 204-206. 2013.</td>
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</table>
Appendix 2. Agree II Rigour of Development scores for the Cancer Australia guideline [26] (two reviewers).

Reviewer #1:

1. Systematic methods were used to search for evidence: 7/7
2. The criteria for selecting the evidence are clearly described: 7/7
3. The strengths and limitations of the body of evidence are clearly described: 7/7
4. The methods for formulating the recommendations are clearly described: 3/7
5. The health benefits, side effects, and risks have been considered in formulating the recommendations: 7/7
6. There is an explicit link between the recommendations and the supporting evidence: 4/7
7. The guideline has been externally reviewed by experts prior to its publication: 5/7
8. A procedure for updating the guideline is provided: 2/7

Reviewer #2

1. Systematic methods were used to search for evidence: 7/7
2. The criteria for selecting the evidence are clearly described: 7/7
3. The strengths and limitations of the body of evidence are clearly described: 4/7
4. The methods for formulating the recommendations are clearly described: 3/7
5. The health benefits, side effects, and risks have been considered in formulating the recommendations: 4/7
6. There is an explicit link between the recommendations and the supporting evidence: 5/7
7. The guideline has been externally reviewed by experts prior to its publication: 4/7
8. A procedure for updating the guideline is provided: 4/7
Appendix 3. Search strategy.

1. (follow up care or follow up plan or follow up visit or follow up examination or clinical follow up or routine follow up or follow up model or follow up strategies or follow up methods or follow up program or routine test or postoperative surveillance or ovarian cancer surveillance or (surveillance and survivors)).mp.

2. aftercare/

3. postoperative care/

4. Ovarian Neoplasms/

5. (Ovarian and (cancer or carcinoma or tumour)).mp.

6. (1 or 2 or 3) and (4 or 5)

7. limit 6 to yr="2013 -Current"

8. limit 33 to English language
Appendix 4. PRISMA flow diagram of search for primary literature and systematic reviews.

355 English-language non-duplicate records identified through database searching (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials searched January 2010 to March 2015)

355 records title only or title and abstract screened

not relevant n=339
conference abstract n=12

4 full-text articles assessed for eligibility

3 articles excluded
(individual studies published before final search date for Clarke et al (July 2013))

1 systematic reviews and zero primary studies included