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Evidence-Based Series 4-5

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

Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation

H. Lukka, H. Hirte, A. Fyles, G. Thomas, M. Fung Kee Fung, M. Johnston, and members of the Gynecology Cancer Disease Site Group

An assessment conducted in November 2023 indicated that Evidence-Based Series (EBS) 4-5 REQUIRES UPDATING. 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)

(See Section 3: Document Review Summary and Tool for details.)

This Evidence-based Series (EBS) consists of 3 sections. You can access the summary and full report here:

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/746

Section 1: Summary
Section 2: Full Report
Section 3: Document Review Summary and Review Tool

Report Date: June 7, 2016

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original June 2004	1966 through June 2004	Full Report	Peer review publication Web publication	NA
Current June, 2016	June 2004 – January 2016	New data found in Section 3: Document Review Summary and Review Tool	Updated web publication	2004 recommendations **TO BE UPDATED**

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Evidence-Based Series 4-5: Section 1- Summary

Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation

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

Original Report Date: June 2004

The 2004 guideline recommendations

REQUIRE AN UPDATE

This means that the recommendations require additional evidence but are relevant for decision making.

ORIGINAL GUIDELINE: August 26, 2002
MOST RECENT LITERATURE SEARCH: June 2004
NEW EVIDENCE ADDED TO GUIDELINE REPORT: June 2004

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

Guideline Question

For women with cervical cancer in whom radiotherapy is considered appropriate, does the addition of concurrent platinum-based chemotherapy improve survival and quality of life with acceptable toxicity?

Target Population

These recommendations apply to women with cervical cancer for whom primary treatment with radiotherapy is being considered:
- those with locally advanced cervical cancer,

- those with bulky clinical stage IB (>4 cm) cervical cancer, who are treated with radiotherapy,
- those with high-risk early-stage cervical cancer (node-positive or margin-positive), who will be treated with radiotherapy following hysterectomy.

Recommendations

- Women with cervical cancer for whom treatment with radiotherapy is being considered (described above) should be offered concurrent cisplatin with their course of radiotherapy.
- There are no direct comparisons of different cisplatin regimens. Based on the review of the available toxicity data from the randomized controlled trials, the Disease Site Group felt that cisplatinum should be given weekly (40 mg/m^2).

Qualifying Statements

- Despite this recommendation, other schedules and doses have been used; thus, there is no conclusive evidence that one dose and schedule is better than the other.
- There is insufficient evidence available to make recommendations on the addition of 5-fluorouracil to cisplatin during radiotherapy

Methods

Entries to MEDLINE (1966 through June 2004), EMBASE (1980 through week 25, 2004), CANCERLIT (1975 through October 2002), and Cochrane Library (2004, Issue 2) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology from 1999 to 2004 were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by members of the Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gynecology Cancer Disease Site Group, comprised of medical oncologists, radiation oncologists, a pathologist, an oncology nurse and patient representatives.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Eight randomized controlled trials were eligible for the evidence review: six compared cisplatin-based chemotherapy plus radiotherapy to radiotherapy alone (in one of those trials, para-aortic radiotherapy was added to pelvic radiotherapy in the control arm) and two compared cisplatin-based chemotherapy plus radiotherapy to radiotherapy plus hydroxyurea.
- The guideline authors pooled survival data from published reports. Pooled survival rates detected a statistically significant effect in favour of cisplatin-based chemotherapy plus radiotherapy compared with radiotherapy alone or with hydroxyurea (relative risk of death, 0.74; 95% confidence interval, 0.64 to 0.86).

- The pooled relative risk of death among the six trials that enrolled only women with locally advanced cervical cancer was 0.78 (95% confidence interval, 0.67 to 0.90) in favour of cisplatin-based chemotherapy and radiotherapy.
- The pooled relative risk for the two trials in high-risk early-stage disease also demonstrated a significant benefit for the addition of cisplatin-based chemotherapy to radiotherapy (relative risk, 0.56; 95% confidence interval, 0.41 to 0.77).
- Rates of serious hematologic, gastrointestinal and genitourinary acute adverse effects are higher with cisplatin-based chemotherapy plus radiotherapy than with radiotherapy alone.

For further information about this practice guideline, please contact the authors through the PEBC via:
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The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit https://www.cancercareontario.ca for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

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Evidence-Based Series 4-5: Section 2 – Full Report

Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation

H. Lukka, H. Hirte, A. Fyles, G. Thomas, M. Fung Kee Fung, M. Johnston, and members of the Gynecology Cancer Disease Site Group

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

Original Report Date: June 2004

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NEW EVIDENCE ADDED TO GUIDELINE REPORT: June 2004

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

FULL REPORT

I. *QUESTION*

For women with cervical cancer in whom radiotherapy is considered appropriate does the addition of concurrent platinum-based chemotherapy improve survival and quality of life with acceptable toxicity?

II. CHOICE OF TOPIC AND RATIONALE

Cancer of the cervix is the second most common gynecological malignancy worldwide. Between 1992 and 1996, 2,897 women in Ontario were diagnosed with cervical cancer and 821 women died of this disease (1). The use of cervical screening has greatly reduced the incidence of

invasive cervical cancer in Western countries, but it continues to pose a significant health problem in the rest of the world (2).

Women with early cervical cancer can be treated successfully with either radical surgery or radical radiotherapy. Patients with large cervical tumours, extension to pelvic tissues or pelvic lymph-node involvement are sometimes treated with a combination of external beam radiotherapy and intracavitary treatment.

In an attempt to enhance the effectiveness of treatment with radiotherapy (RT), investigators have explored the use of concurrent chemotherapy and radiotherapy. The aim of such approaches has been to improve the therapeutic index by sensitizing tumour cells to radiation and to eradicate micrometastases while limiting damage to normal tissue.

Results from five randomized controlled trials of radiotherapy plus cisplatin-based chemotherapy were published in 1999 (3-7). This new evidence prompted many clinicians in Ontario to offer concurrent cisplatin-based chemotherapy plus radiotherapy to women who require radiotherapy for the treatment of locally advanced cervical cancer. Results of a trial by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) were presented at the 2000 meeting of the American Society of Clinical Oncology (ASCO) (8). Of the recently reported trials, all but the NCIC CTG trial showed a significant benefit when cisplatin-containing chemotherapy was added to radiation therapy. Because of this discrepancy, the provincial Gynecology Disease Site Group (DSG) felt that it would be timely to conduct a comprehensive literature review and meta-analysis to assess the role of concurrent platinum with radiotherapy for the treatment of cervical cancer.

III. *METHODS*

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (9). Evidence was selected and reviewed by members of the Gynecology Cancer Disease Site Group (Gynecology DSG) and methodologists. Members of the Gynecology DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on concurrent platinum-based chemotherapy plus radiotherapy as a primary treatment for cervical cancer developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

The MEDLINE database was searched from 1966 to March 2002 using the strategy described in Appendix 1. The same search strategy was used to find additional citations in the CANCERLIT (1975 to October 2001) and HealthStar (1975 to January 2002) databases. The Cochrane Library (Issue 1, 2002) was also searched for randomized trials and systematic reviews. The reference lists of papers and review articles identified by these sources were scanned as a source of additional citations. All searches were restricted to English-language publications. The proceedings of the 1999, 2000 and 2001 ASCO meetings were scanned for abstracts reporting recent clinical trial results. The Canadian Medical Association (CMA) Infobase (http://www.cma.ca/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) and other Web sites were searched for existing evidence-based practice guidelines.

Update

The original literature search has been updated using MEDLINE (through June 2004), EMBASE (through week 25 2004), CANCERLIT (through October 2002), the Cochrane Library (Issue 2, 2004), and the 2002-2004 proceedings of the annual meeting of the American Society of Clinical Oncology.

Inclusion Criteria

Articles were selected for inclusion in this practice guideline report if they met all of the following criteria:

1. Reported results of randomized controlled trials (RCT) or meta-analyses comparing concurrent platinum-based chemotherapy plus radiotherapy with radiotherapy alone or radiotherapy plus non-platinum-based chemotherapy;
2. Included patients with cervical cancer (please see Appendix 2 for staging information);
3. Reported data on survival for each intervention group.

Clinical trial results reported in either full papers or abstracts were eligible. Clinical practice guidelines from other guideline-development groups were also eligible for inclusion.

Exclusion Criteria

1. Because resources were not available for translation, non-English-language publications were excluded.
2. Trials of platinum-based neoadjuvant chemotherapy were not included because the mechanism of action of concurrent platinum and radiotherapy (possibly additive effect) is likely different from a neoadjuvant chemotherapy approach (of debulking).

Synthesizing the Evidence

Two of the authors independently reviewed the eligible papers and extracted data regarding the number of patients randomized, disease stage, type of systemic therapy, radiation dose and fractionation, nature of the control group, median follow-up time, completeness of follow-up and numbers of deaths in each group. Disagreements were resolved by consensus. In addition to the information presented in a meeting abstract, data from the NCIC CTG trial was obtained from the investigators (personal communication).

To estimate the overall effect on survival of the addition of chemotherapy, mortality data (the number of patients who had died by the end of the study and the number of patients included in the survival analysis by the investigators) were abstracted from the published reports of individual RCTs and pooled using the Review Manager software (RevMan 4.1) provided by the Cochrane

Collaboration (Metaview © Update Software). Combining data in this manner assumes a constant hazard ratio of risks for the groups being compared. Results are expressed as relative risks (also know as risk ratios) with 95% confidence intervals (CI), where a relative risk (RR) for mortality less than one indicates that the experimental treatment (platinum-based chemotherapy plus radiotherapy) improved survival compared with the control treatment. Conversely, a relative risk greater than one suggests that patients in the control group experienced lower mortality. The relative risk is calculated by taking the ratio of the proportion of patients who have died in the experimental treatment group to the proportion of patients who have died in the control group. The random-effects model was used for pooling across studies in preference to the fixed-effects model, as the more conservative estimate of effect (10).

Six sets of studies were identified for subgroup analyses: 1) those that enrolled women with locally advanced disease 2) those that enrolled women with high-risk early-stage (stages IB and IIA) disease, 3) those that administered radiotherapy alone in the control group, 4) those where hydroxyurea was added to radiotherapy in the control group, 5) those where cisplatin was given as a single agent with radiotherapy and 6) those where cisplatin plus 5-fluorouracil was used with radiotherapy.

IV. *RESULTS*

Literature Search Results

No existing evidence-based clinical practice guidelines were found.

The National Health Service Centre for Reviews and Dissemination at the University of York has completed a review of the evidence on the management of gynecologic cancers that includes a brief summary of evidence from randomized controlled trials of platinum-based chemotherapy plus radiotherapy versus radiotherapy alone (11). The York review includes five of the nine reports discussed below and was completed before results of the NCIC CTG trial became available. Survival data were described in the review but were not pooled. When the Gynecology DSG started developing this practice guideline, a Cochrane review on concomitant chemotherapy and radiotherapy for cancer of the cervix, based on published data, was underway. Published in September 2001 (12), it is discussed below.

Nine reports of randomized trials of concurrent cisplatin-based chemoradiotherapy met the eligibility criteria (3-8,13-15). Results of two of these trials were reported in abstract form (8,13), while the others were reported in journal articles. According to an abstract prepared for the 1991 meeting of the American Society of Clinical Oncology, only 18 of 47 patients allocated to chemoradiotherapy were evaluable in the study by Mickiewicz et al (13). Because the results reported in this abstract are likely to be biased, they have not been included in this review of the evidence.

Update

Since the completion of the guideline, the RCT by Pearcey et al that was originally presented in abstract form (8) has now been published in full (1u). Another article reporting long term follow-up results from a previously reported trial (Morris, 1999 RTOG 90-01 (3)) has also been published (2u). Finally, one new RCT comparing cisplatin and radiation therapy to radiation therapy alone has been published (3u).

Outcomes

In September 2001, Green et al published a systematic review and meta-analysis based on the methods used by the Cochrane Collaboration (12). Randomized trials were eligible for inclusion if they compared concomitant cytotoxic chemotherapy plus radiotherapy (with or without surgery) to radiotherapy (with or without surgery). Trials that also included hydroxyurea in the control group were eligible because the authors of the systematic review judged it to be an inactive agent. Seven trials of non-cisplatin-containing chemotherapy, that were not eligible for this practice guideline report, were included. Ten randomized trials of cisplatin-containing chemotherapy were eligible for the review by Green et al: the eight studies eligible for this practice guideline report plus two unpublished studies.

For the published trials, Green et al based their meta-analysis on data available from published reports. For overall or progression-free survival, hazard ratios and associated variances were abstracted from reports or were estimated based on other information available in the reports, such as survival curves. Numbers of recurrences and adverse events were also abstracted. Fixed-effect models were used for all meta-analyses. Green et al conducted subgroup analyses to explore potential sources of variance. One of these restricted the meta-analysis to trials of cisplatin-based chemotherapy plus radiotherapy versus control, the group of studies of interest for this practice guideline.

The conclusions of the published meta-analysis (12) were consistent with those already reached by the PGI guideline authors, who had completed their review and meta-analysis by September 2001. Green et al were able to obtain hazard ratios for survival for eight trials: seven of those described below under 'Evidence from Randomized Trials' (3-8,15) and one unpublished trial by Leborgne. Green et al detected a significant improvement in survival when cisplatin-based chemotherapy was added to radiotherapy, demonstrated by a pooled hazard ratio for death of 0.70 (95% CI, 0.61 to 0.80; $p<0.0001$). They also calculated the overall hazard ratio for progression-free survival and odds ratio for distant recurrence, using data from all eight published trials (3-8,14,15) plus the unpublished study. The pooled hazard ratio for death or progression was 0.63 (95% CI, 0.56 to 0.72; $p=0.003$) and the pooled odds ratio for distant recurrence was 0.60 (95% CI, 0.46 to 0.77; $p<0.0001$), both in favour of cisplatin-based chemotherapy. They also pooled toxicity data across all trials, including two that used non-platinum-based chemotherapy in the experimental arm, and detected statistically significantly higher rates of hematologic and gastrointestinal adverse effects when concomitant chemotherapy was added to radiotherapy.

Evidence from Randomized Trials

Eight randomized trials included in this systematic review are listed in Table 1. None were double-blind. Six trial reports gave descriptions of sample size calculations (3-7,15). Only one trial included all randomized patients in the survival analysis (15). All eligible patients were counted in the denominator for the survival analysis, except for the trials by Morris et al and Whitney et al (3,5) where small numbers of patients were lost to follow-up (Table 1). None of the trial reports described the method used to conceal allocation up to the time of randomization. All of the full reports of RCTs included detailed descriptions of eligibility criteria and three described the number of patients lost to follow-up (3,14,15).

Table 1. Randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy.

Study	FIGO Stage	Treatment Group	Control Group	# Patients	Median Follow-up (months)
Locally advanced cervical cancer, radiotherapy alone as a control					
Wong, 1989 (14)	IIB-IIIB	XRT + weekly CP†	XRT	64	range: 42 to 72§
Tseng, 1997 (15)	IIB-IIIB	XRT + CP/bleo/VCR	XRT	122	47
Morris, 1999 (3) (RTOG 90-01)	IB-IVA	XRT + CP/5FU	XRT*	386	43
Pearcey, 2000 (8) [abs] (NCIC CTG)	IB-IVA	XRT + CP	XRT	253	65
Locally advanced cervical cancer, radiotherapy plus hydroxyurea as a control					
Rose, 1999 (4) (GOG-120)	IIB-IIIB	XRT + CP‡	XRT + HU	526	35§
Whitney, 1999 (5) (GOG-85)	IIB-IIIB	XRT + CP/5FU	XRT + HU	368	104 (among survivors)
Bulky stage IB cervical cancer					
Keys, 1999 (6) (GOG-123)	bulky IB	XRT + CP + hysterectomy	XRT + hysterectomy	369	36
Postoperative high-risk cervical cancer					
Peters, 2000 (7) (SWOG 8797)	IA2-IIA	Hysterectomy + pelvic lymphadenectomy + XRT + CP/5FU	Hysterectomy + pelvic lymphadenectomy + XRT	243	42

bleo= bleomycin; CP= cisplatin; FIGO= International Federation of Obstetrics and Gynecology; GOG= Gynecologic Oncology Group; HU= hydoxyurea; NCIC CTG= National Cancer Institute of Canada Clinical Trials Group; RTOG= Radiation Therapy Oncology Group; SWOG= Southwest Oncology Group; VCR = vincristine; XRT = radiotherapy; 5FU = 5-fluorouracil;

* Pelvic + para-aortic radiotherapy; all other XRT regimens consisted of pelvic radiotherapy

† Study included a second treatment arm of XRT + cisplatin twice weekly

‡ Study included a second treatment arm of XRT + cisplatin/fluorouracil/hydroxyurea

§ Value for all 3 treatment groups

Update

Table 1A. Randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy.

Study	FIGO Stage	Treatment Group	Control Group	# Patients	Median Follow-up (months)
Locally advanced cervical cancer, radiotherapy alone as a control					
Pearcey, 2002 (1u) (NCIC CTG)	IB-IVA	XRT + CP	XRT	253	82
Eifel, 2004 (RTOG 90-01) (2u)	IB-IVA	XRT + CP/5FU	XRT*	386	79
Singh, 2003 (3u)	IIB-IIIB	XRT + CP	XRT	84	35 (treatment) 33 (control)

CP= cisplatin; NCIC CTG= National Cancer Institute of Canada Clinical Trials Group; XRT = radiotherapy

Some authors (2,16) have commented on the relatively low doses of radiation used in the study by Keys et al (6) and the low total dose of radiotherapy and protracted treatment time in the study by Rose et al (4). A beneficial effect of using concurrent cisplatin-based chemotherapy with standard doses of radiotherapy was also observed in the RTOG study (3). Even though the use of cisplatin with radiotherapy appeared to be beneficial, doubt remains about the potential magnitude of benefit associated with concurrent cisplatin when an optimum radiotherapy regimen is given.

Details about participants and treatments are given in Tables 2 and 3. Women with bulky stage IB disease were included in two of the trials in locally advanced cervical cancer (3,8). Chemotherapy was administered in the control arm for two of the trials (4,5); the others used radiotherapy alone as the control treatment. The interventions used in the control arms of the six

published studies in locally advanced cervical cancer were usually based on previous studies conducted by the individual co-operative clinical trial groups. Based on the published results of the RTOG-79-20 trial (17), the Radiation Therapy Oncology Group (RTOG) added para-aortic lymph-node irradiation to pelvic irradiation in the control group of the RTOG 90-01 (3). For this study, patients were required to have negative para-aortic lymph nodes on lymphadenectomy following para-aortic lymph-node dissection. The Gynecologic Oncology Group (GOG) has traditionally used hydroxyurea in combination with radiotherapy as the standard treatment, because of the results from their placebo-controlled randomized trial of the addition of hydroxyurea to pelvic irradiation (GOG-4) (18). Patients treated with hydroxyurea had a significantly better response than those treated with the placebo. The GOG-4 trial has been criticized because data from only 51% of the patients randomized were included in the survival analysis (18).

Two studies had a control arm and two active treatment arms (4,14). In both cases, survival results from the two active treatments were very similar. The active treatment that was most consistent with the treatments used in the other eligible trials (i.e., weekly cisplatin as a single agent) was chosen for inclusion in the meta-analysis of survival data. Details of the second treatment arm in both trials are described below.

The trial by Wong et al was a three arm study. Patients in two arms of the study received cisplatin and radiotherapy. The third arm was a control arm in which patients received radiotherapy only. The first treatment group received weekly administration of cisplatin and the other treatment group was given twice-weekly administration (14). A dose of 25 mg/m^2 was used in both treatment groups. The study by Wong et al is described as a randomized trial; whether all patients were randomized is unclear from the published reports. Survival curves were not published, but at the last follow-up 11 of 22 patients in the weekly cisplatin group and 11 of 17 in the twice-weekly group were alive (14). Only data from the weekly-cisplatin-plus-radiotherapy and the radiotherapy-alone groups were included in the meta-analysis of survival data described below.

The trial by Rose et al also included three treatment groups (4). Patients were randomized to weekly cisplatin (40 mg/m^2) plus radiotherapy, cisplatin/fluorouracil/hydroxyurea (50 mg/m^2 cisplatin on days 1 and 29, 4 g/m^2 fluorouracil as a 96-hour infusion, 2 g/m^2 hydroxyurea orally twice weekly) plus radiotherapy, or radiotherapy plus hydroxyurea. Survival curves for the two cisplatin groups were almost identical and were both significantly different from the survival experience among the radiotherapy plus hydroxyurea group. The relative risk of death, adjusted for clinical stage of disease, was 0.61 (95% CI, 0.44 to 0.85) for weekly cisplatin plus radiotherapy and 0.58 (95% CI, 0.41 to 0.81) for cisplatin/fluorouracil/hydroxyurea plus radiotherapy, compared with radiotherapy plus hydroxyurea. Data from the weekly cisplatin-plus-radiotherapy active treatment group and the radiotherapy-plus-hydroxyurea control group have been included in the meta-analysis.

Two studies were restricted to patients with high-risk early-stage disease (6,7). In the study reported by Keys et al (GOG-123), patients underwent hysterectomy three to six weeks after completing radiotherapy (6). Only women without evidence of para-aortic lymph-node involvement were eligible. Women participating in the Southwest Oncology Group (SWOG) study were randomized to chemoradiotherapy or radiotherapy after radical hysterectomy and pelvic lymphadenectomy (7). Patients with positive pelvic lymph nodes, positive margins or microscopic involvement of the parametrium were eligible.

Table 2. Randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy: patient characteristics.

Study	# randomized/ #eligible/ # analyzed	Histology	Method of Staging	Stage of disease - number of patients (%)				
				IB/ IIA	IIB	IIIA	IIIB	IVA
Locally advanced cervical cancer, radiotherapy alone as a control								
Wong, 1989 (14)	66/64/64	63 squamous cell (98%) 1 adenocarcinoma	clinical	-	45 (70%)	3 (5%)	16 (25%)	
Tseng, 1997 (15)	122/122/122	squamous cell (100%)	clinical & surgical, FIGO (1991)	-	58 (48%) > 4 cm		64 (52%)	
Morris, 1999 (3) (RTOG 90-01)	403/386/386*	350 squamous cell (90%) 14 adenosquamous 24 adenocarcinoma	clinical & surgical, FIGO (1995)	130 (34%)	140 (36%)	110 (28%)		8 (2%)
Pearcey, 2000 (8) [abstract] (NCIC CTG)	259/253/253	squamous cell (100%)	clinical, FIGO	stages IB, IIA, IIB > 5 cm, III or IVA; number of patients with each stage not reported				
Locally advanced cervical cancer, radiotherapy plus hydroxyurea as a control								
Rose, 1999 (4) (GOG-120)	575/526/526	472 squamous cell (90%) 30 adenosquamous 18 adenocarcinoma 6 other	clinical & surgical, FIGO	-	275 (52%)	15 (3%)	220 (42%)	16 (3%)
Whitney, 1999 (5) (GOG-85)	388/368/368†	335 squamous cell (91%) 19 adenosquamous 14 adenocarcinoma	clinical & surgical, FIGO	-	228 (62%)	10 (3%)	118 (32%)	12 (3%)
Bulky stage IB cervical cancer								
Keys, 1999 (6) (GOG-123)	374/369/369	299 squamous cell (81%) 27 adenosquamous 23 adenocarcinoma 20 other	clinical & surgical	stage IB > 4 cm	-	-	-	-
Postoperative high-risk cervical cancer								
Peters, 2000 (7) (SWOG 8797)	268/243/243	193 squamous cell (79%) 19 adenosquamous 31 adenocarcinoma	surgical	Ia2, IB, IIA	-	-	-	-

* no follow-up data for 2 patients; †no follow-up data for 6 patients; FIGO = International Federation of Obstetrics and Gynecology

Update

Table 2a. Randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy: patient characteristics.

Study	# randomized/ #eligible/ # analyzed	Histology	Method of Staging	Stage of disease - number of patients (%)				
				IB/ IIA	IIB	IIIA	IIIB	IVA
Locally advanced cervical cancer, radiotherapy alone as a control								
Pearcey, 2002 (1u) (NCIC CTG)	259/253/253	squamous cell (100%)	clinical, FIGO	stages IB, IIA, IIB > 5 cm, III or IVA; number of patients with each stage not reported				
Eifel, 2004 (RTOG 90-01) (2u)	403/386/386*	350 squamous cell (90%) 14 adenosquamous 24 adenocarcinoma	clinical & surgical, FIGO (1995)	130 (34%)	140 (36%)	110 (28%)		8 (2%)
Singh, 2003 (3u)	96/84/84	squamous cell (100%)	clinical	--	53 (63%)	3 (4%)	28 (33%)	--

* no follow-up data for 2 patients; †no follow-up data for 6 patients

Table 3. Randomized trials of cisplatin-based chemotherapy plus radiotherapy (RT) versus radiotherapy: description of management.

Study	Chemotherapy (Cisplatin group)	External radiation-whole pelvis	Intracavitary radiation
Locally advanced cervical cancer, radiotherapy alone as a control			
Wong, 1989 (14)	cisplatin - 25 mg/m^2 weekly	2.5 G/day 4X week to a total dose of 40 Gy	stage II: 3500 mg/hour 1 week after completion of external beam radiotherapy, followed by 2500-3000 mg/hour 7-10 days later stage III: 4000 mg/hour in 1 application
Tseng, 1997 (15)	cisplatin - 50 mg/m^2 on day 1 of 3-week cycle + vincristine (1 mg/m^2) on day 2 + bleomycin (25 mg/m^2) on days 2,3,4	2 Gy/day to a total dose of 44 Gy in 22 fractions over 30-35 days	25.8 Gy to point A in 6 courses (4.3 Gy each) starting 1-2 weeks after completing external beam radiotherapy
Morris, 1999 (3) (RTOG 90-01)	cisplatin - 75 mg/m^2 on day 1of 3-week cycle + fluorouracil (4 g/m^2) as a 96-hour infusion	1.8 Gy/day to a total dose of 45 Gy*	total cumulative dose at point A of at least 85 Gy, in 3 applications after completing external beam radiotherapy
Pearcey, 2000 (8) [abstract] (NCIC CTG)	cisplatin - 40 mg/m^2 once a week	1.8 Gy/day (5X week) to a total dose of 45 Gy	total cumulative dose at point A of 24-35 Gy, within 2 weeks after completing external beam radiotherapy
Locally advanced cervical cancer, radiotherapy plus hydroxyurea as a control			
Rose, 1999 (4) (GOG-120)	cisplatin - 40 mg/m^2 once a week	total dose of 40.8 Gy in 24 fractions or 51 Gy in 30 fractions**	40.8 Gy (Stage 2B patients) or 30 Gy (Stage 3 or 4A patients) to point A in 1 or 2 applications after completing external beam RT (low-dose)
Whitney, 1999 (5) (GOG-85)	cisplatin - 50 mg/m^2 on days 1 and 29 + fluorouracil (4 g/m^2) as a 96-hour infusion	stage IIB: total dose of 40.8 Gy in 24 fractions + parametrial + boost to bring total dose at point B to 55 Gy** stage III or IVa: total dose of 51 Gy in 30 fractions + boost to bring total dose at point B to 60 Gy**	30-40 Gy in 1 or 2 applications 1-3 weeks after completing external beam RT (low-dose)
Bulky stage IB cervical cancer			
Keys, 1999 (6) (GOG-123)	cisplatin - 40 mg/m^2 once a week	1.8-2.0 Gy/day (5X week) to a total dose of 45 Gy	30 Gy to point A in 1 or 2 applications after completing external beam radiotherapy
Postoperative high-risk cervical cancer			

Peters, 2000 (7) (SWOG 8797)	cisplatin - 70 mg/m^2 on day 1 of 3-week cycle + fluorouracil (4 g/m^2) as a 96-hour infusion	1.7 Gy/day to a total dose of 49.3 Gy in 29 fractions	not applicable

* chemoradiotherapy group also received radiation to the para-aortic lymph nodes; ** plus hydroxyurea

Update

Table 3a. Randomized trials of cisplatin-based chemotherapy plus radiotherapy (RT) versus radiotherapy: description of management.

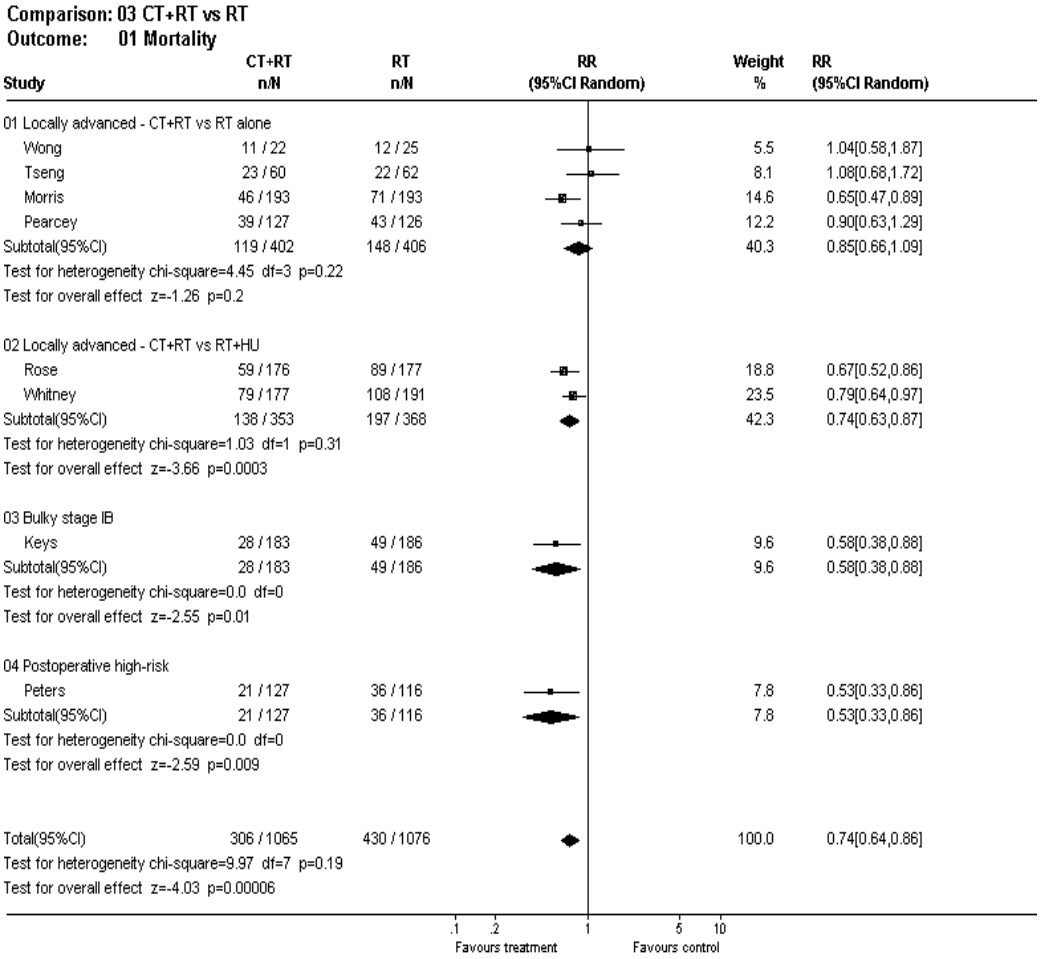
Study	Chemotherapy (cisplatin group)	External radiation-whole pelvis	Intracavitary radiation
Locally advanced cervical cancer, radiotherapy alone as a control			
Pearcey, 2002 (1u) (NCIC CTG)	cisplatin - 40 mg/m^2 once a week	1.8 Gy/day (5X week) to a total dose of 45 Gy	total cumulative dose at point A of 24-35 Gy, within 2 weeks after completing external beam radiotherapy
Eifel, 2004 (RTOG 90-01) (2u)	cisplatin - 75 mg/m^2 on day 1of 3-week cycle + fluorouracil (4 g/m^2) as a 96-hour infusion	1.8 Gy/day to a total dose of 45 Gy*	total cumulative dose at point A of at least 85 Gy, in 3 applications after completing external beam radiotherapy
Singh, 2003 (3u)	cisplatin - 16 mg/m^2 5 days/week every 3 weeks during external radiation	2.0 Gy/day to a total dose of 50 Gy	total cumulative dose at point A of 23-25 Gy, 1-2 weeks after completing external beam radiotherapy

* chemoradiotherapy group also received radiation to the para-aortic lymph nodes

Survival

Figure 1 shows the relative risk of death for the individual trials and overall. The data is based, on the number of deaths by the end of the study. At the time of the published reports, all trials had followed at least half of the patients enrolled for three years or more. There was no significant heterogeneity detected among the study results (Q_{HET}=9.87). The meta-analysis involving a total of 2141 patients detected a statistically significant effect in favour of cisplatin-based chemotherapy plus radiotherapy compared with control (RR, 0.74; 95% CI, 0.64 to 0.86; p< 0.01). This translates into an absolute reduction in the risk of death of 11% (95% CI, 7% to 15%) with cisplatin-based chemotherapy.

Figure 1. Pooled analysis of eight randomized trials of cisplatin-based chemotherapy plus RT versus RT: risk ratio (relative risk) for death.



NB, the following data were used for this meta-analysis:
- 3-year mortality data for the Pearcey et al trial,
- data from the weekly cisplatin treatment arm of three-armed trials by Wong et al and Rose et al.

RR = relative risk; CI = confidence interval; CT = chemotherapy; RT = radiotherapy; HU = hydroxyurea

When the trial by Wong et al (14) (which may or may not have included proper randomization) was left out of the meta-analysis, the overall pooled RR was 0.73 (95% CI, 0.63 to 0.84). This analysis was based on the absolute number of deaths in each group. When four-year mortality rates, abstracted from survival curves in the six papers (3-7,15), were combined with the three-year mortality rates of Pearcey et al (8) and the numbers of deaths by the end of the trial by Wong et al (14), the pooled relative risk of death was 0.78 (95% CI 0.67 to 0.90; p-value on test for heterogeneity >0.10). The reports by Pearcey et al (8) and Wong et al (14) did not include survival curves or four-year death rates.

Subgroup analyses found that the relative risk of death was statistically significant in all four groups of trials described in the Methods section in favour of combined therapy (Table 4). The relative risk of death was similar in studies using different control interventions (radiotherapy alone or radiotherapy plus hydroxyurea) and different experimental interventions (cisplatin alone or cisplatin plus 5-fluorouracil).

Update

Results from Pearcey et al (1u) full publication are the same as those reported in their abstract (8). The results of the long term results of the RTOG 90-01 trial (2u) reported that after a median of 6.6 years, 228 patients were alive (59%). The eight year overall survival was significantly greater for the patients who had received chemotherapy in addition to radiation therapy compared to those who received radiation therapy alone (67% versus 41%, p<0.0001, respectively). After eight years, patients who received chemotherapy had significantly longer disease-free survival (p<0.0001) and significantly fewer locoregional recurrences (p<0.0001) and distant metastases (p=0.001) than patients not treated with chemotherapy.

The small RCT by Singh et al (3u) randomized 84 women with advanced cervical cancer to receive platinum-based chemotherapy with radiation therapy or radiation therapy alone. This trial did not report a significant difference in overall survival between the treatment arms, however, they did report a significant difference in complete response rates between the treatment arms. Patients treated with chemotherapy were significantly more likely to respond to treatment than patients who did not receive chemotherapy (79% versus 58%, p<0.05, respectively). It is important to recognize that this was a small study that was most likely not powered to detect a survival difference between the treatment arms.

Table 4. Subgroup analyses.

	# trials	References	Relative risk of death	95% confidence interval
All trials	8	3-8,14,15	0.74	0.64 to 0.86
Locally advanced disease	6	3,4,5,8,14,15	0.78	0.67 to 0.90
High-risk early-stage disease	2	6,7	0.56	0.41 to 0.77
Radiotherapy alone in control group	6	3,6-8,14,15	0.75	0.60 to 0.94
Radiotherapy plus hydroxyurea in control group	2	4,5	0.74	0.63 to 0.87
Cisplatin alone plus radiotherapy in experimental group	4	3,5,7,10	0.74	0.59 to 0.93
Cisplatin/5FU plus radiotherapy in experimental group	3	1,6,11	0.70	0.56 to 0.86

Quality of life

Only the NCIC CTG study has evaluated the effects of treatment on quality of life (8). However, these data have not been reported yet.

Disease-free survival

Disease-free survival data were reported for seven trials (3-7,14,15). Five trials detected a significant difference in favour of the addition of cisplatin-based chemotherapy to radiotherapy (3-7). The relative risks reported in Table 5 are based on life-table analyses.

Table 5. Disease-free survival rates from randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy (RT) alone.

Study	Median follow-up (months)	Treatment groups	Alive without disease at study end	Relative risk of progression or death (95% CI)
Locally advanced cervical cancer, radiotherapy alone as a control				
Wong, 1989 (14)	range: 42-72	XRT + weekly CP XRT + twice-weekly CP XRT	10/22 (45%) 10/17 (59%) 13/25 (52%)	not reported p=0.83
Tseng, 1997 (15)	47	XRT + CP/bleo/VCR XRT	31/60 (52%) 33/62 (53%)	not reported p=0.92
Morris, 1999 (3) (RTOG 90-01)	43	XRT + CP/5FU XRT (pelvis + para-aortic lymph nodes)	134/193 (69%) 90/193 (47%)	0.48 (0.35 to 0.66)
Locally advanced cervical cancer, radiotherapy plus hydroxyurea as a control				
Rose, 1999 (4) (GOG-120)	35	XRT + CP XRT + CP/5FU/HU XRT + HU	109/176 (62%) 106/173 (61%) 73/177 (41%)	0.57 (0.42 to 0.78) 0.55 (0.40 to 0.75)
Whitney, 1999 (5) (GOG-85)	104	XRT + CP/5FU XRT + HU	90/177 (51%) 76/191 (40%)	0.79 (0.62 to 0.99)
Bulky stage IB cervical cancer				
Keys, 1999 (6) (GOG-123)	36	XRT + CP + hysterectomy XRT + hysterectomy	144/183 (79%) 117/186 (63%)	0.51 (0.34 to 0.75)
Postoperative high-risk cervical cancer				
Peters, 1999 (7) (SWOG 8797)	42	Hysterectomy + XRT + CP/5FU Hysterectomy + XRT	103/127 (81%) 75/116 (65%)	not reported p=0.003

bleo= bleomycin; CP= cisplatin; 5FU= 5-fluorouracil; HU= hydoxyurea; VCR= vincristine; XRT= radiotherapy

Update

Table 5a. Disease-free survival rates from randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy (RT) alone.

Study	Median follow-up (months)	Treatment groups	Alive without disease at study end	Relative risk of progression or death (95% CI)
Locally advanced cervical cancer, radiotherapy alone as a control				
Eifel, 2004 (RTOG 90-01) (2u)	79	XRT + CP/5FU XRT	134/194 (69%) 85/195 (47%)	0.48 (0.35 to 0.67)
Singh, 2003 (3u)	35 (treatment) 33 (control)	XRT + CP XRT	29/43 (67%) 18/41 (44%)	not reported

CP= cisplatin; 5FU= 5-fluorouracil; XRT= radiotherapy

Disease recurrence

Rates of local recurrence and distant metastases are given in Table 6. Lower rates of recurrence with cisplatin-based chemotherapy plus RT, compared with RT alone, were

observed in six of eight trials (3-8), but only Morris et al reported that the difference between treatment groups was statistically significant (3).

Table 6. Recurrence rates from randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy (RT) alone.

Study	Treatment groups	% of patients with recurrence	
		Local	Distant
Locally advanced cervical cancer, radiotherapy alone as a control			
Wong, 1989 (14)	XRT + weekly CP	55%	
	XRT + twice-weekly CP	41%	
	XRT	48%	
Tseng, 1997 (15)	XRT + CP/bleo/VCR	23%	22%
	XRT	18%	29%
Morris, 1999 (3) (RTOG 90-01)	XRT + CP/5FU	19%	14%
	XRT (pelvis + para-aortic lymph nodes)	35%*	33%*
Pearcey, 2000 (8) (NCIC CTG) [abstract]	XRT + CP	17%	not reported
	XRT	22%	
Locally advanced cervical cancer, radiotherapy plus hydroxyurea as a control			
			lung metastases:
Rose, 1999 (4) (GOG-120)	XRT + CP	19%	3%
	XRT + CP/5FU/HU	20%	4%
	XRT + HU	30%	10%
Whitney, 1999 (5) (GOG-85)	XRT + CP/5FU	25%	18%
	XRT + HU	30%	21%
Bulky stage IB cervical cancer			
Keys, 1999 (6) (GOG-123)	XRT + CP	9%	12%
	XRT	21%	16%
Postoperative high-risk cervical cancer			
Peters, 1999 (7) (SWOG 8797)	XRT + CP/5FU	6%	10%
	XRT	17%	16%

* $p<0.001$

bleo= bleomycin; CP= cisplatin; 5FU= 5-fluorouracil; HU= hydoxyurea; VCR= vincristine; XRT= radiotherapy

Update

Table 6a. Recurrence rates from randomized trials of cisplatin-based chemotherapy plus radiotherapy versus radiotherapy (RT) alone.

Study	Treatment groups	% of patients with recurrence	
		Local	Distant
Locally advanced cervical cancer, radiotherapy alone as a control			
Pearcey, 2002 (1u) (NCIC CTG)	XRT + CP XRT	27% 33%	51% 45%
Eifel, 2004 (RTOG 90-01) (2u)	XRT + CP/5FU XRT	18% 34%	18% 31%
Singh, 2003 (3u)	XRT + CP XRT	19% 37%	7% 7%

Adverse effects

Observed rates of acute hematologic and gastrointestinal adverse effects were higher with cisplatin-based chemotherapy plus radiotherapy compared with radiotherapy alone, but none of the studies reported any statistically significant differences (Table 7a). There was one case of grade 3 or 4 infection in each group in the trial by Peters et al (7) and two patients with fever in the twice-weekly cisplatin arm of the trial by Wong et al (14). Two treatment-related deaths occurred in the chemoradiotherapy group in the study by Tseng et al (15), one due to neutropenic sepsis and the other due to a small bowel obstruction with perforation and sepsis.

Table 7a. Percent of patients experiencing grade 3/4 acute adverse effects in randomized trials of cisplatin-based chemotherapy plus XRT versus XRT alone.

Study	Treatment groups	Hematologic	Gastrointestinal	Genitourinary
Wong, 1989 (14)	XRT + weekly CP XRT + twice-weekly CP XRT	18% 47% 0	0 0 0	not reported
Tseng, 1997 (15)	XRT + CP/bleo/VCR XRT	18% 13%	15% 8%	8% 0
Morris, 1999 (3) (RTOG 90-01)	XRT + CP/5FU XRT	37% 1%	9% 1%	1% 0
Pearcey, 2000 (8) (NCIC CTG) [abstract]	XRT + CP XRT	data not reported but abstract stated that the acute complication rate was higher in the chemoradiotherapy group		
Keys, 1999 (6) (GOG-123)	XRT + CP XRT	21% 2%	14% 5%	2% 3%
Peters, 1999 (7) (SWOG 8797)	XRT + CP/5FU XRT	35% 1%	14% 2%	1% 0

bleo= bleomycin; CP= cisplatin; 5FU= 5-fluorouracil; HU= hydoxyurea; VCR= vincristine; XRT= radiotherapy

Update

Table 7ai. Percent of patients experiencing grade 3/4 acute adverse effects in randomized trials of cisplatin-based chemotherapy plus XRT versus XRT alone.

Study	Treatment groups	Hematologic	Gastrointestinal	Genitourinary
Pearcey, 2002 (1u)	XRT + CP XRT	0% 1%	7% 13%	17% 10%
Eifel, 2004 (RTOG 90-01) (2u)	XRT + CP/5FU XRT	not reported	not reported	not reported
Singh, 2003 (3u)	XRT + CP XRT	2% 0%	0% 0%	not reported

CP= cisplatin; XRT= radiotherapy

Table 7b summarized the acute toxicity data from trials that administered hydroxyurea to the control group. In Rose et al's trial, the rate of grade 3/4 leukopenia was significantly higher when cisplatin/5-fluorouracil/hydoxyurea was added to radiotherapy compared with cisplatin or hydroxyurea alone ($p<0.001$) (4). Whitney et al found that significantly more patients developed grade 3/4 leukopenia with hydroxyurea compared with cisplatin/5-fluorouracil ($p<0.00001$) (5). Only one patient (in the radiotherapy plus hydoxyurea group) developed grade 4 fever (4).

Table 7b. Percent of patients experiencing grade 3/4 acute adverse effects in randomized trials of cisplatin-based chemotherapy plus XRT versus XRT plus hydroxyurea.

Study	Treatment groups	Hematologic	Gastrointestinal	Genitourinary
Rose, 1999 (4)	XRT + CP	13%	7%	3%
(GOG-120)	XRT + CP/5FU/HU	27%*	10%	1%
	XRT + HU	12%	8%	2%
Whitney, 1999 (5)	XRT + CP/5FU	4%	8%	1%
(GOG-85)	XRT + HU	25%*	4%	2%

bleo= bleomycin; CP= cisplatin; 5FU= 5-fluorouracil; HU= hydoxyurea; VCR= vincristine; XRT= radiotherapy
* statistically significant difference

Tseng et al reported that 23% of the chemoradiotherapy group experienced late complications from treatment (proctitis, cystitis, intestinal obstruction or fistula) in contrast with 13% of the radiotherapy-alone group (15). In the RTOG 90-01 study reported by Morris et al, late complications were reported for 12% of patients with chemoradiotherapy and 11% with radiotherapy alone (3). Whitney et al conducted a life-table analysis of late complication data from the GOG-85 trial, and found major complication rates of 16% for both treatment groups at three years (5).

V. *INTERPRETIVE SUMMARY*

Three groups of patients are represented among the RCTs reviewed. There were six studies in women with locally advanced cervical cancer (3-5,8,14,15), one study in those with large stage IB tumours prior to surgery (6) and one study in patients with high-risk cervical cancer (stage I or IIA) following surgery (node positive and resection margin positive) (7).

Studies investigating the use of concurrent cisplatin and radiotherapy have used various 'standard' treatments in the control arms: one study used pelvic and para-aortic radiotherapy

(3), two used radiotherapy plus concurrent hydroxyurea (4,5) and the remaining trials used pelvic radiotherapy alone as the control treatment (6-8,14,15). There were also differences among trials with respect to the experimental treatment: four trials used cisplatin alone (4,6,8,14) and four used cisplatin in combination with other agents (3,5,7,15). The Canadian NCIC CTG trial is the largest study that investigated the specific question of the benefit of adding concurrent cisplatin to pelvic radiotherapy (8). The study by Wong et al also investigated cisplatin as a single agent versus pelvic radiotherapy alone, but it was a smaller study and there is some confusion about the randomization process (15,19). Despite this, it has been published and described as randomized and has therefore been included in our systematic review of the evidence. The GOG-123 trial of cisplatin plus radiotherapy followed by hysterectomy versus radiotherapy followed by hysterectomy was restricted to women with bulky stage IB disease (6).

Clinical trial methodologists debate the relative merits of meta-analysis compared with a large, well-conducted randomized trial. Generally, a large, well-conducted RCT has merit over a meta-analysis (20). Where only studies of moderate size are available, meta-analysis is a useful approach to synthesizing the data (21), as is the case for the evidence available from randomized trials investigating concurrent cisplatin and radiotherapy in localized cervical cancer. Survival was chosen as the primary outcome for the meta-analysis because improvement in the duration of survival following treatment is important for patients and would likely result in a significant change in clinical practice. The meta-analysis confirmed an overall survival benefit associated with the use of concurrent cisplatin-based chemotherapy and radiotherapy compared to a variety of controls across different stages of disease (i.e., locally advanced cervical cancer, large stage IB tumours prior to surgery and high-risk disease following surgery) and where different treatment approaches were used. Three subgroup analyses also showed a statistically significant difference in survival rates in favour of concurrent cisplatin-based chemotherapy plus radiotherapy. Meta-analysis was restricted to trials in patients with locally advanced cervical cancer in one case and to trials where radiotherapy alone was used as a control in the second; both showed a statistically significant difference in survival rates in favour of concurrent cisplatin and radiotherapy. A third analysis looked at two subgroups of trials: those using cisplatin alone in the chemotherapy arm and those using cisplatin plus 5-fluorouracil.

Although the studies by Morris et al, Rose et al and Whitney et al have shown statistically significant differences in survival between concurrent chemotherapy plus radiotherapy and radiotherapy (3-5), studies in the same patient population by Wong et al, Tseng et al and Pearcey et al did not detect statistically significant differences (8,14,15). The largest study, conducted in Canada by the NCIC CTG, asking the clear question of the benefit of adding concurrent cisplatin to pelvic irradiation, did not detect any survival advantage for chemoradiotherapy (8). Various reasons have been hypothesized for the differences in outcome among the studies included in this meta-analysis. These include differences among studies in stage of disease and tumour types, chemotherapy regimen, administration and quality assurance of radiotherapy, protraction of radiotherapy schedules, use of brachytherapy and hemoglobin level (at presentation and during treatment) (22). The impact of differences among studies on outcome can be assessed only in a meta-analysis based on individual-patient data. It is also possible that a consistent benefit of combined cisplatin and radiotherapy may exist in subgroups of patients across all studies, a hypothesis best investigated using individual patient data.

At present, it is unclear if cisplatin acts synergistically with radiotherapy to improve local control and survival or if it also acts on micrometastatic disease. Several studies noted a reduction in both local recurrence and distant recurrence rates (3,4,6,7). It is unclear if the latter observation is a consequence of improved local control or if cisplatin has a direct effect

on systemic micrometastatic disease. Since the doses of concurrent chemotherapy used in these studies are far less than those usually given for the treatment of solid tumours, the effect of the chemotherapy on micrometastatic disease is questionable. The observed difference in the rates of distant recurrence in these studies may be a consequence of improved local control.

Most radiation oncologists recognize that poorer local control results are seen when protracted radiotherapy is used (23) or when suboptimal doses of radiotherapy are employed. Some authors (2,16) have commented on the relatively low doses of radiation used in the study by Keys et al (6) and the low total dose of radiotherapy and protracted treatment time in the study by Rose et al (4). A beneficial effect of using concurrent cisplatin-based chemotherapy with standard doses of radiotherapy was also observed in the RTOG study (3). Even though the use of cisplatin with radiotherapy appeared to be beneficial, doubt remains about the potential magnitude of benefit associated with concurrent cisplatin when an optimum radiotherapy regimen is given. Further review of individual patient data with analysis of time, dose and fractionation variables may provide some insight on the impact of treatment factors on clinically important outcomes.

VI. ONGOING TRIALS

The Physician Data Query (PDQ) clinical trial database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing randomized trials.

Protocol ID(s)	Title and details of trial
GOG 165	A randomized trial of cisplatin plus radiation versus 5-FU plus radiation in patients with locally advanced cervical cancer. This trial is now closed to recruitment.
DUT-KWF-CKVO-9407	Phase III randomized trial of carboplatin (300 mg/m^2 on days 1, 29 and 57) and 5-fluorouracil (600 mg/m^2/day on days 1-4, 29-32 and 57-60) plus radiotherapy versus radiotherapy alone in patients with previously untreated locally advanced cervical cancer (FIGO stage IB/IIA >4 cm or stages IIB, III, IVA). External beam radiation is given in fractions of 1.8 Gy/day, five days/week to a total dose of 45 Gy over five weeks. This trial is now closed to recruitment.

VII. *DISEASE SITE GROUP CONSENSUS PROCESS*

The Gynecology DSG reviewed the evidence from seven randomized trials that addressed the role of radiotherapy plus cisplatin-based chemotherapy in various stages of cervical cancer (3-7,14,15). Meta-analysis of survival data from published reports of these trials detected a significant effect for cisplatin-based chemoradiation compared with control (radiotherapy alone or radiotherapy plus hydroxyurea). The DSG members in attendance concluded that:

- there is a moderate but statistically significant effect on survival of adding concurrent cisplatin-based chemotherapy to radiotherapy in the treatment of locally advanced cervical cancer;
- there is insufficient evidence available to support the addition of 5-fluorouracil to cisplatin.

When the systematic review was incorporated into a draft guideline report, there was debate about the importance of evidence from the Canadian NCIC CTG study in the context of the other evidence available from individual trials and from the meta-analysis. The Canadian trial was not large but was considered to be the 'cleanest' study in that it compared cisplatin as a single agent plus radiotherapy to radiotherapy alone and the radiotherapy was given

according to current practice in Ontario. There was concern that the radiotherapy regimens used in some of the other studies may have been inadequate. The DSG decided to base its recommendations on their meta-analysis but acknowledged that there may be differences in approaches to radiotherapy between non-Canadian and Canadian practitioners. Because of the variable quality of the radiotherapy regimens used in the trials and the potential impact on study results, the evidence from other trials may not be generalizable to the Canadian setting.

After reviewing all of the evidence, the DSG recommends that women with cervical cancer for whom primary treatment with radiotherapy is being considered should be offered concurrent cisplatin with their course of radiotherapy.

The DSG discussed the optimal dose of cisplatin. No evidence was available from direct comparisons of different doses of cisplatin and it is possible that doses lower than those used in the randomized controlled trials may be effective. The DSG recommends that cisplatin be given at the dose used in the randomized controlled trials that found a benefit for cisplatin (i.e., 40 mg/m^2). Based on a review of the toxicity data from the randomized controlled trials, the DSG recommends that cisplatin be given weekly.

The definition of the target population for the guideline was reviewed and refined to make it clearer, especially for stage IB disease. Unfortunately, survival data from the subgroup of women with stage IB cervical cancer who participated in the randomized controlled trials in locally advance disease were not available (3,8).

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Based on the evidence described above, the Gynecology DSG drafted the following recommendations:

Target Population

These recommendations apply to women with cervical cancer for whom primary treatment with radiotherapy is being considered:

- those with locally advanced cervical cancer,
- those with bulky clinical stage IB (>4 cm) cervical cancer, who are treated with radiotherapy,
- those with high-risk early-stage cervical cancer (node-positive or margin-positive), who will be treated with radiotherapy following hysterectomy.

Draft Recommendations

- Women with cervical cancer for whom treatment with radiotherapy is being considered (described above) should be offered concurrent cisplatin with their course of radiotherapy.
- There are no direct comparisons of different cisplatin regimens. Based on the review of the available toxicity data from the randomized controlled trials, the DSG felt that cisplatinum should be given weekly (40 mg/m^2).

Qualifying Statements

- Despite this recommendation, other schedules and doses have been used; thus, there is no conclusive evidence that one dose and schedule is better than the other.
- There is insufficient evidence available to make recommendations on the addition of 5-fluorouracil to cisplatin during radiotherapy.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 105 practitioners in Ontario (41 medical oncologists, 20 radiation oncologists, 20 surgeons, 2 hematologists, 4 pathologists and 18 gynecologists). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology DSG reviewed the results of the survey.

Results

Fifty-three responses were received out of the 105 surveys sent (49.5% response rate). Responses include returned completed surveys as well as phone, fax and email responses. Of the practitioners who responded, 22 (42%) indicated that the report was relevant to their clinical practice and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 8.

Table 8. Practitioner responses to eight items on the practitioner feedback survey.

	Number (%)			Number Missing
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**	
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	21 (95%)	0	1 (5%)	0
There is a need for a clinical practice guideline on this topic.	19 (86%)	2 (9%)	1 (5%)	0
The literature search is relevant and complete.	20 (90%)	1 (5%)	1 (5%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	21 (95%)	0	1 (5%)	0
The draft recommendations in this report are clear.	21 (95%)	0	1 (5%)	0
I agree with the draft recommendations as stated.	20 (90%)	1 (5%)	1 (5%)	0
This report should be approved as a practice guideline.	19 (86%)	2 (9%)	1 (5%)	0
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**	
	19 (90%)	1 (5%)	1 (5%)	1

Summary of Written Comments

Thirteen respondents (59%) provided written comments. The main points contained in the written comments were:

1. The DSG recommends an optimal dose of cisplatin at 40mg/m2, but there is an unacceptable rate of grade 3/4 toxicity. Perhaps recommend a lower weekly dose.
2. A weekly dose of 40mg/m^2 platinum has become the internationally accepted standard; unfortunately, the toxicity (hematological) is more excessive than reported, and the majority of patients cannot tolerate six weeks at this dose.
3. Excluding studies not using platinum biases the results.
4. The guideline excludes GOG #165 (not yet published but closed) comparing 5-fluorouracil to weekly platinum.
5. The guideline does not state that platinum is not recommended for node-negative stage 1B patients where radiotherapy alone is recommended.
6. The results section of the guideline needs discussion regarding cisplatin versus q3wk cisplatin/5-fluorouracil in order to justify the statement in the interpretive summary stating that there "is no evidence to support the addition of 5-fluorouracil to cisplatin".
7. Cancer of the cervix is the second most common gynecologic malignancy world-wide and the 11th most frequently diagnosed cancer in Canadian women. Endometrial cancer is the most common gynecological cancer and the fourth most common cancer (after lung, breast, colon).

Modifications/Actions

1. The Gynecology DSG discussed the option to include a statement regarding prescribing lower dosages of cisplatin to eliminate some of the adverse effects, but the group agreed that there was not sufficient evidence to indicate that lower dosages are as effective and result in significantly fewer adverse effects.
2. The Gynecology DSG discussed the toxicity of weekly dose of 40mg/m^2 platinum and concluded that this dose is tolerable. Eighty-six percent of patients in Pearcey et al's study (8) comparing radiotherapy with and without cisplatin for patients with cervical cancer were able to tolerate the weekly dose of 40mg/m^2 platinum.
3. The Gynecology DSG chose to include only platinum-based chemotherapy studies because the majority of the high quality research focuses on platinum-based chemotherapy. The DSG is not prepared to make recommendations on non-platinum chemotherapy regimens at this time because there is insufficient evidence available.
4. The GOG #165 trial was added to the Ongoing Trials section.
5. The practice guideline does not make any recommendations for node-negative stage IB patients because this subset of patients was not included in the target population.
6. The statement in the DSG Consensus section stating that there was no evidence to support the addition of 5-fluoroouracil to cisplatin, was modified to "there is insufficient evidence available..."
7. The reference relating to the prevalence of cervical cancer in the Choice of Topic and Rationale was checked and corrected.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All eleven members of the PGCC returned ballots and approved the guideline as written. Three members provided suggestions

for consideration by the Gynecology DSG. The PGCC offered some stylistic and grammatical suggestions and also suggestions such as the inclusion of additional tables.

Modifications/Actions

The Gynecology DSG modified the guideline as per the stylistic and grammatical suggestions of the PGCC and noted the PGCC's additional suggestions for future updates and re-writes.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Gynecology DSG and the Practice Guidelines Coordinating Committee.

Target Population

These recommendations apply to women with cervical cancer for whom primary treatment with radiotherapy is being considered:

- those with locally advanced cervical cancer,
- those with bulky clinical stage IB (>4 cm) cervical cancer, who are treated with radiotherapy,
- those with high-risk early-stage cervical cancer (node-positive or margin-positive), who will be treated with radiotherapy following hysterectomy.

Recommendations

- Women with cervical cancer for whom treatment with radiotherapy is being considered (described above) should be offered concurrent cisplatin with their course of radiotherapy.
- There are no direct comparisons of different cisplatin regimens. Based on the review of the available toxicity data from the randomized controlled trials the DSG felt that cisplatinum should be given weekly (40 mg/m^2).

Qualifying Statements

- Despite this recommendation, other schedules and doses have been used; thus, there is no conclusive evidence that one dose and schedule is better than the other.
- There is insufficient evidence available to make recommendations on the addition of 5-fluorouracil to cisplatin during radiotherapy.

X. JOURNAL REFERENCE

Lukka H, Hirte H, Fyles A, Thomas G, Elit L, Johnston M, et al; on behalf of the Cancer Care Ontario Practice Guidelines Initiative Gynecology Disease Site Group. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer—a meta-analysis. *Clin Oncol* 2002;14(3):203-12.

XI. ACKNOWLEDGEMENTS

The Gynecology Disease Site Group would like to thank Dr Himu Lukka, Dr Hal Hirte, Dr Anthony Fyles, Dr Gillian Thomas, Dr Michael Fung Kee Fung, Mary Johnston and Alexandra Chambers for taking the lead in drafting, revising and updating this practice guideline report.

For a complete list of the Gynecology DSG members, please visit the CCO website at http://www.cancercare.on.ca/.

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Update

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Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 4-5: Section 3

Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation

Dr. Laurie Elit, Lisa Durocher & Annelise Kohler, and Gynecology Cancer Disease Site Group

Review Date: XX XX, 2016

The 2004 guideline recommendations

REQUIRE AN UPDATE

This means that the recommendations require additional evidence but are relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in June 2004. In October 2015, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist [LD] conducted an updated search of the literature. A clinical expert (LE) reviewed and interpreted the new eligible evidence and proposed the existing recommendations should be updated. The Gynecology Cancer Disease Site Group voted that the recommendations found in Section 1 (Guideline Recommendations) require an update on June 7th 2016.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

For women with cervical cancer in whom radiotherapy is considered appropriate, does the addition of concurrent platinum-based chemotherapy improve survival and quality of life with acceptable toxicity?

Literature Search and New Evidence

The new search [2004 - 2016] yielded a total of 269 practice guidelines, 258 publications of 56 systematic reviews and 202 publications of primary studies. The results of

the included 4 guidelines, 1 systematic review and 13 primary studies can be found in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The new data supports the existing recommendations. However, there are a few new options to other chemotherapy types that are not described in the original guideline. Also a few anticipated studies are due to be published in the next year. Hence, the Gynecology Cancer DSG decided to update the 2004 recommendations.

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program in evidence-based care | programme de soins fondé sur des preuves

Document Review Tool

Number and title of document under review	EBS 4-5 Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation
Current Report Date	June 2004
Clinical Expert	Dr. Laurie Elit
Research Coordinator	Lisa Durocher & Annelise Kohler
Date Assessed	October 23rd, 2015
Approval Date and Review Outcome (once completed)	To be Updated

Original Question(s):

For women with cervical cancer in whom radiotherapy is considered appropriate, does the addition of concurrent platinum-based chemotherapy improve survival and quality of life with acceptable toxicity?

Target Population:

Women with cervical cancer for whom primary treatment with radiotherapy is being considered:
-those with locally advanced cervical cancer
- those with bulky clinical stage IB (>4 cm) cervical cancer who are treated with radiotherapy
- those with high-risk early-stage cervical cancer (node positive or margin positive) who will be treated with radiotherapy following hysterectomy".

Study Selection Criteria:

Inclusion criteria:
1.Reported results from randomized control trials (RCTs) or meta-analyses that compare platinum-based chemotherapy plus radiation either to radiotherapy alone or to radiotherapy plus non-platinum-based chemotherapy
2. Included patients with cervical cancer
3. Reported survival data for each intervention group

Exclusion criteria:
1. If the publications were not written in English
2. If the studies included trials of platinum-based neoadjuvant chemotherapy

Search Details:
June 2004 to January 2016 Week 2 (Medline, Embase, Cochrane Library).

Brief Summary/Discussion of New Evidence:
Of 269 hits from the National Guidelines Clearinghouse, SAGE, NICE, SIGN, CMA, Cochrane Library, and AHRQ, a total of 4 guidelines were found. Of 258 hits from Medline (June 2004 to January week 2) and Embase (June 2004 to January week 2), a total of 14 references were found, 1 systematic review and 13 primary studies.

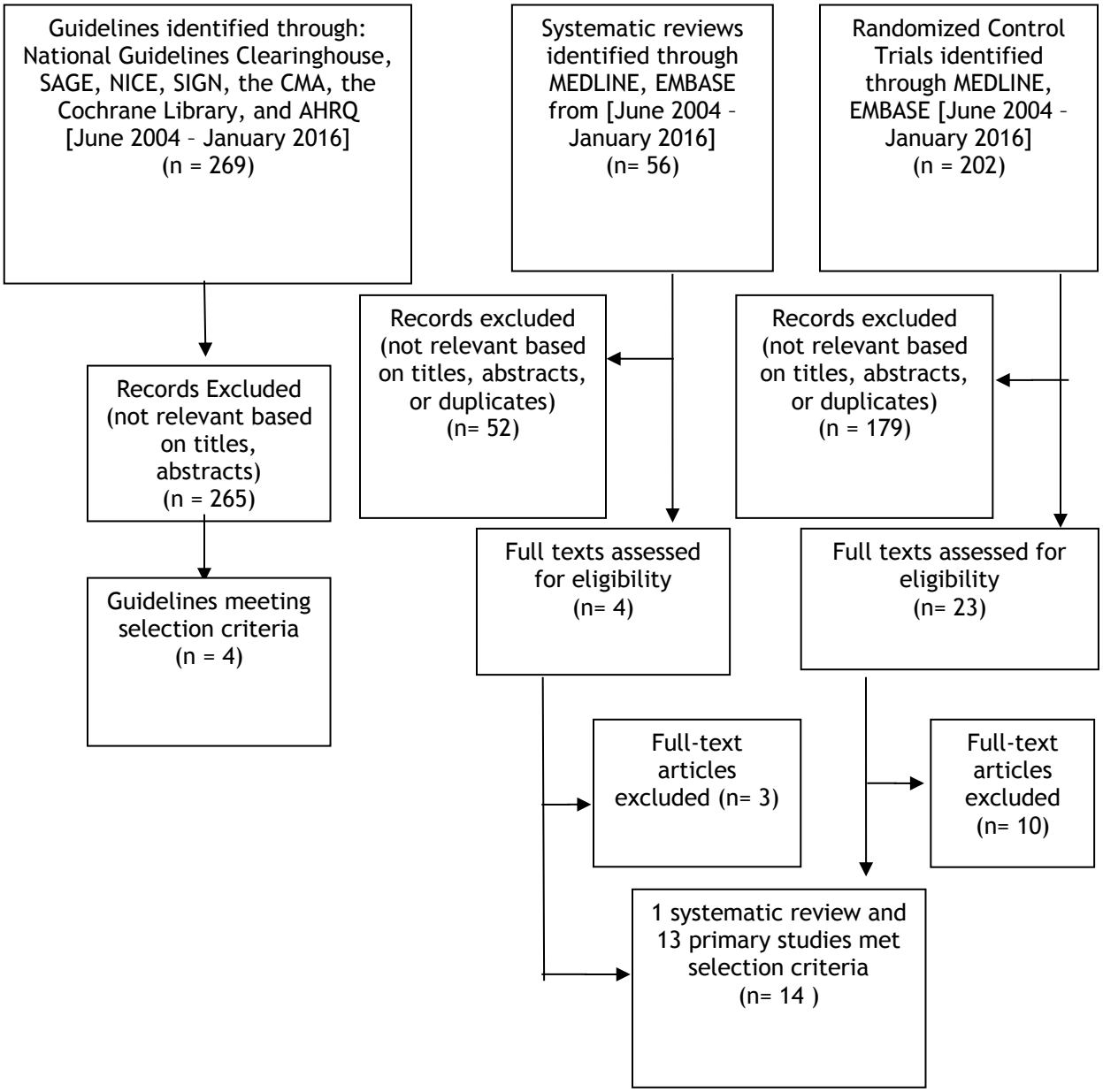

Table 1: Clinical Practice Guidelines retrieved from: the National Guidelines Clearinghouse, Standards and Guidelines Evidence Directory of Cancer Guidelines, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, The Canadian Medical Association, the Cochrane Library, and the Agency for Healthcare Research and Quality

Reference	Working Group	Recommendations
Alberta Provincial Gynecologic Oncology Team. Cancer of the uterine cervix. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 16 p. (Clinical practice guideline; no. GYNE-004). 2012	Alberta Provincial Gynecologic Oncology Team	Cisplatin should be administered at a dose of 40 mg/m^2 (max = 80) intravenously over 1 hour weekly for 5–6 cycles during EBRT (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008). Recommended for patients stage IB2 to IVB if patients are medically fit: Pelvic RT + concurrent chemotherapy (cisplatin × 5–6 cycles) followed by brachytherapy
A national clinical practice guideline for the management of cervical cancer. Vergote I, Vlayen J, Robays J, Stordeur S, Stemkens D, Smit Y, Bourgain C, De Gre`ve J, Kridelka F, Scalliet P, Simon P, Stroobants S, Van Dam P, Van Limbergen E, Villeirs G 2011	Belgian Healthcare Knowledge Centre	For treatment of non-metastatic cervical cancer, Patients with a clinical stage IA2, IB, or IIA carcinoma of the cervix and risk factors for recurrence (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium) who have undergone radical hysterectomy and pelvic lymphadenectomy should be considered for adjuvant treatment with concurrent platinum-based chemoradiotherapy. In case the preoperative staging indicates that postoperative treatment will be needed, concomitant cisplatin-based chemoradiotherapy is recommended instead of surgery
Cervical cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. C. Haie-Meder, P. Morice & M. Castiglione 2009	European Society for Medical Oncology (ESMO) Guidelines Working Group	FIGO stage IB2–IVA Concomitant chemoradiation represents the standard . This modality is superior to radiotherapy alone for local control, metastasis rate, disease-free and overall survival, with an increase in toxic (gastrointestinal and haematological) side-effects. Patients with advanced stage III and IVA may benefit less than patients with stage IB2–IIA/B. Platinum-based regimens for chemoradiation remain the standard. External irradiation is combined with brachytherapy and the total treatment duration should remain <55 days. Complementary extrafascial hysterectomy is an option.
Management of Cervical cancer. A national clinical guideline. SIGN guideline no. 99 2008	Scottish Intercollegiate Guidelines Network	Any patient with cervical cancer considered suitable for radical radiotherapy treatment should have concurrent chemoradiotherapy with a platinum based chemotherapy, if fit enough. Patients who have undergone surgery for cervical carcinoma and have positive nodes should be considered for adjuvant treatment with concurrent chemoradiotherapy with platinum based chemotherapy. Patients who have undergone surgery for cervical carcinoma, have negative nodes and any two of the following risk factors should be considered for adjuvant treatment with radiotherapy, if fit enough: greater than a third stromal invasion lymphovascular space invasion tumour diameter of >4 cm.

Table 2. Systematic reviews meeting inclusion criteria for EBS #4-5

Author, year, reference	Inclusion criteria	Methods	Intervention/ Comparison	Brief results
Wang et al. 2011 Meta- analysis	Studies were included if they were: RCT comparing RTCT with	Cochrane Library, Medline EMBASE, Chinese biomedicine literature database, Chinese scientific full text database and Chinese journal full text database.	RTCT vs RT, and the analysis of the survival rates	N – 18 RCTS, 3,517 patients 3 year survival rate (n = 709, 3 trials) RTCT vs RT RR 1.13, (95% CI 1.04-1.24),

	RT; patients were required to have primary, previously untreated; histologically or cytologically confirmed carcinoma of the cervix; no evidence of extrahepatic metastases.	Also reference lists of relevant articles and expert identified eligible trials (published and unpublished). Date range of search not specified.		p =0.006 5 year survival rate (n = 1564, 8 trials) RTCT vs RT= RR 1.22 (95% CI 1.13-1.31), p <0.00001

RCT – Randomized Controlled Trial; RT- Radiotherapy; RTCT- Radiochemotherapy

Table 3. Primary studies meeting inclusion criteria for EBS #4-5

Author, year, etc	Procedure and population	Methods	Intervention	Brief results
Hospital volume				
Disilvestro 2014	Patients with primary, untreated, histologically confirmed invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix- clinical stage IB2 or IIA or IIB, IIIB, or IVA.	Prospective, randomized phase III trial comparing TPZ to standard CIS-based RTCT. Feb 2006 and September 2009.	CIS : 40mg/m2 on days 1, 8, 15,22,29, and 36 CIS + TPZ: TPX 290 mg/m2 and CIS 75 mg/m2 ond ays 1, 15, 29 and TPZ 220mg/m2 on days 8,10,12,22,24 and 26 of RTCT RT: 23 to 25 fractions of 1.8 Gy to a total of 41.4 to 45 Gy	N =379, median follow up 28.3 months (interquartile range, 22.2 to 39.1 months) **CIS vs CIS & TPZ** 3 year PFS: 64.4% vs 63.0% unadjusted HR = 1.047 (95% CI 0.748-1.466), p = 0.7869 3 year OS: 70.6% vs 70.5% unadjusted HR = 1.047 (95% CI 0.710 to 1.531), p = 0.8333
Duenas-Gonzalez 2011	Patients with stage IIB to IVA pre-operative cervical carcinoma	Randomized phase III open label study comparing Gemcitabine + Cisplatin + RT to CIS-based RTCT. May 2002 to March 2004	Gemcitabine/CIS: 40mg/m2 CIS and 125mg/m2 gemcitabine once weekly for 6 weeks. CIS: 40mg/m2 weekly for 6 weeks RT: 50.4 in 28 fractions of 1.8 Gy/d, 5 days a week (6 cycles) *Patients were also administered BCT after initial chemoradiotherapy. After that, gemcitabine/CIS: 1000mg/m2 gemcitabine (day 1 and 8) and 50mg/m2 CIS (day 1). For 2 consecutive 21-day cycles	N = 515, median follow up 46.9 months **Gemcitabine/CIS vs. CIS-based RTCT** 3 year PFS: 74.4% vs. 65%. P = 0.029 overall PFS: (HR, 0.68; 95% CI, 0.49 to 0.95; p=.0227) OS: (HR, 0.68; 95%CI, 0.49 to 0.95; P=.0224)

Li 2014	Patients with stage IIB-IIIB squamous cell carcinoma of the cervix	Multi-center randomized control study comparing CIS-based RTCT to RT. January 2005 to January 2008	CIS: 20 mg/m2 for 5 days, at 21-day intervals (5 cycles) RT: 2 Gy 5 days/week up to a total dose of 46 Gy/23 fractions	N = 192, median follow up not reported **CIS-based RTCT vs. RT** Overall response rate: 67% vs. 53%. (P < 0.05) OS: Not reported in percentages - 68 months (3 to 85) and 61 months (4 to 83). (P = 0.009). PFS: Not reported in percentages - 62 months (3 to 83) and 51 months (4 to 81). (P = 0.025).
Nagy 2009	Patients with pathologically confirmed stage IIB, IIIA, or IIIB squamous cell carcinoma. Patients with prior cancer or cervical carcinoma were excluded.	Randomized monocentric phase III study comparing CIS-based RTCT to RT. March 26, 1999 to August 14, 2002	CIS: 20mg/m2 for 5 days RT: 2 Gy daily, 5 times a week to a total dose of 46 Gy/23 fractions	N = 566, median follow up 62.8 months **CIS-based RTCT vs. RT** 5-year survival rate: 74% vs. 64%. p < 0.05 5 year survival rate in operated patients: 88% vs. 85%; p = 0.42 5 year survival non-operated patients: 60% vs. 47%; p < 0.01.
Pu 2013	Patients with stage IB or IIA cervical cancer receiving radical hysterectomies and pelvic lymphatic dissection	Randomized control trial comparing CIS-based RTCT to Docetaxel/CIS RTCT. April 2003 to April 2008	CIS: 40mg/m2 weekly (5 cycles) Docetaxel/CIS: 30mg/m2 docetaxel and 30mg/m2 CIS weekly (5 cycles) RT: 46 – 54 Gy	N = 285, median follow up 60 months **CIS-based RTCT vs. Docetaxel/CIS RTCT** 5-year OS: 74.3 % vs. 82.8% HR for death was 0.65 in the Docetaxel/CIS group (95 % CI: 0.39–1.09, P = 0.098). RFS: 69.3 % vs. 79.3 % The HR for recurrence was 0.64 in the Docetaxel/CIS group (95 % CI: 0.40–1.03, P = 0.061).
Sehouli 2012	Patients with stage IB – IIB cervical cancer following hysterectomy	Open label Phase III randomized trial comparing Paclitaxel plus carboplatin plus RT to Cis-based RTCT. April 2003 to September 2008	CIS: 40 mg/m2 weekly Paclitaxel + Carboplatin: 175 mg/m2 tri-weekly (4 cycles) RT: 1.8 Gy 5 times a week up to a total of 50.4 Gy	N = 263, median follow up 42.5 months for Paclitaxel+Carboplatin+RT and 37 months for CIS; (p=0.13) **Paclitaxel + Carboplatin + RT vs. CIS-based RTCT** 2 year PFS: 87.2% vs. 81.8%. p = 0.25 (HR: 0.483; 95% CI 0.25–0.92; P = 0.028) 5-year OS: 84.2% vs. 77.4%. p = 0.34 (HR: 0.59; 95% CI 0.3–1.18; P = 0.137)

Wang 2010	Patients with pathologically confirmed stage II or III cervical squamous cell carcinoma	Randomized control trial comparing CIS-based RTCT with TP regimen to RT with TP regimen. June 2005 to April 2010	CIS: 40 mg/m2 weekly RT: 46-50 Gy TP: Docetaxel 60 mg/m2 on day 1, Cisplatin 40 mg on days 1-3, repeated every 21 day	N = 156, median follow up was not explicitly stated but patients were followed up anytime between 1 year and 3 years. **CIS-based RTCT with TP vs. RT with TP** 1 year OS: 88.57% vs. 70.77%. p<0.05 3 year OS: 82.14% vs. 57.69%. p<0.05
Zuliani 2014	Patients with stage IIIB squamous cell carcinoma of the cervix.	Randomized control clinical trial comparing CIS-based RTCT to RT. September 2003 to June 2013	CIS: 40 mg/m2 weekly RT: 1.8 Gy per fraction up to a total of 45 Gy	N = 147, median follow up 43.2 months (50% central range, 28.8 to 63.1 months) **CIS-based RTCT vs. RT** 3 year OS: 68% vs. 64% 5 year OS: 56% vs. 54% Overall OS: (HR, 0.67; 95% CI, 0.38 to 1.17; P = .16).
Ryu 2011 (looking at frequency of cisplatin-based RTCT)	Patients with histologically proven Stage IIB – IVA cervical cancer. Patients had adequate hematologic, renal, and hepatic function.	Open label randomized control trial comparing weekly CIS-based RTCT to tri-weekly CIS-based RTCT. January 2002 to December 2004	Weekly CIS: 40 mg/m2 once a week (6 cycles) Tri-weekly CIS: 75 mg/ once every 3 weeks (3 cycles) RT: 1.8–2.0 Gy daily up to a total of 50 Gy	N = 104, median follow up not reported **Weekly RTCT vs. tri-weekly RTCT** 5 year OS: 66.5% vs. 88.7% (HR, 0.375, 95% CI 0.154–0.914, p = 0.03)
Garipagaoglu 2004	Patients with biopsy proven squamous cell carcinoma of the cervix, stages IIB or IIIB, tumour size>4 cm, with adequate haematologic, renal and hepatic functions, and no prior chemotherapy, radiotherapy or pelvic surgery	Prospective randomized control pilot study comparing CIS-based RTCT to RT. January 1996 and March 1997	CIS: 20 mg/m2 on days 1,2,3,4,5,6,22,23,24,25,26,27 RT: 2 Gy daily up to a total of 46–50 Gy.	N =44, median follow up 40 months (3 – 62 months) **RT vs. CIS-based RTCT** 5-year OS: 51.3%, 52.0% vs. 48.9%. (p=0.7) 5 year DFS: 63.24%, 67.5% vs. 58.7%. (p=0.3)

Zeng 2008	Patients with stage IIB to IIIB cervical squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma. No history of radiotherapy, chemotherapy, hysterectomy, or transabdominal operation for cervical cancer.	Randomized control trial comparing RT to RT-BP, RT-TP, and RT-FP from January 2003 to December 2004	RT-BT: 30 mg of bleomycin + 20 mg/m2 cisplatin once a week (6 cycles) RT-TP: 40 mg/m2 taxol +80 mg/m2 carboplatin once a week (6 cycles) RT-FP: 750 mg/m2 5-fluorouracil + 20 mg/m2 cisplatin once a week (6 cycles) RT: 2Gy five times a week up to a total of 40-50 Gy	N = 285, median follow up 42 months (1 to 60) **RT vs. RT-BT, RT-TP, RT-FP** 3 year survival: 65% vs. 75%, (p = 0.042) 3 year survival of RT-BT, RT-TP, and RT-FP respectively: 74%, 80%, 71%, (p=0.792)
Nagy 2012	pathologically confirmed squamous cell carcinoma; Patients with prior cancer Or previously treated cervical cancer were excluded. stages IIB, IIIA, and IIIB	Prospectice phase III randomized control trial comparing 5-days-straight CIS-based RTCT to weekly CIS-based RTCT from March 2003 to March 2005	CIS (5 days straight): 20 mg/m2 per day, days 1 to 5 every 21 days CIS (weekly): 40 mg/m2 per day weekly RT: 2 Gy 5 days/week up to a total of 46 Gy/23 fractions	N = 326, median follow up 68.1 months **5-days-straight CIS vs. weekly CIS** 5 year OS: 75%, 78% vs 72% (CI, 70%-79%), p = 0.14. 5 year DFS: 71%, 73% vs 69% (CI, 66%-76%), p = 0.09. 5 year local relapse-free survival: 87% vs. 77%; (p = 0.01) .
Plesinac-Karapandzic 2006	Patients with IIB to IVA adenocarcinoma or squamous cell carcinoma of the cervix.	Prospective randomized control trial comparing CIS-based RTCT to RT from May 2002 to March 2003	CIS: 100mg/m2. Unclear what the schedule was. RT: 1.8 Gy per day up to a total of 45 Gy	N = 184, median follow up 7 months (range 4-24) **CIS-based RTCT vs. RT** 2 year OS: 17% (p=0.239)

OS – overall survival; DFS – disease free survival; PFS – progression free survival; RFS – recurrence free survival; RT – radiotherapy; RTCT – chemoradiotherapy; RT-BP – radiotherapy with bleomycin and cisplatin; RT-TP – radiotherapy with taxol and carboplatin; RT-FP – radiotherapy with 5-fluorouracil and cisplatin; CIS - cisplatin; TPZ – tirapazamine; HR – hazard ratio; BCT - brachytherapy

Table 4. Ongoing Randomized Control Trials retrieved from www.clinicaltrials.gov

Interventions	Official title	Status	Protocol ID	Estimated primary completion date	Last updated
RT vs. CIS-based RTCT or paclitaxel and bolus cisplatin RTCT	A Multicenter Trial of Benefits of Adding Chemotherapy as the Adjuvant Post-surgery Therapy for Cervical Cancer With Adverse Pathological Prognostic Factors	Currently recruiting patients	NCT00806117	December 2018	November 19, 2014
CIS-based RTCT vs. CIS-based RTCT + paclitaxel/carboplatin	Randomized Controlled Trial Comparing Concurrent Chemoradiation Versus Concurrent Chemoradiation	Currently recruiting patients	NCT02036164	January 2018	November 18, 2015

	Followed by Adjuvant Chemotherapy in Locally Advanced Cervical Cancer Patients				
CIS-based RTCT vs. CIS-based RTCT + paclitaxel / carboplatin	Phase III Randomized Study of Concurrent Chemotherapy and Pelvic Radiation Therapy With or Without Adjuvant Chemotherapy in High-Risk Patients With Early-Stage Cervical Carcinoma Following Radical Hysterectomy	Currently Recruiting patients	NCT00980954	August 2021	November 11, 2015
CIS-based RTCT vs. CIS-based RTCT + paclitaxel/ carboplatin	A Phase III Trial of Adjuvant Chemotherapy Following Chemoradiation as Primary Treatment for Locally Advanced Cervical Cancer Compared to Chemoradiation Alone: The OUTBACK Trial	Currently recruiting patients	NCT01414608	July 2018	February 9, 2016
CIS-based RTCT vs. carboplatin/paclitaxel followed by CIS-based RTCT	A Phase III Multicentre Trial of Weekly Induction Chemotherapy Followed by Standard Chemoradiation Versus Standard Chemoradiation Alone in Patients With Locally Advanced Cervical Cancer	Currently recruiting patients	NCT01566240	September 2016	August 21, 2015
RT vs. CIS-based RTCT + 1. fluorouracil, 2. bleomycin/ifosfamide, 3. Vindesine/bleomycin/mytomycin, 4. Vinblastine/bleomycin, or 5. methotrexate	A Randomized Phase III Study of Chemotherapy and Radiotherapy Versus Radiotherapy Alone as Adjuvant Treatment to Patients With Node Positive Stages IB or IIA Cervix Cancer	Completed	NCT00003209	December 1999	July 10, 2012

RT vs. CIS-based RTCT	Randomized Phase III Clinical Trial of Adjuvant Radiotherapy Versus Chemoradiation in Intermediate Risk, Stage I/IIA Cervical Cancer Treated With Initial Radical Hysterectomy and Pelvic Lymphadenectomy	Currently Recruiting patients	NCT01101451	December 2020	February 9, 2016
Rt vs. CIS-based RTCT	Concomitant Chemo-radiation in Advanced Stage Carcinoma Cervix: A Phase III Randomized Trial	Ongoing/active but not recruiting patients	NCT00193791	May 2015	April 22, 2015
CIS-based RTCT vs. CIS-based RTCT +paclitaxel	A Multicenter, Prospective, Randomized Trial of Adjuvant Chemotherapy for Early-Stage Cervical Cancer Patients	Ongoing but not recruiting	NCT01755897	December 2015	April 11, 2015
RT vs. CIS-based RTCT + paclitaxel	Phase III Randomized Trial of Comparing Chemoradiotherapy vs. Radiotherapy Alone in Lymph Node Negative Patients With Early-Stage Cervical Cancer Following Radical Hysterectomy	Currently Recruiting	NCT01756170	December 2013	December 19, 2012

CIS-based RTCT vs. CIS-based RTCT + tirapazamine	A Phase III, Randomized Trial of Weekly Cisplatin and Radiation Versus Cisplatin and Tirapazamine and Radiation in Stage IB2, IIA, IIIB and IVA Cervical Carcinoma Limited to the Pelvis	Completed	NCT00262821	August 2010	June 18, 2014
CIS-based RTCT vs. CIS-based RTCT + gemcitabine	Phase 3 Randomized Comparison of Concurrent Gemcitabine, Cisplatin, and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Cancer of the Cervix Stages IIB to IVA	Completed	NCT00191100	April 2008	August 8, 2009
CIS-based RTCT + paclitaxel vs. Carboplatin-based RTCT + paclitaxel	A Randomized Phase III Trial of Paclitaxel Plus Cisplatin Versus Paclitaxel Plus Carboplatin in Stage IVb, Persistent, or Recurrent Cervical Cancer (JCOG0505, CC-TPTC-P3)	Unknown	NCT00295789	November 2011	June 13, 2010
CIS/paclitaxel vs. CIS/gemcitabine vs. CIS/vinorelbine vs. CIS/topotecan	A Randomized Phase III Trial Of Paclitaxel Plus Cisplatin Versus Vinorelbine Plus Cisplatin Versus Gemcitabine Plus Cisplatin Versus Topotecan Plus Cisplatin In Stage IVB, Recurrent Or Persistent Carcinoma of the Cervix	Completed	NCT00064077	January 2011	May 27, 2015

Clinical Expert Interest Declaration: No potential conflict of interest was declared by the clinical expert.	
Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.	
1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	No
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	a) Yes b) No.
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	Yes
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	N/A
Review Outcome	To be updated.
DSG/GDG Approval Date	May 27, 2016.
DSG/GDG Commentary	

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Search Strategy

Database: Ovid MEDLINE(R)
July 2004- January 2016

Search Strategy:

1 exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
2 (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
3 random allocation/ or double blind method/ or single blind method/
4 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
5 or/1-4
6 (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
7 (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
8 (6 or 7) and random$.tw.
9 (clinic$ adj trial$1).tw.
10 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
11 placebos/
12 (placebo? or random allocation or randomly allocated or allocated randomly).tw.
13 (allocated adj2 random).tw.
14 or/9-13
15 5 or 8 or 14
16 (comment or letter or editorial or news or newspaper article or patient education handout or case reports or historical article).pt. (
17 15 not 16
18 exp animals/ not humans/
19 17 not 18
20 exp antineoplastic agents/
21 chemother:.mp.
22 (systemic adj therap:).tw.
23 (systemic adj treatment:).tw.
24 20 or 21 or 22 or 23

25 (radiotherap$ or radiation$ or irradiat$ or chemo-radiation$ or chemo-radiotherap$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26 24 and 25
27 exp uterine cervical neoplasm:/
28 exp carcinoma, adenosquamous/
29 exp carcinoma, squamous cell/
30 *carcinoma/dt, rt
31 cervical cancer.tw.
32 27 or 31
33 28 or 29 or 30
34 32 and 33
35 19 and 26 and 34
36 (200407: or 200408: or 200409: or 200410: or 200411: or 200412: or 2005: or 2006: or 2007: or 2008: or 2009: or 201:).ed.
37 35 and 36

Database: EMBASE
July 2004- January 2016
Search Strategy:

1 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2 randomization/ or single blind procedure/ or double blind procedure/
3 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4 or/1-3
5 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6 5 and random$.tw.
7 (clinic$ adj trial$1).tw.
8 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9 placebo/
10 (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11 (allocated adj2 random).tw.
12 or/7-11
13 4 or 6 or 12
14 (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
15 13 not 14
16 animal/ not human/
17 15 not 16
18 exp cancer chemotherapy/
19 chemother:.mp.
20 (systemic adj therap:).tw.
21 (systemic adj treatment:).tw.
22 or/18-21
23 (radiotherap$ or radiation$ or irradiat$ or chemo-radiation$ or chemo-radiotherap$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24 22 and 23
25 exp uterine cervical neoplasm:/
26 exp carcinoma, adenosquamous/
27 exp carcinoma, squamous cell/
28 *carcinoma/dt, rt
29 cervical cancer.tw.

30 25 or 29
31 26 or 27 or 28
32 30 and 31
33 17 and 24 and 32
34 (200407: or 200408: or 200409: or 200410: or 200411: or 200412: or 2005: or 2006: or 2007: or 2008: or 2009: or 201:).dd.
35 33 and 34

Outcome Definitions

EDUCATION AND INFORMATION – A document in EDUCATION AND INFORMATION is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word "EDUCATION AND INFORMATION".

ENDORSED – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

DELAY – A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

UPDATE – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.