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Evidence-Based Series 4-20 Version 2 IN REVIEW

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

Systemic Therapy for Recurrent, Metastatic, or Persistent Cervical Cancer

H. Hirte, E.B. Kennedy, M. Fung-Kee-Fung, L. Elit,
and the Gynecologic Cancer Disease Site Group

Report Date: November 24, 2014

An assessment conducted in November 2020 placed Evidence-based Series (EBS) 4-20 Version 2 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 4-20 Version 2 is comprised of 3 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/516

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development, and External Review Process**

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Systemic Therapy for Recurrent, Metastatic, or Persistent Cervical Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version July 5, 2006	1966-2006	Full Report	Web Publication	N/A
Version 2, November 24, 2014	2006-2014	Full Report	Updated Web Publication	Update of 2006 Recommendations

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Evidence-Based Series 4-20 Version 2: Section 1

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

Systemic Therapy for Recurrent, Metastatic, or Persistent Cervical Cancer: Guideline Recommendations

H. Hirte, E.B. Kennedy, M. Fung-Kee-Fung, L. Elit, and the Gynecologic Cancer Disease Site Group

Report Date: November 24, 2014

GUIDELINE OBJECTIVES

The objective of this guideline is to update a previous guideline on chemotherapy options for women with recurrent, metastatic, or persistent cervical cancer. The primary outcomes of interest are overall survival rate and quality of life. Other outcomes of interest include response rate, progression-free survival rate, and adverse effects. Second-line or higher therapy options are outside the scope of this guideline.

TARGET POPULATION

These recommendations apply to women with metastatic, recurrent, or persistent cervical cancer for whom systemic therapy is indicated. This includes women with squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.

INTENDED USERS

The intended users of this guideline are gynecologic oncologists or oncologists treating gynecologic cancers in the province of Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

RECOMMENDATION 1
It is recommended that all patients with recurrent, metastatic or persistent cervical cancer be offered the opportunity to participate in randomized clinical trials, if available, that evaluate the efficacy of and adverse effects of systemic therapy regimens.

Summary of Key Evidence and Justification for Recommendation 1

This recommendation is the opinion of the Working Group and was adopted from the previous version of this guideline.

RECOMMENDATION 2
Cisplatin with paclitaxel is recommended for this patient population, and cisplatin in other combinations, including cisplatin-vinorelbine, cisplatin-gemcitabine, and cisplatin-topotecan may also be considered. The substitution of carboplatin for cisplatin in these combinations is also recommended for this target population because carboplatin is associated with fewer adverse effects and greater ease of administration. The selection of combination chemotherapy will depend on toxicity profile, patient preference, and other factors; for example, cisplatin combinations may be preferred in cases of allergic reaction or of difficulty with bone marrow suppression.

Summary of Key Evidence and Justification for Recommendation 2

GOG-0204 [2] which included patients with a performance status ≤1 (meaning that they were restricted in physically strenuous activities but ambulatory) [3], compared the combinations cisplatin-vinorelbine, cisplatin-gemcitabine, and cisplatin-topotecan with the reference arm cisplatin-paclitaxel, with OS as the primary endpoint. This study was terminated early because the comparator groups were unlikely to demonstrate any of the combinations statistically superior to the reference arm, thus justifying the recommendation that each of these combinations could be considered options for the target population.

Paclitaxel (175 mg/m^2 of body surface area for 3 hours on day 1 [3h d1]) in combination with carboplatin (area under the curve [AUC]5 1h d1) has been tested as an alternative to the standard, but more toxic, paclitaxel (135 mg/m^2 24h d1) and cisplatin (50 mg/m^2 2h d2) in a Japan Clinical Oncology Group phase III noninferiority trial in stage IVB, persistent, or recurrent cervical cancer (JCOG-0505) [1]. This study, published as an abstract, followed 253 patients for 17.4 months and demonstrated the noninferiority of carboplatin-paclitaxel compared with cisplatin-paclitaxel (overall survival rate [OS] 17.5 versus 18.3 months; hazard ratio [HR], 0.99; adjusted 90% confidence interval [CI], 0.79 to 1.25; noninferiority p=0.032). Lower rates of neutropenia, febrile neutropenia, creatinine levels, and early treatment discontinuation due to adverse effects were experienced by patients in the carboplatin combination group, as well as higher rates of thrombocytopenia and neuropathy. There was a significantly higher nonhospitalization period, a proxy for quality of life, for patients in the carboplatin-paclitaxel arm. Based on these results, and on the feasibility of administration, carboplatin-paclitaxel is recommended as a treatment option for recurrent, metastatic, or persistent cervical cancer.

RECOMMENDATION 3

Bevacizumab in combination with cisplatin-paclitaxel is recommended for a specific subset of the target population, which includes only patients that match the characteristics of the GOG-0240 study population [4]. Carboplatin may be substituted for cisplatin in this patient population, based on the justification given under Key Evidence and Justification below.

The subset includes patients with primary stage IVB (has spread to parts of the body away from the cervix, such as the liver, intestines, lungs, or bones) [5], recurrent, or persistent disease not amenable to curative treatment with surgery and/or radiotherapy, who have performance status scores of ≤1, adequate renal, hepatic, and bone marrow function, and not including those patients previously treated with chemotherapy for recurrence or those with nonhealing wounds, active bleeding conditions or inadequately anticoagulated thromboembolism. In addition, GOG-0240 did not include patients with stage IIIB cancer (local extension to pelvic sidewall) or IVA cancer (invasion into bladder or rectum). For more details on the GOG-0240 patient population, see the study details provided at clinicaltrials.gov [6].

Contraindications to bevacizumab include:

- Uncontrolled hypertension
- Arterial thromboembolic events within last 6 months (includes cerebrovascular accident [CVA], transient ischemic attack [TIA], or myocardial infarction [MI])
- Surgical procedure within 28 days
- Full dose anticoagulation

Summary of Key Evidence and Justification for Recommendation 3

Results detected a significant overall survival rate advantage of chemotherapy with cisplatin (50 mg/m^2) and paclitaxel (135 or 175 mg/m^2 d1) or topotecan (0.75 mg/m^2 d1 to d3) and paclitaxel (175 mg/m^2 d1) with bevacizumab (15 mg/kg of body weight d1) (HR], 0.71; 98% CI, 0.54-0.95; p=0.004, one-sided) versus these chemotherapy options without bevacizumab. Cycles were repeated at 21-day intervals. There was also a significant difference in OS for cisplatin-paclitaxel with bevacizumab compared with cisplatin-paclitaxel without bevacizumab (median OS: 17.5 versus 14.3 months, HR, 0.68; 95% CI, 0.48-0.97; p=0.04, one-sided). Patients in the bevacizumab arm experienced more hypertension of grade 2 or higher, thromboembolitic events of grade 3 or higher, and gastrointestinal fistula of grade 3 or higher; however, no significant differences in quality of life were detected. As in GOG-0204, patients in this trial had a performance status of ≤1. The discontinuation rate was 25% with patients in the bevacizumab group versus 16% of patients in the group that did not receive bevacizumab.

Although GOG-0240 tested bevacizumab with cisplatin and paclitaxel, the noninferiority of carboplatin-paclitaxel demonstrated in JCOG-0505, its more favourable toxicity profile and ease of administration, as well as its demonstrated efficacy in other disease sites [7] provide support for the recommendation for carboplatin.

Qualifying Statement for Recommendation 3

There may be a risk of thrombocytopenia with the combination of carboplatin and bevacizumab. However, estimates of the level of risk for this adverse event are not available, as the combination was not tested in the patient population for this guideline.

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Updating

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at: https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=122178

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Evidence-Based Series #4-20 version 2: Section 2

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

Systemic Therapy for Recurrent, Metastatic, or Persistent Cervical Cancer: Evidentiary Base

H. Hirte, E.B. Kennedy, M. Fung-Kee-Fung, L. Elit, and the Gynecologic Cancer Disease Site Group

Report Date: November 24, 2014

INTRODUCTION

There were approximately 610 new cases and 150 deaths from carcinoma of the cervix in Ontario in 2013 [1]. The prognosis for early-stage cervical cancer is good due to effective screening practices and early treatment options; however, the five-year survival rate for women with cancer that has spread beyond the true pelvis to adjacent organs is only 17% [2]. Therefore, treatment options that can improve survival rates while maintaining quality of life are needed.

A PEBC guideline was developed in 2006 to recommend chemotherapy options for patients with recurrent, metastatic, or persistent cervical cancer. The evidence base at that time consisted of 15 studies, including trials of single-agent cisplatin, combination-agent cisplatin, other platinum containing agents, and nonplatinum-containing agents [4]. Of 13 trials that assessed survival rate, only one trial, a comparison of cisplatin versus cisplatin and topotecan, demonstrated a statistically significant and clinically meaningful improvement in median survival time of 2.9 months in favour of the combination therapy. On this basis, the previous version of this guideline recommended treatment with cisplatin-topotecan over single-agent cisplatin. In current practice, however, clinicians in Ontario use cisplatin or carboplatin, which has fewer side-effects and is more feasible to administer, in combination with paclitaxel to treat recurrent, metastatic, or persistent cervical cancer, based on the results of clinical trials conducted since the publication of the previous version of this guideline [5,6].

More recently, other researchers have initiated the trial of novel biological agents, motivated by conventional chemotherapy's modest impact on long-term survival rate. Cumulative side-effects and platinum resistance resulting from initial treatment of locally

advanced cervical cancer with cisplatin-based chemoradiation also provide the rationale for studying novel biological agents or noncisplatin containing agents in this patient population [6]. For example, bevacizumab is a biological agent that inhibits the growth of tumours by limiting the formation of tumour vasculature through binding and inactivating the angiogenesis-stimulating vascular endothelial growth factor [7]. This version of the guideline will update the evidence base with results from randomized trials that have been published since 2006, including a phase III trial of bevacizumab. The objective is to explore whether new therapeutic options show significantly improved outcomes for women with recurrent, metastatic, or persistent cervical cancer, or whether new options are available that may be suitable for women who have experienced cumulative side-effects or who do not tolerate the currently available treatment options.

RESEARCH QUESTION

What are the systemic therapy options for women with recurrent, metastatic, or persistent cervical cancer? The primary outcomes of interest are overall survival rate and quality of life. Other outcomes of interest include response rate, progression-free survival rate, and adverse effects.

METHODS

This evidentiary base was developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (8). Evidence was selected and reviewed by members of the Gynecologic Cancer Disease Site Group's Working Group, which included individuals with expertise in gynecologic oncology and health research methodology.

The body of evidence in this review is comprised of phase III randomized controlled trial data. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is funded by, but maintains editorial independent from the Ontario Ministry of Health and Long-Term Care. The systematic review conducted in 2006 for the previous version of this guideline has been published in a peer-reviewed journal [4].

Literature Search Strategy

The literature was searched using MEDLINE and EMBASE (March 2006 to April 2014), the Cochrane Library Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2014), and Cochrane Controlled Trials Register (Issue 3 of 12, March 2014), the Canadian Medical Association Infobase, and the National Guidelines Clearinghouse. The conference proceedings of the American Society of Clinical Oncology (2007-2013) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources and recent review articles were searched for additional trials.

The literature search of the electronic databases combined keywords such as "recurrent OR metastatic OR persistent) AND "cervical" AND "chemotherapy" (see Appendix 1 for complete search strategy).

The website clinicaltrials.gov was searched with the keywords (recurrent OR metastatic OR persistent) AND "cervical" AND "chemotherapy" AND "randomized", and a filter was used to limit results to Phase II-IV trials. Phase II trials were excluded at the article screening stage.

Study Selection Criteria

Inclusion Criteria

Articles were included in the systematic review of the evidence if they were fully published reports or abstracts and met the following criteria:

1. Phase III randomized controlled trials (RCT) comparing chemotherapy to other chemotherapeutic agents or no further treatment for recurrent, metastatic, or persistent cervical cancer and reporting at least one of the following outcomes: complete or partial response rate, overall or progression-free survival rate, adverse effects, or health-related quality of life (HRQOL). RCTs reporting on heterogeneous populations (e.g., women with a range of disease stages) were included if results were given separately for patients with recurrent, metastatic, or persistent cervical cancer. The search was limited to phase III trials because the Working Group determined that this level of evidence would be the minimum necessary to create new recommendations for clinical practice.
2. Systematic reviews based on RCTs were also eligible.

Exclusion Criteria

Articles were excluded if they were:

1. Non-English–language publications.
2. Studies evaluating the role of radiotherapy administered with chemotherapy.

Synthesizing the Evidence

The Working Group decided that a meta-analysis of Phase III trials would be conducted if more than one study was found that compared the same patient populations and treatment regimens.

RESULTS

Search for Existing Systematic Reviews

No systematic reviews were located that met the inclusion criteria for this guideline.

Primary Literature Systematic Review

Four phase III randomized controlled trials met the inclusion criteria for this review, including:

1. A trial of cisplatin-paclitaxel as the reference arm, compared with three other cisplatin combinations (GOG-0204) [6];
2. A 2-by-2 factorial design comparing two types of combination chemotherapy with and without the addition of the biological agent bevacizumab (GOG-0240) [8];
3. A trial to assess the noninferiority of carboplatin-paclitaxel compared with cisplatin-paclitaxel (JCOG-0505) [5].
4. A trial of cisplatin versus methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) [9], which was discontinued early due to 4 deaths among 64 patients in the MVAC arm and did not meet its accrual objectives. This trial had inadequate power for statistical comparison and was therefore excluded from the analysis. The flow diagram in Appendix 2 provides more information regarding the number of studies identified in the literature search.

The previous version of this guideline included 15 trials published between 1966 and February 2006 that compared various single and combination chemotherapy agents. There was no overlap of the comparisons assessed in the 2006 PEBC guideline on this topic up to 2006, and the current update (Table 1).

A meta-analysis was not considered because there was considerable heterogeneity regarding the therapy combinations under assessment.

Table 1. Comparison of evidence-base for Hirte et al 2007 [4] and the updated evidence base (to April 2014).

Randomized controlled trials		Evidence-base for Hirte et al 2007 [4] (1966 – February 2006) Author Year (ref)	New evidence (Phase III trials) (March 2006 – April 2014) Author Year, Protocol (ref)
Single agent cisplatin	**cisplatin vs**		
	cisplatin+topotecan	Long et al. 2005 [9]	
	cisplatin+paclitaxel	Moore et al. 2004 [10]	
	BEMP	Vermorken et al. 2001 [11]	
	cisplatin+mitolactol cisplatin+Ifosfamide	Omura et al. 1997 [12]	
	cisplatin+irinotecan irinotecan	Garin et al. 2001 [13]	
	cisplatin+mitomycin-C MVBC	Alberts et al. 1987 [14]	
	PIF	Cadron et al. 2005 [15]	
Combination agent cisplatin	**cisplatin plus**		
	ifosfamide vs CIB	Bloss et al. 2002 [16]	
	methotrexate vs hydroxyurea	Bezwoda et al. 1986 [17]	
	paclitaxel vs cisplatin+vinorelbine cisplatin+topotecan cisplatin+gemcitabine		Monk et al. 2009 GOG-0204 [6]
	paclitaxel vs topotecan+paclitaxel		Tewari et al. 2014 GOG-0240 [8]
	paclitaxel vs carboplatin+paclitaxel		Kitagawa et al. 2012 (abstract) JCOG-0505 [5]
Other platinum containing agents	**carboplatin versus**		
	Iproplatin	McGuire and Abeloff 1989 [18]	
	Iproplatin	Lira-Puerto et al. 1991 [19]	
	Teniposide	Thomsen et al. 1998 [20]	
Nonplatinum containing agents	**adriamycin versus**		
	adriamycin+vincristine adriamycin+cyclophosphamide	Wallace et al. 1978 [21]	
	adriamycin+bleomycin bleomycin	Barlow et al. 1973 [22]	
	adriamycin+bleomycin	Greenberg 1977 et al. [23]	
Biological agents	**bevacizumab plus**		
	cisplatin or topotecan+paclitaxel vs cisplatin or topotecan+paclitaxel without bevacizumab		Tewari et al. 2014 GOG-0240 [8]

Randomized controlled trials	**Evidence-base for Hirte et al 2007 [4] (1966 – February 2006) Author Year (ref)**	**New evidence (Phase III trials) (March 2006 – April 2014) Author Year, Protocol (ref)**

Abbreviations: RCT = randomized controlled trial, ref= reference, vs = versus, BEMP = bleomycin + vindesine + mytomycin-C + cisplatin, CIB = bleomycin + cisplatin + ifosfamide; MVBC = mitomycin-C + vincristine + bleomycin + cisplatin, PIF = cisplatin + ifosfamide + 5-fluorouracil.

Study Design and Quality (Table 2)

The results of the study quality assessment of the three new studies are presented in Table 2. Two studies were fully published and one was available as an abstract. Neither of the two fully published studies provided information on randomization method, sequence generation, or allocation concealment, therefore the risk of bias associated with these factors could not be assessed. One study was open-label [8], a characteristic which increases risk of bias, and blinding was not mentioned in the other [6]. Outcomes were not selectively reported and power calculations were described in both. Intent-to-treat (ITT) analysis was used in one study [8], but not the other [6], however the latter study stated that a full ITT analysis gave similar results. Funding and support were provided by government [6,8] and industry [8]. Baseline characteristics were balanced where reported, although baseline characteristics were not reported for a portion of the patients in one of the studies [6]. Details are provided on how interim analyses were planned for GOG-0204 [6] and GOG-0240 [8], however the second and final analysis in GOG-0240 occurred before the prespecified number of deaths to achieve power had been accrued.

Insufficient details were available to assess most aspects of the quality of JCOG-0505, which was funded by the Ministry of Health, Labour and Welfare in Japan, and was published in abstract form [5].

Table 2. Study design and quality.

Study Year (Protocol) Ref	Phase/Randomization method/allocation concealment	Blinding	Selective outcome reporting	ITT	Funding source	Power calculation described	Baseline characteristics	Comments
Monk et al. 2009 (GOG-0204) [6]	Phase III multicentre study; randomization method and allocation concealment not described	Blinding not mentioned	No	No but "a full ITT analysis including ineligible patients also gave similar results"	US National Institutes of Health	Yes	Balanced for DS and PS for analysis of primary outcome (OS); not clear for other outcomes because 41 pts from a previous study were included and not described.	None
Tewari et al. 2014 (GOG-0240) [8]	Phase III 2-by-2 factorial design; randomization method and allocation concealment not described; 15 pts crossed over to bev and 33 pts on bev crossed over to other salvage therapy.	Open-label	No	Yes	US National Cancer Institute and Genentech Inc.	Yes	Balanced	Second interim analysis not mentioned in study protocol
Kitagawa et al. 2012 (JCOG-0505) [5] [24]	Phase III/Minimization method with institution, PS, histology, and tumour sites as balancing factors at the data centre/allocation concealment not mentioned	Not mentioned	No	Unknown	The Ministry of Health, Labour and Welfare of Japan	Yes	Unknown	Results published in an abstract

Ref = reference, ITT = intent-to-treat analysis planned, DS = disease status, PS = performance status, OS = overall survival rate, pts = patients, bev = bevacizumab.

Study Characteristics (Table 3)

GOG-0204 compared the reference arm cisplatin-paclitaxel with three other doublet combinations, with overall survival rate as the primary outcome, and response rate, progression-free survival rate, adverse effects, and quality of life (QOL) being secondary objectives [6].

In GOG-0240, the two primary hypotheses were whether the addition of bevacizumab to chemotherapy improves survival rates and whether combining paclitaxel with topotecan rather than with cisplatin improves survival rates. Primary outcomes were overall survival rate and frequency and severity of adverse effects, and secondary outcomes were progression-free survival rate and tumour response.

All patients in both studies had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, meaning that they were at least ambulatory and able to complete work of a light or sedentary nature [25]. Prior surgery was not reported for either study. Patients were ineligible if they had received prior chemotherapy for metastatic disease in one study [6] and ineligible if they had received prior chemotherapy for recurrence of cancer in the other [8]. Prior platinum radiation therapy was common in patients in both groups, ranging from 64% to 73% in the GOG-0204 study arms [6], and 71% to 77% in the GOG-0240 study arms [8]. In all arms of both studies, the percentage with Stage IVB cancer (advanced; cancer has spread to parts of the body away from the cervix, such as the liver,

intestines, lungs, or bones) was 16% to 18%. Over two-thirds had recurrent cancer (range among arms: 69% to 78%) and prevalence of persistent cancer in study arms ranged from 6% to 14%. Percentage of patients with disease confined to the pelvis was not reported in GOG-0204 [6], while in GOG-0240, 54% of patients in the entire study group had disease confined to the pelvis [8].

JCOG-0505 was designed to test noninferiority of carboplatin-paclitaxel compared with cisplatin-paclitaxel. The percentage receiving prior platinum was not reported, and all patients had stage IVB or recurrent disease [5].

Table 3. Study characteristics.

Author Year (Protocol) (ref)	# of pts.	Trial arms	Dose and schedule*	Prior platinum radiation therapy (%)	Stage IVB (%)	Recurrent (%)	Persistent (%)
Monk et al. 2009 (GOG-0204) [6]	118	Cis-pac	50 mg/m^2 d2 135 mg/m^2 d1 over 24hrs	68	17	72	12
	117	Cis-vin	50 mg/m^2 d1 30 mg/m^2 d1+d8	73	16	71	13
	119	Cis-gem	50 mg/m^2 d1 1000 mg/m^2 d1+d8	64	18	71	11
	118	Cis-topo	50 mg/m^2 d1 0.75 mg/m^2 d1+d2+d3	73	18	69	13
Tewari et al. 2014** (GOG-0240) [8]	114	Cis- pac	50 mg/m^2 135 mg/m^2 or 175 mg/m^2 d1	75	16	78	6
	111	Topo-pac	0.75 mg/m^2 d1 to d3 175 mg/m^2 d1	73	17	69	14
	115	Cis-pac-bev	50 mg/m^2 135 mg/m^2 or 175 mg/m^2 d1 15mg/kg on d1	77	17	71	12
	112	Topo-pac-bev	0.75 mg/m^2 d1 to d3 175 mg/m^2 d1 15mg/kg d1	74	18	70	13
Kitagawa et al. 2012 abstract (JCOG-0505) [5]	253	Cis-pac	50 mg/m^2 d2 over 2 hrs 135 mg/m^2 d1 over 24 hrs	Pts had received 0 to 1 prior platinum (% not reported)		100	0
		Carbo-pac	AUC5 d1 over 1 hr 175 mg/m^2 d1over 3 hrs				

*all treatment regimens were administered on a 21-day cycle. **Three options for administration of paclitaxel were available at the discretion of the investigator. Ref = reference, pts = patients, Cis-pac = cisplatin-paclitaxel, Cis-vin=cisplatin-vinorelbine, Cis-gem=cisplatin-gemcitabine, Cis-topo=cisplatin-topotecan, d=day, Topo-pac= topotecan-paclitaxel, bev=bevacizumab, Carbo-pac = carboplatin-paclitaxel.

GOG-0204 [6] Study Outcomes:

Survival Rate and Response Rate (Table 4)

A planned interim analysis after 232 deaths resulted in a recommendation for early closure of this trial because the comparator groups were unlikely to demonstrate a statistically significant benefit. Median overall survival time in months was 12.9 (cisplatin-paclitaxel), 10.0 (cisplatin-vinorelbine), 10.3 (cisplatin-gemcitabine), and 10.3 (cisplatin-topotecan) ($p>0.05$). There was also no significant difference in progression-free survival

rates among groups. Rates of complete, partial, and overall response are also presented in Table 4.

Adverse Events and QOL (Table 5)

Several adverse events differed significantly by treatment group, including risk of grade 3 or higher leucopenia (lower for cisplatin-gemcitabine), neutropenia (lower for cisplatin-gemcitabine), thrombocytopenia (higher for cisplatin-gemcitabine and cisplatin-topotecan), anemia (lower for cisplatin-paclitaxel), and infection (lower for cisplatin-paclitaxel) (Table 5).

HRQOL was assessed with the Functional Assessment of Cancer Therapy – Cervix Trial Outcome Index (FACT-Cx TOI), which includes items to assess physical well-being, functional well-being, and additional items specific to cervical cancer, and does not include emotional or social well-being. Study authors considered a difference of 4 to 5 points between groups to be significant and completion of QOL surveys was balanced between treatment groups. The first four of 11 items from the Functional Assessment of Cancer Therapy – Gynecologic Oncology Group - Neurotoxicity index (FACT-GOG-NTX) [26]that specifically assessed patients' experience of neurotoxicity were also used as well as worst pain experienced according to the Brief Pain Inventory [27]. There were no significant differences in QOL reported [28], however, due to early closure of the study, power for the HRQOL analysis was reduced from 85% to 55%.

GOG-0240 [8] Study Outcomes:

Survival Rate and Response Rate (Table 4)

A data freeze and interim analysis triggered after 173 study deaths at a median follow-up of 12.5 months found that cisplatin-paclitaxel was associated with a significantly longer progression-free survival time (PFS) compared with topotecan-paclitaxel (7.6 months versus 5.7 months, p=0.008); however, there was no difference in overall survival time (OS) (15 months versus 12.5 months, p=0.88). On the basis of these results, the Gynecologic Oncology Group's Data Safety Monitoring Board (DSMB) concluded that topotecan-paclitaxel was not superior to cisplatin-paclitaxel, and recommended the release of these data to investigators and patients.

The results of the comparison of "chemotherapy" (cisplatin-paclitaxel and topotecan-paclitaxel groups combined) with and without bevacizumab were released according to the recommendation of the DSMB after a second data freeze conducted after a median follow-up of 20.8 months. These results detected a significant reduction in the hazard ratio for death within the bevacizumab arm (17.0 months versus 13.3 months; HR, 0.71; 98% CI, 0.54 to 0.95; p=0.004, one-sided). There was also a significant difference in OS for cisplatin-paclitaxel with bevacizumab compared with cisplatin-paclitaxel without bevacizumab (median OS: 17.5 versus 14.3 months; HR, 0.68; 95% CI, 0.48 to 0.97; p=0.04, one-sided). Although the analysis was not powered to detect subgroup differences, patients in the subgroup that had received previous platinum radiation therapy performed better when treated with bevacizumab compared with treatment without bevacizumab. Response rates are presented in Table 4.

Adverse Events and QOL (Table 5)

In GOG-0240, several adverse events were more common in patients in the bevacizumab group, including significantly more grade 2 or higher cases of hypertension, gastrointestinal or genitourinary fistulas of grade 3 or higher, and grade 3 or higher thromboembolism. Myeloid growth factor was permitted for hospitalized patients with grade 3 or higher febrile neutropenia and hypertension was controlled in patients taking

bevacizumab. Treatment delays were permitted to allow for recovery from toxic effects before initiating a new cycle. Treatment with bevacizumab was interrupted or discontinued for certain adverse events, with dose reduction not an option, however dose modifications were allowed for chemotherapy treatments. Twenty-five percent of patients in the chemotherapy-bevacizumab group and 16% of patients in the chemotherapy-alone group discontinued treatment due to adverse events. Fatal adverse events were reported in four patients who received chemotherapy alone and four patients who received chemotherapy plus bevacizumab. Although not specified as an outcome of the trial, HRQOL was assessed using the same self-reporting tools described under GOG-0204 above. There was no significant difference in HRQOL measures for patients in the chemotherapy-only group compared with patients in the chemotherapy-bevacizumab group [29].

JCOG-0505 [5] Study Outcomes:

Survival Rate and Response Rate (Table 4)

JCOG-0505 demonstrated the noninferiority of carboplatin-paclitaxel compared with cisplatin-paclitaxel with respect to overall survival time (18.3 versus 17.5 months, $p=0.032$) and progression-free survival time (6.9 versus 6.2 months, $p>0.05$).

Adverse Events and QOL (Table 5)

Fewer adverse effects were experienced by patients in the carboplatin-paclitaxel group in JCOG-0505 compared with patients in the cisplatin-paclitaxel group, and patients in the group receiving carboplatin reported significantly more time out of hospital (61.9% versus 46.4%, $p<0.0001$), which is a proxy measure for quality of life.

Table 4. Study outcomes: response rate and survival rate.

Author Year, Protocol (Ref)	# of pts	Treatment Arms	CR	PR	CR+PR	Median Survival Time (mo.)	Median PFS (mo.)
Monk et al. 2009, GOG-0204 [6]	118	Cis-pace	3 (2.9%)	27 (26%)	30 (29.1%)	12.9	5.8
	117	Cis-vin	8 (7.4%)	20 (19%)	28 (25.9%)	10.0	4.0
	119	Cis-gem	1 (0.9%)	24 (21%)	25 (22.3%)	10.3	4.7
	118	Cis-topo	2 (1.8%)	24 (22%)	26 (23.4%)	10.3	4.6
						p>0.05	p>0.05
Tewari et al. 2014, GOG-0240 [8]	229	Cis-pac (+/- bev)	NR	NR	89 (38.9%)	15	7.6
	223	Cis-topo (+/- bev)	NR	NR	64 (28.7%) sig level NR	12.5 one-sided p=0.88	5.7 **(p=0.008)**
	225	Cis-pac or topo-pac	14 (6.2)	67 (28.8)	36%	13.3	5.9
	227	(Cis-pac or topo-pac) + bev	28 (12.3) **p=0.03**	81 (36)	48% **p=0.008**	17.0 one-sided **p=0.004**	8.2 0.002
	114	Cis-pac	9 (7.9)	42 (37)	45%	14.3	NR
	115	Cis-pac + bev	17 (15)	41 (35)	50% p=0.51	17.6 one-sided p=0.04	NR
	111	Topo-pac	11 (9.9)	19 (17)	27%	12.7	NR
	112	Topo-pac +bev	5 (4.5)	48 (43)	47% **p=0.002**	16.2 one-sided p=0.09	NR
Kitagawa et al. 2012 (JCOG-0505) [5]	253	Cis-pac Carbo-pac	NR	NR	NR	18.3 17.6 Noninferiority p=0.032	6.9 6.2 p>0.05

Notes: Ref = reference, pts = patients, CR = complete response; PR = partial response; mo = months, PFS, progression-free survival time, Cis-pac = cisplatin-paclitaxel, Cis-vin = cisplatin-vinorelbine, Cis-gem = cisplatin-gemcitabine, Cis-topo = cisplatin-topotecan, Topo-pac = topotecan-paclitaxel, bev = bevacizumab, NR = not reported. **Bolded** values are statistically significant ($p<0.05$). Tests are two-sided unless otherwise noted (note that one-sided p-values in GOG-0240 used a significance level of 0.025).

Table 5. Adverse events (grade 3 to 4 adverse events, unless otherwise noted).

Author Year (Ref)	# of pts	Trial Arms	Neutro-penia‡ (%)	Febrile neutron-penia (%)	Thrombo-cytopenia (%)	Thrombo-embolism (%)	Leuko-penia (%)	Anemia (%)	Hyper-tension† (%)	Neuro-pathy (%)	Infection (%)	GI or GU fistula (%)	Nausea (%)	Vomiting (%)	Pain* (%)	Deaths (#)
Monk 2009 [6]	118	Cis-pac	78	13	7	5	63	17	NR	2	13	16	14	20	10	2
	117	Cis-vin	78	14	8	6	68	29		3	8	13	12	13	10	4
	119	Cis-gem	42	6	42	0	43	34		1	9	10	6	10	13	2
	118	Cis-topo	83 **p<.0001**	10	83 **p<.0001**	6	71 **p<.0001**	35 **p=0.02**		5	5 **p=0.04**	10	8	8	6	3
Tewari 2014 [8]	219	Chemo	26‡	5	NR	1	NR	NR	2	NR	NR	<1	NR	NR	Not sig	5
	220	Chemo + bev	35 **p=0.04**	5 p=1.00		8 **p=0.001**			25 **p<0.001**			6 **p=0.002**				6
	114	Cis-pac (no bev	48	Not sig	NR	NR	36	NR	NR	9	Not sig	NR	8	5	NR	1
	111	Topo-pac (no bev)	64				53			2			3	3		4
Kitagawa 2012 (JCOG-0505) [5]	253	Cis-pac	85.1	16	3.3	NR	NR	NR	NR	Motor: 0.8 Sensory: 0	NR	NR	NR	NR	NR	NR
		Cb-pac	76.4	7.3	23.6					Motor: 2.4 Sensory: 4.9						

Ref = reference, pet = patients, GI = gastrointestinal, GU = genitourinary, Cis-pac = cisplatin-paclitaxel, Cis-vin = cisplatin-vinorelbine, Cis-gem = cisplatin-gemcitabine, Cis-topo = cisplatin-topotecan, NR= not reported, Not sig = not statistically significant, bev=bevacizumab, Topo-pac = topotecan-paclitaxel, Cb-pac=carboplatin-paclitaxel.

Bolded values are statistically significant (p<0.05).

*Grade 2 or higher.

† Grade 2 or higher hypertension defined as recurrent or continuous hypertension for a period of more than 24 hours.

‡ Grade 4 or higher.

DISCUSSION

In the population of women with metastatic, recurrent, or persistent cervical cancer, incremental improvements in length of overall survival time are significant, and quality of life is also a primary outcome of interest for patients and their families. The previous version of this guideline recommended cisplatin-topotecan for patients with recurrent, metastatic, or persistent cervical cancer, based on an overall survival rate advantage for combination chemotherapy versus cisplatin alone. In the eight years since the previous guideline was released, two new fully published phase III RCTs as well as an abstract have been published that meet the inclusion criteria for this systematic review and guideline. These three studies present advances in the knowledge of effective treatments for this patient population, and the emergence of biological therapy in particular represents a new frontier for treatment options.

Two studies of platinum-containing combination therapy established that three different platinum-containing chemotherapy doublets were not superior to cisplatin-paclitaxel, and that carboplatin-paclitaxel is not inferior and results in fewer adverse events compared with cisplatin-paclitaxel. The choice of combination therapy should be guided by patient and clinician preference, the toxicity profiles of the therapy combination, and ease of administration.

In a recently published study, the addition of the biological agent bevacizumab to cisplatin or topotecan combined with paclitaxel resulted in a statistically significant improvement in overall survival rates. In this trial, although self-reported health-related quality of life was not significantly lower in patients in the bevacizumab group, there was a higher rate of adverse events, including more gastrointestinal and genitourinary fistulas, which is a concern. As a result, the addition of this agent is only recommended for the specific subset of the population that is relatively healthy (performance status 0 to 1) and has other characteristics detailed in the recommendations contained in Section 1 of this report. In addition, the consultation and approval process for this guideline elicited concerns that the cost and increase in adverse effects associated with adding bevacizumab may not be worth the small change in outcome given the ultimately dismal prognosis for this group of patients as a whole.

Despite the positive results with the addition of bevacizumab to chemotherapy, the prognosis for our target patient population remains poor, and alternatives to conventional therapy are still needed, such as the exploitation of the genetic diversity of cervical cancer, and potential immunotherapeutic approaches [30]. Accruing enough patients to obtain sufficient power to test novel strategies is a challenge with a small prevalent population and cost concerns; however, more research is needed to improve efficacy and reduce adverse effects associated with treatment of recurrent, metastatic, or persistent cervical cancer.

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- Elizabeth Chan for conducting a data audit.
- Janet Rowe for copy editing.

A complete list of the members of the Gynecologic Cancer Disease Site Group and the Working Group, with their affiliations and conflict of interest information, is provided in Section 2, Appendix 3.

Appendix 1. Literature Search Strategy.

MEDLINE

1. exp cervix neoplasms/
2. (cerv$ and (neoplasm$ or cancer$ or carcin$ or tumo$ or malig$)).tw.
3. 1 or 2
4. (advance$ or metasta$ or recur$ or persistent).tw.
5. 3 and 4
6. exp drug therapy/
7. exp drug therapy combination/
8. exp chemotherapy/
9. chemothera$.tw.
10. or/ 6-9
11. 5 and 10
12. meta-analysis as topic/
13. meta analysis.pt.
14. (meta analy$ or metaanaly$).tw.
15. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
16. (systematic adj (review$ or overview?)).tw.
17. (exp Review Literature as topic/or review.pt or exp review/) and systematic.tw.
18. or/ 12-17
19. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or chinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
20. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
21. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
22. (study adj selection).ab.
23. 21 or 22
24. review.pt.
25. 23 and 24
26. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
27. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
28. random allocation/ or double blind method/ or single blind method/
29. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
30. or/ 26-29
31. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
32. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
33. (31 or 32) and random$.tw.
34. (clinic$ adj trial$1).tw.
35. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
36. placebos/
37. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
38. (allocated adj2 random).tw.
39. or/ 34-38
40. 18 or 19 or 20 or 25 or 30 or 33 or 39
41. 11 and 40

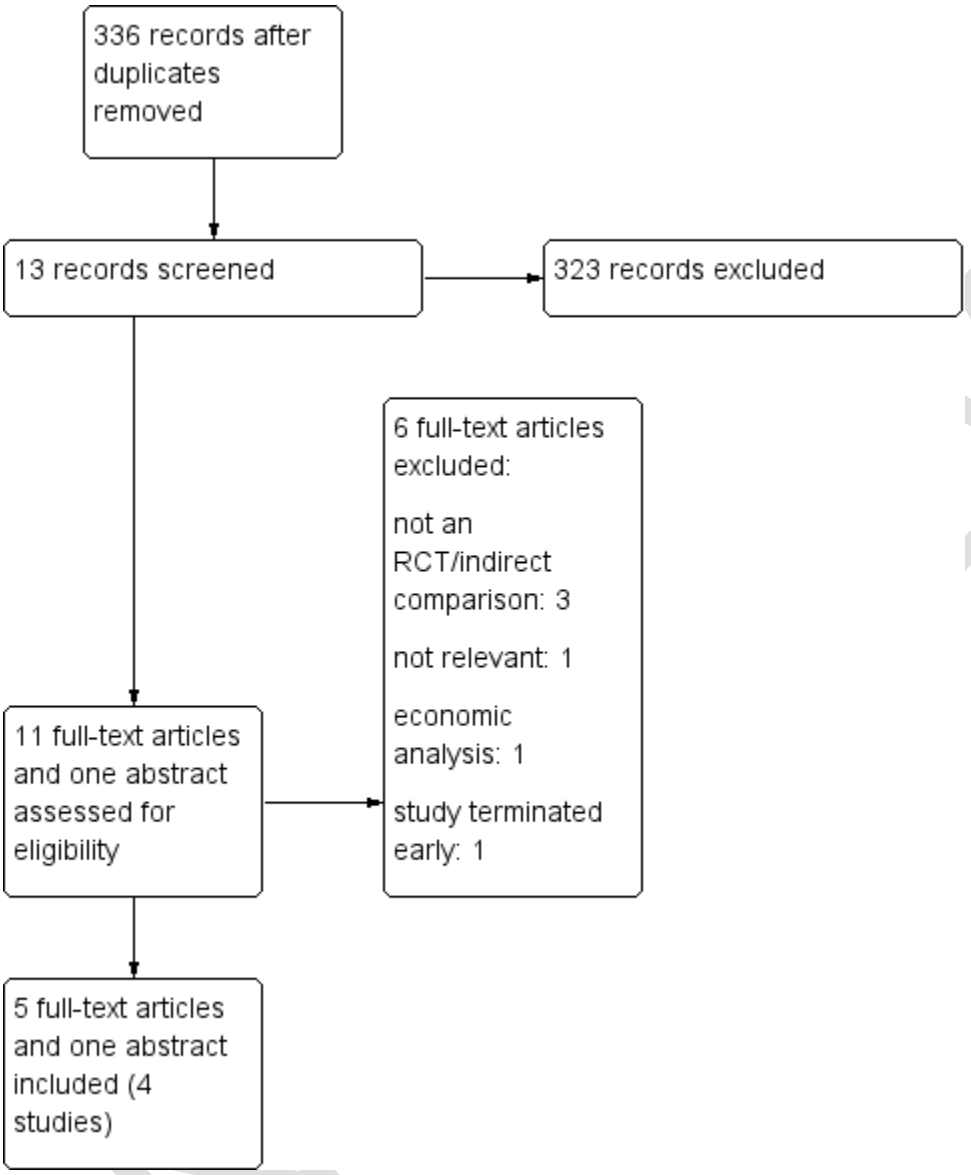
42. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
43. 41 not 42
44. limit 43 to English
45. Animal/
46. Human/
47. 45 not 46
48. 44 not 47
49. (200602$ or 200603$ or 200604$ or 200605$ or 200606$ or 200607$ or 200608$ or 200609$ or 200610$ or 200611$ or 200612$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ed.
50. 48 and 49

EMBASE

1. exp cervix neoplasms/
2. (cerv$ and (neoplasm$ or cancer$ or carcin$ or tumo$ or malig$)).tw.
3. 1 or 2
4. (advance$ or metasta$ or recur$ or persistent).tw.
5. 3 and 4
6. exp drug therapy/
7. exp drug therapy combination/
8. exp chemotherapy/
9. chemothera$.tw.
10. or/ 6-9
11. 5 and 10
12. exp Meta Analysis/ or exp "Systematic Review"/
13. (meta analy$ or metaanaly$).tw.
14. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
15. (systematic adj (review$ or overview?)).tw.
16. exp "Review"/ or review.pt.
17. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
18. (study adj selection).ab.
19. 16 and (17 or 18)
20. or/ 12-15, 19
21. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or chinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
22. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
23. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
24. randomization / or single blind procedure/ or double blind procedure/
25. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
26. or/ 23-25
27. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
28. 27 and random$.tw.
29. (clinic$ adj trial$1).tw.

30. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
31. placebo/
32. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
33. (allocated adj2 random).tw.
34. or/ 29-33
35. 20 or 21 or 22 or 26 or 28 or 34
36. 11 and 35
37. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
38. 36 not 37
39. limit 38 to English
40. Animal/
41. Human/
42. 40 not 41
43. 39 not 42
44. (200602$ or 200603$ or 200604$ or 200605$ or 200606$ or 200607$ or 200608$ or 200609$ or 200610$ or 200611$ or 200612$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).dd.
45. 43 and 44

Appendix 2. Literature search flow diagram. Search strategy 2006- April 2014.



Appendix 3. 4-20 Version 2 Guideline Working Group and Expert Panel members.

Working Group

- Dr. Hal Hirte, Medical Oncologist, Juravinski Cancer Centre, Hamilton, Ontario
- Dr. Laurie Elit, Gynecologic Oncologist, Juravinski Cancer Centre, Hamilton, Ontario
- Dr. Michael Fung-Kee-Fung, Gynecologic Oncologist, Ottawa General Hospital, Ottawa, Ontario
- Ms. Erin Kennedy, Health Research Methodologist, PEBC, Cancer Care Ontario/McMaster University, Hamilton, Ontario

Expert Panel

- Dr. Al Covens, Gynecologic Oncologist, Sunnybrook Health Sciences Centre, Toronto, Ontario
- Dr. Jason Dodge, Gynecologic Oncologist, Royal Victoria Hospital, Barrie, Ontario
- Dr. Julie Ann Francis, Gynecologic Oncologist, Kingston General Hospital, Kingston, Ontario
- Dr. Anthony Fyles, Radiation Oncologist, Princess Margaret Hospital, Toronto, Ontario
- Dr. Tien Le, Gynecologic Oncologist, The Ottawa Hospital, Ottawa, Ontario
- Dr. Joan Murphy, Gynecologic Oncologist, University Health Network, Toronto, Ontario
- Dr. Michel Prefontaine, Gynecologic Oncologist, London Health Sciences Centre, London, Ontario

Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Gynecologic Cancer Disease Site Group members, and internal and external reviewers were asked to disclose potential conflicts of interest. One author, Laurie Elit, reported having authored an editorial, commentary or other opinion regarding the objects of study. The other authors and disease site group members did not report any conflicts of interest.

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Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 4-20 Version 2: Section 3

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

Systemic Therapy for Recurrent, Metastatic, or Persistent Cervical Cancer: Development Methods, Recommendations Development and External Review Process

H. Hirte, E.B. Kennedy, M. Fung-Kee-Fung, L. Elit, and the Gynecologic Cancer Disease Site Group

Report Date: November 24, 2014

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer care system, Cancer Care Ontario (CCO) [1]. 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 care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health-care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines

Development Cycle [1, 2]. The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS is comprised of the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved, and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: Development Methods, Recommendations Development, and External Review Process*. Summarizes the EBS development process, the recommendations development process, and the results of the formal external review of the draft version of the EBS.

FORMATION OF WORKING GROUP

The Gynecologic Oncology Disease Site Group (Gyne DSG) asked the PEBC to develop a guideline on chemotherapy for metastatic, recurrent, or persistent cervical cancer. A Working Group was identified from the DSG membership. This Working Group consisted of three gynecologic oncologists and one health research methodologist. The DSG acted as the Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

OBJECTIVE

The Working Group developed the following objective for this guideline, consistent with the previous version of the guideline:

- The objective of this guideline is to recommend chemotherapeutic options for women with metastatic, recurrent, or persistent cervical cancer for whom first-line treatment with chemotherapy is indicated.

GUIDELINE REVIEW

Almost all PEBC document projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as "the use and/or modification of (a) guideline(s) produced in one cultural and organizational setting for application in a different context" [3]. This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with *de novo* recommendations development.

For this document, a search was conducted of the Inventory of Cancer Guidelines (fhswedge.csu.mcmaster.ca/cepftp/qasite/ICG.html), the National Guidelines Clearinghouse (guideline.gov) and the Canadian Medical Association Infobase (www.cpginfobase.com). Only guidelines published after 2007 were considered. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the Appraisal of Guidelines for Research and Evaluation AGREE II instrument [4]. No guidelines were found that were relevant to this systematic review.

EVIDENTIARY BASE DEVELOPMENT

Using the objective described above, a search for existing systematic reviews and a systematic review of the primary literature were conducted, as described in Section 2 of this report.

INITIAL RECOMMENDATIONS

The Working Group began with the recommendations from the original version of this guideline, and then considered the new evidence in terms of its aggregate evidence quality and potential for bias, and considered the balance of benefits and harms in the new trial data compared with the data identified in 2006. After considering the new evidence, it was determined that new recommendations were required.

INTERNAL REVIEW

PEBC documents undergo internal review by an Expert Panel and the Report Approval Panel. The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels approved the document before it was sent to External Review.

Expert Panel Review and Approval

The PEBC Gyne DSG acted as the Expert Panel for this document. The members of this group were required to submit conflict-of-interest declarations prior to reviewing the document. These declarations are described at the end of this section. The document must be approved by formal vote. In order to be approved, 75% of the Gyne DSG membership must cast a vote or abstain, and of those that voted, 75% must approve the document. At the time of the voting, Gyne DSG members could suggest changes to the document and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

The Gyne DSG reviewed the document from July 11, 2014 to August 22, 2014. Responses were received from seven of nine Expert Panel members (78%), and all members approved the document with some providing suggestions that would improve the clarity of the document, including the following:

Comment	Guideline Development Group Response
I am concerned that the cost and extra toxicity associated with adding bevacizumabis not worth the small change in outcome given the ultimately dismal prognosis for this group as a whole. Would not be unreasonable perhaps in selected patients but not something I would recommend to most in this patient population – and not sure I would recommend funding it.	No changes made to recommendations. Added this concern to the discussion in Section 2.
Clarify whether we mean statistically or clinically significant 2.9 month improvement in survival time with the addition of bevacizumab.	Changed wording to clarify that we mean "statistically" significant.
Suggestion to add "oncologists treating	Added.

Comment	Guideline Development Group Response
gynecologic cancers" to the intended users.	

Report Approval Panel Review and Approval

The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of two clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In August 2014, the RAP reviewed this document. The RAP approved the document on August 25, 2014. Key issues raised by the Report Approval Panel included the following:

Comment	Guideline Development Group Response
Why make a recommendation for use of bevacizumab with carboplatin-paclitaxel when the pivotal randomized controlled trial used *cisplatin*-paclitaxel? There is potential for safety concern as carboplatin causes more thrombocytopenia, and bleeding is a risk with bevacizumab.	Added mention of carboplatin-paclitaxel with bevacizumab results in lung cancer: http://www.nejm.org/doi/full/10.1056/NEJMoa061884. Added a paragraph at the end of Recommendation 3 in Section 1 to justify our recommendation, and designation of the JCOG-0505 trial as a noninferiority trial. Also note that bleeding was a rare event in patients in the group that received bevacizumab and carboplatin in *Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365(26):2473-83.*
The distinction between recurrent, metastatic, and persistent I expect has clear definitions within the field. If definitions are helpful, please include. For example, I assume there is a time frame when a growing persistent mass is called persistent versus recurrent.	The working group agreed that the definitions for these terms are accepted within the field.
I wonder whether asking the reader to refer to the study details for GOG-0240 on page 2 is necessary as part of the recommendation? This and the list of conditions that is a contraindication to bevacizumab seems to detract from highlighting the key factors (recurrent or persistent disease, not candidates for curative surgery, patients treated with chemotherapy for recurrence?) that	Kept reference to study details and contraindications in the recommendations section (Section 1). We want to highlight that this recommendation is for a very specific subpopulation.

Comment	Guideline Development Group Response
would indicate the use of bevacizumab. It may be better situated in the discussion/text.	
The strategy of framing the recommendations around the treatment is less intuitive then one that frames the recommendation around the type of patients. Recommendation for combination chemotherapy: - for patients with advanced or recurrent cancer, where systemic therapy is recommended, carboplatin with paclitaxel is recommended. For recommendation for bevacizumab: - For patients with primary stage IVB, recurrent, or persistent disease, not amenable to curative treatment with surgery and/or radiotherapy, the addition of bevacizumab to carboplatin-paclitaxel can be considered	Working group decided that the organization of the guideline would be kept in its original format.
I am not sure what is meant by "patients treated with chemotherapy for recurrence" on page 2. Does it mean that patients who have had chemotherapy to treat recurrence as in recommendation 1, they cannot subsequently be started on bevacizumab?	Yes this is correct as the guideline is limited to first-line chemotherapy for recurrence.
Reference for the previous guideline (page 2, paragraph 2) would be helpful to alert the reader this is an update of a previous guideline early on in the document.	Added in the guideline objectives that this is an update.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from several specified content

experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the draft document with recommendations modified as suggested by reviewers was circulated to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, several targeted peer reviewers considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on September 22, 2014. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call) where necessary. The Working Group reviewed the results of the survey. The three reviewers rated the guideline highly on methods, presentation, recommendations, completeness of reporting, information included, and quality.

Professional Consultation: Feedback was obtained through a brief online survey of health-care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on September 22, 2014. The consultation period ended on October 24, 2014. The Working Group reviewed the results of the survey.

Results

Targeted Peer Review: Three reviewers, located in the Canadian provinces of British Columbia, Quebec, and Alberta, provided a response. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	1	2
2. Rate the guideline presentation.	0	0	1	0	2
3. Rate the guideline recommendations.	0	0	0	2	1
4. Rate the completeness of reporting.	0	0	0	1	2
5. Does this document provide sufficient information to inform your decisions? If	0	0	0	1	2

not, what areas are missing?					
6. Rate the overall quality of the guideline report.	0	0	0	1	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	1	2
8. I would recommend this guideline for use in practice.	0	0	0	1	2

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

Access to bevacizumab and funding approval were considered potential barriers to implementation of this guideline report.

Table 2. Summary of written comments by targeted peer reviewers and modifications/actions taken.

Written Comment	***Modifications/Actions/Comments***
Question of cost-effectiveness of three months of additional overall survival, given rise in blood pressure, fistula, venous thromboembolism, and discontinuation rate of 25% versus 16% without bevacizumab.	Although the working group is aware of the cost issues associated with bevacizumab, the question of cost-effectiveness was outside the scope of this guideline development process. Based on this comment the concern related to discontinuation rate was added to the recommendations.
Improve readability of tables by making column for trial arm bigger, especially in Table 3.	This suggestion was incorporated into Table 3.
I however believe that recommendation 2 is made strongly for literature that may not be that strong. Recommendation 2 emphasizes carboplatin-paclitaxel as the standard of care for first line chemotherapy based on the JCOG-0505 trial. I have several reservations that make me wonder whether such a strong recommendation can be made: 1. Trial only reported partially, in abstract form. 2. Single trial, results not reproduced. 3. Different population from our target population. 4. Some results in the trial appear strange (such as higher false negative rate with cisplatin compared with carboplatin). All these reservations make me wonder whether carboplatin-paclitaxel should be recognized as *the* standard (in opposition to *a* standard) as in my opinion quality of evidence may not be high enough at this point. Not all clinicians are convinced that	The working group agreed, and in light of this comment and others received in the professional consultation, the wording of the recommendation was changed to recognize carboplatin-paclitaxel as *a* standard, rather than *the* standard.

carboplatin=cisplatin in all cervical cancers. Evidence may be insufficient.	
Do these results apply to the adenocarcinoma subgroup?	We clarified that these results only apply to patients with squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix. Note that 68% of patients in GOG-0240 had squamous cell carcinoma, 19% had adenocarcinoma unspecified, and 10% had adenosquamous carcinoma. A subgroup analysis only found a significant difference for the squamous cell carcinoma group, however the confidence intervals around the estimates for the other types were wide and the comparisons were underpowered to detect differences.
Are recommendations for second-line therapy possible, or outside the scope of the guideline?	Recommendations for second-line therapy are outside the scope of the guideline. A note to this effect was added.

Professional Consultation: The professional consultation resulted in 18 replies from Ontario, Quebec, and Nova Scotia. Key results of the feedback survey are summarized in Table 3.

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

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	*0*	*0*	*4 (22%)*	*8 (44%)*	*6 (33%)*
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	*0*	*0*	*4 (22%)*	*6 (33%)*	*8 (44%)*
3. I would recommend this guideline for use in practice.	*0*	*1 (6%)*	*2 (11%)*	*9 (50%)*	*6 (33%)*

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

The main barrier noted by many of the participants in the professional consultation was lack of funding for bevacizumab. The bevacizumab recommendation was thought not to be feasible given the current climate of financial restraint.

Table 4. Summary of written comments by professional consultants and modifications/actions taken.

Summary of Written Comments	*Modifications/Actions/Comments*
The risks are rather severe for the mere three months survival time benefit.	The working group agrees, and only recommends the bev treatment option for a very specific subset of patients.
Low quality/lack of evidence: • There are no comparative trials of the carboplatin-paclitaxol-bevacizumab triplet and no information on the efficacy or toxicity/quality of life. The recommendations are premature…the conclusions/recommendations do not belong in the guideline. • The body of evidence in support of the recommended chemotherapy approaches is not robust. • Not sure if evidence from JCOG-0505 is enough to conclude on the efficacy, however do agree on the ease of use.	As above, state that this is considered an option, rather than the #1 preference.
• Review whether full-dose anticoagulation is a contraindication with bevacizumab.	Checked protocol and supplementary materials. Patients with inadequately anticoagulated thromboembolism were ineligible for participation in the GOG-0240 study.
• It may be helpful to clearly indicate the recommended maximum number of chemotherapy cycles and whether maintenance bevacizumab is recommended. • Also recommendations for reasonable choices for second-line or above: best supportive care, or single agent therapy such as topotecan, adriamycin etc.	Maintenance bev was not studied, therefore is not part of the recommendations. No other therapy options are recommended at this time.
• Clarify that we are talking about squamous cell carcinoma (i.e. was this the patient population in GOG-0240)	GOG-0240 included patients with primary stage IVB, recurrent, or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix. Note that 68% of patients in GOG-0240 had squamous cell carcinoma, 19% had adenocarcinoma unspecified, and 10% had adenosquamous carcinoma. A subgroup analysis only found signicant difference for the squamous cell carcinoma group, however the confidence intervals around the estimates for the other types were wide and the comparisons were underpowered to detect differences.

• Specific regimen (interpreted as carboplatin weekly paclitaxol also).	Specific regimens as stated in the research papers were added to the recommendations.
• More detail on characteristics of patients would be helpful. For example, going beyond Eastern Cooperative Oncology Group performance status, a patient with growing disease in a radiated pelvis and diffuse metastases is not the same as someone with primarily lung metastases.	Instead of an exhaustive list of patient characteristics we have referred readers to clinical trials.gov for more information.
• Address situation where patients cannot tolerate carboplatin: "Cisplatin could be substituted for carboplatin in these combinations (cisplatin-gemcitabine, cisplatin-vinorelbine, and cisplatin-topotecan) when patients cannot tolerate carboplatin." I believe this is important to include, since patients may develop allergic reactions to carboplatin and might still benefit from cisplatin. The cisplatin combinations are evidence-based regimens from a phase III trial, so should probably be mentioned as Cancer Care Ontario evidence-based regimens for patients who can't have carboplatin. • in the paragraph describing the noninferiority of carboplatin, I wonder if we couldn't have a clearer statement supporting the use of cisplatin in certain circumstances for example difficulty with bone marrow suppression, patient allergy etc.; particularly in light of the current funding model.	A statement supporting the use of cisplatin in cases of allergy or bone marrow suppression was added.
• Explain lack of data and emphasize the potential risks of thrombocytopenia with carboplatin and bevacizumab.	Potential risks emphasized and lack of data mentioned in a qualifying statement.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Gynecologic Oncology Disease Site Group and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

REFERENCES

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