The Role of Intraperitoneal Chemotherapy in the First-line Treatment of Women with Stage III Epithelial Ovarian Cancer

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

Practice Guideline Report 4-21 was reviewed and put in the Education and Information section in September 2011. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The reviewed report consists of:

Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Guideline Development and External Review

and is available on the CCO Web site (http://www.cancercare.on.ca) PEBC Gynecologic Cancer Disease Site Group page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gynecologic_cancer/

Release Date: Jun 25, 2012

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Guideline Citation (Vancouver Style): The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer. Toronto (ON): Cancer Care Ontario; 2012 Jun 25 [Education and Information 2011 Sep]. Program in Evidence-based Care Evidence-based Series No.: 4-21 Education and Information 2011.
The Role of Intraperitoneal Chemotherapy in the First-line Treatment of Women with Stage III Epithelial Ovarian Cancer

Guideline Report History

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The Role of Intraperitoneal Chemotherapy in the First-line Treatment of Women with Stage III Epithelial Ovarian Cancer

Guideline Review Summary

Review Date: September 2011

The 2006 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 2006. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Clinical Practice Guideline and Systematic Review in this version are the same as August 2006 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is conducted with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore an update literature search was not conducted. The 2006 guideline and its recommendations on The Role of Intraperitoneal Chemotherapy in the First-line Treatment of Women with Stage III Epithelial Ovarian Cancer have been ARCHIVED.
The Role of Intraperitoneal Chemotherapy in the First-line Treatment of Women with Stage III Epithelial Ovarian Cancer: A Clinical Practice Guideline

Elit L, Oliver T, Covens A, Kwon J, Fung-Kee-Fung M, Hirte H, Oza A, and the Gynecology Cancer Disease Site Group

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

Report Date: August 3, 2006

Question
What is the role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer? Outcomes of interest include response, survival, toxicity, catheter-related complications, and quality of life.

Target Population
These recommendations apply to women with stage III epithelial ovarian cancer for whom first-line chemotherapy after cytoreductive surgery is being considered.

Recommendations
• As front-line therapy, the intravenous administration of a platinum agent and a taxane remains a standard of care for this patient population. Cisplatin-containing intraperitoneal chemotherapy should be offered to patients on the basis of significant improvements in progression-free and overall survival when compared with cisplatin-containing intravenous chemotherapy alone.
  o The survival benefits associated with intraperitoneal chemotherapy must be weighed against the statistically significant increases in toxicity and catheter-related complications.
    • For patients with residual tumour diameter ≤ 1 cm in any one area, significant survival benefits were detected with intraperitoneal chemotherapy.
    • For patients with disease volumes > 1 cm in any one area, the role of intraperitoneal chemotherapy is yet to be defined.
  o The optimal intraperitoneal chemotherapy regimen has yet to be defined. The greatest median survival benefits were detected with intraperitoneal cisplatin and paclitaxel; however, only 42% of patients were able to complete all six cycles of the assigned treatment.
Key Evidence
- Seven randomized trials form the evidence basis for this report. All seven trials investigated the role of intraperitoneal chemotherapy in the front-line treatment of patients with stage II to IV ovarian cancer.
  - Three trials detected statistically significant overall survival benefits with intraperitoneal-containing chemotherapy when compared with intravenous chemotherapy alone.
    - In the three trials, the survival benefits associated with intraperitoneal cisplatin-containing chemotherapy were eight, 11, and 16 months longer than the survival rates observed with intravenous chemotherapy alone. The greatest median survival benefits were detected in patients randomized to receive 135 mg/m² of intravenous paclitaxel on day 1 over 24 hours, 100 mg/m² of intraperitoneal cisplatin on day 2, and 60 mg/m² of intraperitoneal paclitaxel on day 8, repeated every 21 days for six cycles.
  - The remaining four trials were underpowered to detect significant differences between treatment groups.
- With a relative risk of 0.88 (95% confidence interval [CI], 0.81-0.95; number needed to treat [NNT] = 12.5) for overall survival, the pooled data confirms that treatment involving intraperitoneal chemotherapy extends overall survival when compared with intravenous chemotherapy alone.
- Across six trials that reported data, 24% to 75% of patients were unable to complete all of the assigned cycles of the intraperitoneal chemotherapy regimen.
  - Severe adverse events with intraperitoneal chemotherapy were significantly more common when compared with intravenous chemotherapy alone and were often dose limiting.
  - Catheter-related complications included abdominal pain, bleeding, infection, peritonitis, catheter blockage, leakage, movement, malfunction, and/or access problems.
- One trial reported significantly poorer quality of life for patients treated with intraperitoneal chemotherapy when assessed prior to randomization, before the fourth cycle, and at three to six weeks after the sixth cycle. The difference in quality of life scores was not significant at 12 months after the completion of the sixth cycle of chemotherapy.

Future Research
The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer is still emerging. Future research in the randomized setting should focus on the optimal patient population to receive treatment and the optimal intraperitoneal chemotherapy regimen, including the most appropriate agents, infusate volume, schedule, and dose. The role of intraperitoneal chemotherapy in various other patient populations with ovarian cancer such as those with early-stage high-risk disease should also be explored in a prospective fashion.

Funding
The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Contact Information
For further information about this series, please contact Dr. Michael Fung Kee Fung, Chair, Gynecology Cancer Disease Site Group; Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario; Telephone: 613-737-8560, FAX: 613-737-8828

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Evidence-Based Series 4-21: Section 2

The Role of Intraperitoneal Chemotherapy in the First-line Treatment of Women with Stage III Epithelial Ovarian Cancer: A Systematic Review

L. Elit, T. Oliver, A. Covens, J. Kwon, M. Fung-Kee-Fung, H. Hirte, A. Oza, and the Gynecology Cancer Disease Site Group

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

Report Date: August 3, 2006

QUESTION(S)
What is the role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer? Outcomes of interest include response, survival, toxicity, catheter-related complications, and quality of life.

INTRODUCTION
In Canada, ovarian cancer is the fifth leading cause of cancer deaths among women and the leading cause of gynecologic cancer mortality (1). It is estimated that approximately 2,400 new cases and 1,550 deaths from ovarian cancer occurred in 2005, a case fatality ratio of 0.66 or 66% of patients (1). While patients with low-risk stage I disease can expect an approximate survival rate of 90% or better at five years (2), patients diagnosed with advanced regional disease (stage III) or distant disease (stage IV) can expect a five-year survival rate of approximately 30-50% and 13% respectively (2). Unfortunately, approximately 75% of patients present with advanced disease (stage III or IV) upon diagnosis (3,4).

Standard primary treatment for women with advanced ovarian cancer typically involves cytoreductive surgery and intravenous chemotherapy with a platinum agent administered either alone or in combination with a taxane. Despite an initial response rate of approximately 75% with this treatment approach, most patients with advanced disease recur and will ultimately die of complications of the malignancy within five years (3).

The peritoneal cavity is a common site of ovarian cancer presentation or recurrence, and tumours tend to remain confined to the peritoneal cavity for most of their history (5). Given that the disease initially presents on the peritoneum and local patterns of relapse of this disease involve the peritoneum, use of intraperitoneal therapy was explored.

The history of intraperitoneal therapy has both a clinical and pharmacologic basis. In the 1950s, intraperitoneal chemotherapy was used for controlling malignant ascites. In the late 1960s, intraperitoneal access options were explored. In the late 1970s, studies showed the slow clearance of chemotherapy drugs from the peritoneal cavity. This biochemical advantage could be exploited in ovarian cancer where it was possible to administer prolonged concentrations of cisplatin in the peritoneal cavity 10-20 fold higher than with the conventional intravenous route (5). Since intraperitoneal cisplatin was capable of penetrating small-volume tumours (1-3 mm), maximum
chemotherapeutic benefit could be derived for patients with microscopic residual disease or very small-volume macroscopic disease (5). In addition, the use of large doses of intraperitoneal cisplatin meant that not only could the surface of the tumour be exposed to high concentrations of cisplatin but also, with a sufficient amount of drug leak into the circulation, the amount of drug reaching the tumour via capillary flow was approximately doubled in comparison to a maximally tolerated dose of cisplatin delivered intravenously (6).

Controversy surrounding intraperitoneal chemotherapy includes problems experienced with the peritoneal catheters; local symptoms like abdominal distension and dyspnea, which may prohibit use; performance status, which may prohibit use; and delayed absorption, which may be associated with delayed onset and duration of side effects. Other concerns include the local toxicity of antineoplastic agents if they extravasate or cause adhesions; complexity of treatment in terms of time, cost, catheter failures, infection, and bowel obstruction; poor chemotherapy distribution; limited drug penetration into the tumour; or inhibition of drug delivery to the tumour by capillary flow.

Given the poor outcome of women with advanced ovarian cancer, it is imperative to continue to explore for novel therapies. The opportunity for intraperitoneal treatment, especially in the subgroup of patients with minimal residual disease (where the intraperitoneal approach may have a biologic rationale for benefit over and above the standard intravenous route), needs to be explored to the fullest extent. There remains a critical need to examine innovative strategies that may ultimately impact on outcome in this disease.

METHODS
This systematic review was developed by Cancer Care Ontario’s Program in Evidence-Based Care (PEBC). Evidence was selected and extracted by one member of the PEBC Gynecology Cancer Disease Site Group (DSG) and one methodologist. All drafts of the DSG are reviewed, modified, and approved by the Gynecology Cancer DSG, and also by a Report Approval Panel of the PEBC.

This systematic review is a convenient and up-to-date source of the best available evidence on intraperitoneal chemotherapy in the treatment of women with stage III epithelial ovarian cancer. The body of evidence in this review is primarily comprised of randomized controlled data. That evidence forms the basis of a clinical practice guideline developed by the Gynecology Cancer DSG found in Section 1 of this evidence-based series. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy
The literature was searched using MEDLINE (OVID: 1966 through January 2006), EMBASE OVID: (1988 through January 2006), the Cochrane Library (OVID: Issue 4, 2005), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse. In addition, the abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1997-2005) and the European Society for Medical Oncology (2002,2004) were searched for evidence relevant to this report. Reference lists of related papers and recent review articles were also scanned for additional citations.

The literature search of the electronic databases combined disease specific terms (ovarian neoplasms/ or ovar:.ti and cancer.ti. or neoplasms/) with treatment specific terms (intraperitoneal.ti. or ip.ti or peritoneal.ti.) for the following study designs: randomized controlled trials, practice guidelines, systematic reviews, and meta-analyses.

Study Selection Criteria
Articles were to be selected for inclusion in the systematic review of the evidence if they were published reports or published abstracts of randomized trials that compared patients with advanced (stage III) epithelial ovarian cancer to first-line treatment involving intraperitoneal-containing chemotherapy versus first-line treatment involving intravenous chemotherapy only. Trials were to
report data on some or all of the outcomes of interest: response, survival, toxicity, catheter-related complications, and/or quality of life.

Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also considered eligible for inclusion in the systematic review.

Articles were excluded if treatment included immunotherapy, intraperitoneal radioactive phosphorus ($^{32}$P), or hyperthermia. Trials were also excluded if they were reported in a language other than English, and data could not be extracted.

Synthesizing the Evidence
Combining results across trials provides added power for detecting the efficacy of the treatment and improves the reliability or confidence of the point estimate. Where appropriate, data on outcomes of interest are pooled across trials, using Hazards Ratios (HR), or with the Relative Risk (RR) using clinically relevant events or time-points. Data were pooled using Review Manager 4.0.3 (Metaview© Update Software), obtained through the Cochrane Collaboration (www.cochrane.org). Results are expressed as the HR or RR with 95% confidence intervals (CI), where an RR less than 1.0 favours the experimental treatment and an RR greater than 1.0 favours control. The random effects model is generally preferred over the fixed effects model as the more conservative estimate of effect (7). The number of patients needed to treat for one additional patient to benefit (NNT) is calculated using the inverse of the risk difference. Where appropriate, sensitivity analyses are conducted to determine whether particular study characteristics influence the estimate of effect.

RESULTS
Literature Search Results
Seven randomized controlled trials (8-14) and one systematic review with meta-analyses (15) met the inclusion criteria and were deemed eligible for inclusion in the systematic review of the evidence. Table 1 describes the included studies and selected trial characteristics. An additional paper (16), reporting further information on the GOG 172 trial by Armstrong et al (8) was also identified, and data on catheter-related outcomes were extracted from that paper (16).

Trial Quality
All of the identified trials were non-blinded randomized controlled trials (8-14). In four trials, the randomization procedure was reported (8-11), while the remaining trials did not report that information (12-14). Five trials (8-11,13) reported patient accrual with sufficient power to detect significant differences between treatment groups with one-sided (8,9) or two-sided significance (10,11,13) testing at an alpha level of 0.05 (8-11,13). Two trials did not report power calculations (12,14). Two trials were stopped early (11,14), and one trial was extended for increased patient accrual (13). In the trial by Gadduci et al (11), patient accrual was stopped early after 113 patients entered the study. In that trial, only 60% of eligible patients were actually randomized (11). Another study was closed early because of poor patient accrual with the introduction of carboplatin and the shift in community practice toward carboplatin-based chemotherapy (14). In the trial by Alberts et al (13), a separate analysis of patients with disease $\leq$ 0.5 cm was added as part of the study design. In that trial, patient accrual continued for an additional year to achieve a sufficiently large sample size appropriate for analysis (13).

Baseline characteristics were generally similar across treatment groups in all of the seven trials (8-14); however, statistical comparisons between treatment arms were only reported in two trials (10,12). Both trials reported no statistically significant differences in baseline characteristics between treatment groups (10,12).

Across six trials, completeness of follow-up was greater than 80% (8-13). In one trial, the planned analysis included only evaluable patients (14). In that trial of 87 patients randomized to either intravenous or intraperitoneal chemotherapy, results for 62 evaluable patients are reported. Five trials reported an intention-to-treat principle either on eligible patients (8-10,13) or on the whole study population randomized (11). The proportion of patients deemed ineligible after randomization
ranged from 0% to 17% of the patient populations (8-10,12-14). In one trial, the number of patients deemed ineligible was not reported (11). One trial (9) began as a three-arm study, with the third arm of cisplatin and cyclophosphamide being dropped when the results of GOG 111 trial (paclitaxel/cisplatin versus cyclophosphamide/cisplatin) became available (17). Only 66 patients were accrued in that arm, and no results were reported for those patients.

Table 1. Literature search results and trial characteristics.

<table>
<thead>
<tr>
<th>Author Year (Ref) Study</th>
<th>No. of pts.</th>
<th>Trt. arm</th>
<th>Treatment Regimen</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
<th>Cycle</th>
<th>% with all treatment cycles</th>
<th>Residual disease</th>
<th>Volume ≤ 1 cm</th>
<th>Volume &gt; 1 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong 2006 (8) GOG 172</td>
<td>210</td>
<td>IV</td>
<td>Paclitaxel, Cisplatin</td>
<td>135 mg/m²</td>
<td>i.v.</td>
<td>1</td>
<td>q21d x 6</td>
<td>83%</td>
<td>64%</td>
<td>36%</td>
<td>100%</td>
</tr>
<tr>
<td>Markman 2001 (9) GOG 114</td>
<td>227</td>
<td>IV</td>
<td>Paclitaxel, Cisplatin</td>
<td>135 mg/m²</td>
<td>i.p.</td>
<td>2</td>
<td>q21d x 6</td>
<td>42%</td>
<td>62%</td>
<td>38%</td>
<td>100%</td>
</tr>
<tr>
<td>Markman 2001 (9) GOG 114</td>
<td>235</td>
<td>IP</td>
<td>Paclitaxel, Cisplatin</td>
<td>135 mg/m²</td>
<td>i.v.</td>
<td>1</td>
<td>q21d x 6</td>
<td>86%</td>
<td>64%</td>
<td>36%</td>
<td>0%</td>
</tr>
<tr>
<td>Gadducci 2000 (11)</td>
<td>56</td>
<td>IV</td>
<td>Cisplatin, Epipod. Cyclo.</td>
<td>50 mg/m²</td>
<td>i.v.</td>
<td>1</td>
<td>q21d x 6</td>
<td>32%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Gadducci 2000 (11)</td>
<td>57</td>
<td>IP</td>
<td>Cisplatin, Epipod. Cyclo.</td>
<td>50 mg/m²</td>
<td>i.p.</td>
<td>1</td>
<td>q21d x 6</td>
<td>25%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Polyzos 1999 (12)</td>
<td>46</td>
<td>IV</td>
<td>Carboplatin, Cyclo.</td>
<td>350 mg/m²</td>
<td>i.v.</td>
<td>NR</td>
<td>q21d x 6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Polyzos 1999 (12)</td>
<td>44</td>
<td>IP</td>
<td>Carboplatin, Cyclo.</td>
<td>350 mg/m²</td>
<td>i.p.</td>
<td>NR</td>
<td>q21d x 6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Alberts 1996 (13) SWOG/ GOG 104</td>
<td>279</td>
<td>IV</td>
<td>Cyclo. Cisplatin</td>
<td>600 mg/m²</td>
<td>i.v.</td>
<td>1</td>
<td>q21d x 6</td>
<td>58%</td>
<td>74%</td>
<td>26%</td>
<td>72%</td>
</tr>
<tr>
<td>Alberts 1996 (13) SWOG/ GOG 104</td>
<td>267</td>
<td>IP</td>
<td>Cyclo. Cisplatin</td>
<td>600 mg/m²</td>
<td>i.p.</td>
<td>1</td>
<td>q21d x 6</td>
<td>58%</td>
<td>75%</td>
<td>25%</td>
<td>73%</td>
</tr>
<tr>
<td>Kirmani 1994 (14)</td>
<td>33</td>
<td>IV</td>
<td>Cisplatin, Cyclo.</td>
<td>100 mg/m²</td>
<td>i.v.</td>
<td>NR</td>
<td>q21d x 6</td>
<td>60%</td>
<td>NR</td>
<td>NR</td>
<td>45%</td>
</tr>
<tr>
<td>Kirmani 1994 (14)</td>
<td>29</td>
<td>IP</td>
<td>Cisplatin, Epipod.</td>
<td>200 mg/m²</td>
<td>i.p.</td>
<td>NR</td>
<td>q28d x 6</td>
<td>76%</td>
<td>NR</td>
<td>NR</td>
<td>62%</td>
</tr>
</tbody>
</table>

Note. Ref, reference; No. of pts., number of patients; Trt., treatment. IV, i.v., intravenous; IP, i.p., intraperitoneal; NR, not reported; *, same as above; q, every; d, day; cyclo., cyclophosphamide; epipod., epipodophycin.

a Eligible patients who received all cycles of the assigned treatment.
b Patients may have also received 50 mg/m² of doxorubicin or epirubicin depending upon their cardiovascular condition.
c Patients who received all cycles of the planned cisplatin dose.
d Patients with residual disease ≤ 0.5 cm.
Trial Characteristics

To be eligible to participate in the randomized trials, patients had to have newly diagnosed epithelial ovarian cancer that was either stage III (8,9,10,12,13) or ranging from stage II to IV (11,14). In one trial, approximately 12% of patients had stage III primary peritoneal cancer (8). Patients had to have a Southwest Oncology Group (SWOG) performance status ≤ 2 in two trials (10,13), an ECOG performance status of < 2 (11), ≤ 2 (14), or ≤ 3 (12) in three trials, or a Gynecology Oncology Group (GOG) performance status ≤ 2 in two trials (8,9). Where reported, the median age of patients ranged from a low of 52.8 years to a high of 61.0 years (10-14). All of the trials included patients over the age of seventy years (8-14), and three trials included patients who were greater than 80 years of age (8,10,13). Patients had to have adequate blood counts and renal and hepatic function (8-14), and no prior treatment with chemotherapy or radiotherapy (8,9,11,14). Information on patients’ height, weight, body mass index, or menopausal status was not reported in any of the randomized trials (8-14).

Across the trials, the majority of patients were diagnosed with the histologic subtype serous adenocarcinoma (8-14). Trials were conducted in the United States (8,9,13,14), Taiwan (10), Italy (11), and Greece (12). Trial participants were predominantly white (≥ 90%) in three trials (8,9,13), while the remaining trials did not explicitly report information on ethnicity (10-12,14). Where reported, patients were stratified by performance status (12,13), presence of residual disease (8), amount of residual disease (12-14), tumour grade (12), whether second-look surgery was selected (8), time of enrolment (13), and/or cooperative group (13). Minimal residual disease was categorized ≤ 0.5 cm in one trial (13), ≤ 1 cm in four trials (8,9,10,14), < 2 cm in one trial (11), and ≤ 2 cm in two trials (12,13). Patients decided whether to undergo second-look laparotomy at registration in one trial (8) and all patients with negative disease at completion of treatment were requested to have a second-look laparotomy in six trials (9-14).

While there were similarities across the seven studies in terms of treatment regimen, none were directly comparable because either the chemotherapy agents varied or the dosing schedule of similar agents varied. With the exception of one trial (14), all of the studies compared combination chemotherapy that included either cisplatin or carboplatin, being delivered through intravenous versus intraperitoneal injection (8-13). In that one trial, intraperitoneal etoposide was combined with intraperitoneal cisplatin as part of the investigational arm (14). In one trial, patients in both treatment arms may have also received 50 mg/m2 of doxorubicin or epirubicin, depending upon their cardiovascular condition (10). Most of the treatment regimens were scheduled for six cycles of chemotherapy, with the exception of one trial that delivered eight cycles in the investigational arm only (9).

Protocols for treatment modification included cycle delay, (8,9,12,13) dose reduction (8), or the addition of granulocyte stimulating factor (8). Patients were removed from the study if treatment delay was greater than three weeks (8) or due to excess toxicity (13). Dose reductions were not allowed in one trial (9) and not reported in five trials (10-14). Patient crossover due to excess toxicity or catheter-related complications was reported in three trials (8,9,11) and not reported in four trials (10,12-14). One study reported that, if toxicity due to cisplatin in either treatment arm was intolerable, patients were switched to intravenous carboplatin (8).

The type of catheter used was reported to be “implantable” in one trial (8), Tenckhoff in two trials (9,10), Port-A-Cath in two trials (11,14), or “temporary” in two trials (11,12) and was not reported in one trial (13).

Across the seven trials, the proportion of patients who received all cycles of the assigned chemotherapy ranged from 32% to 96% of patients in the control arms and 25% to 76% of patients in the treatment arms involving intraperitoneal-containing chemotherapy (8-14).

Primary outcomes were pathological response rate (9,10,13,14), progression-free survival (8,9), and/or overall survival (8,9,11,13). Quality of life was assessed using the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) instrument in one trial (8) and was not reported in the remaining trials (9-14).
Outcomes

Table 2 displays response and survival results for the seven randomized trials identified in the review of the evidence. Response, progression-free survival, and median survival were the primary outcomes of interest. Five-year overall survival was also generally reported or data were available through extraction from survival curves, however statistical estimates of differences between treatment groups were not provided in any of the randomized trials. One trial also reported disease-free survival as a study end-point (14). In that one study (14), disease-free survival rates are presented in Table 2 under the progression-free survival column.

Table 2. Response rates and survival outcomes.

<table>
<thead>
<tr>
<th>Author Year (Ref)</th>
<th>No. of pts</th>
<th>Trt. arms</th>
<th>Second Look Surgery</th>
<th>Progression-free Survival</th>
<th>Overall Survival</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of pts</td>
<td>% with Complete Response</td>
</tr>
<tr>
<td>Armstrong 2006 (8)</td>
<td>210</td>
<td>IV IP</td>
<td>72 69</td>
<td></td>
<td>41% 57% p=NA</td>
</tr>
<tr>
<td>Markman 2001 (9)</td>
<td>227</td>
<td>IV IP</td>
<td>193 182</td>
<td>NR NR</td>
<td>22 months 28 months p=0.01&lt;sup&gt;a&lt;/sup&gt; RR 0.78 (0.66-0.94)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yen 2001 (10)</td>
<td>63</td>
<td>IV IP</td>
<td>73 total</td>
<td>38% 36% p=0.99</td>
<td>NR NR</td>
</tr>
<tr>
<td>Gadducci 2000 (11)</td>
<td>56</td>
<td>IV IP</td>
<td>34 33</td>
<td>39%&lt;sup&gt;c&lt;/sup&gt; 43%&lt;sup&gt;c&lt;/sup&gt; p=NS</td>
<td>25 months 42 months p=0.13</td>
</tr>
<tr>
<td>Polyzos 1999 (12)</td>
<td>46</td>
<td>IV IP</td>
<td>6 4</td>
<td>48%&lt;sup&gt;d&lt;/sup&gt; 45%&lt;sup&gt;d&lt;/sup&gt; p=NS</td>
<td>19 months 18 months p=NS</td>
</tr>
<tr>
<td>Alberts 1996 (13)</td>
<td>279</td>
<td>IV IP</td>
<td>158 139</td>
<td>36% 47% p=NA</td>
<td>NR NR</td>
</tr>
<tr>
<td>Kirmani 1994 (14)</td>
<td>33</td>
<td>IV IP</td>
<td>19 16</td>
<td>58% 56% p=NS</td>
<td>14 months 12 months p=0.46</td>
</tr>
</tbody>
</table>

Note. Ref, Reference; No. of Pts., number of patients; trt., treatment; RR, relative risk; HR, Hazard Ratio; NR, not reported; NS, not significant; NA, not applicable.

<sup>a</sup> One tailed significance testing.
<sup>b</sup> 90% confidence intervals.
<sup>c</sup> Clinical complete response based on the intention to treat population of 128 patients.
<sup>d</sup> Clinical complete response based on the entire study population.
<sup>e</sup> Disease-free survival.
<sup>f</sup> Data extracted by reviewer from survival curve and denoted as an approximation.
<sup>g</sup> Where data were not available, five-year survival was extracted by the reviewer from the survival curves and denoted as approximations.

Response Rates after Second-Look Surgery

No statistically significant differences in clinical or pathologically confirmed complete response rates were reported between any of the treatment arms in any of the trials (8-14). Armstrong et al (8) reported a 16% difference in complete pathological response in favour of intraperitoneal versus intravenous chemotherapy, but only a small proportion of patients actually received second-look surgery, and response was not a planned study end point. In two trials (9,13), results from second-look surgery were a planned end point but were deemed to be unreliable given low procedure rates (9,13), and a disproportionate number of procedures performed between treatment groups (9,13).
Markman et al (9) did not report results for complete response, while Alberts et al (13) reported an 11% difference in complete response in favour of patients who received intraperitoneal chemotherapy. Across the studies, complete pathologic response rates ranged from 36% to 58% with intravenous chemotherapy and 36% to 56% with intraperitoneal chemotherapy (8,10-14).

**Progression-Free Survival**

Two trials, detected statistically significant six-month improvements in progression-free survival in favour of patients treated with intraperitoneal-containing chemotherapy versus intravenous chemotherapy (8,9). In one trial (9) after adjusting for important prognostic factors (residual disease status, cell type, and histologic grade), the relative risk estimate decreased slightly from RR = 0.78 (90% CI, 0.66 to 0.94) to RR = 0.75 (90% CI, not reported).

Of the remaining studies, two underpowered trials (11,12) reported no statistically significant differences between treatment groups, and three trials did not report results for that outcome (10,13,14). One trial (13) reported that the amount of residual disease at the start of treatment (≤ 0.5 cm versus >0.5 cm to 2 cm) was the most important factor in determining response. This was regardless of the type of treatment administered (p=0.005). One trial that reported disease-free survival as an outcome of interest reported no statistically significant differences between treatment arms (14).

While not a study end-point in any of the randomized trials (8-14), there were sufficient information from three randomized trials (8,9,11) to extract data for pooling progression-free survival at five years. The remaining trials did not report data sufficient for pooling (10,12-14). As seen in Figure 1, with a relative risk of 0.91 (95% CI, 0.85-0.98, NNT = 14) the pooled data indicate that treatment involving intraperitoneal chemotherapy extends progression-free survival to a greater extent than intravenous chemotherapy alone.

**Survival**

Three trials reported statistically significant improvements in median survival with intraperitoneal-containing chemotherapy when compared with intravenous chemotherapy (8,9,13). The improvements in median survival were 16, 11, and 8 months in the three trials, respectively (8,9,13).

In the trial by Armstrong et al (8), there were no significant differences in outcomes between patients with gross residual disease and those with no visible residual disease, nor were there differences when results were analyzed by the number eligible versus the number of patients randomized. In that trial, patients in the treatment arm received an extra dose of intraperitoneal paclitaxel on day 8.

In the trial by Markman et al (9), results were similar when adjusted for disease volume, histology, or age (9). In that trial, patients in the treatment arm received eight cycles of chemotherapy, compared with six cycles of chemotherapy in the intravenous arm.

In the trial by Alberts et al (13), the factors associated with improved survival were absence of gross disease (p<0.001) younger age (p<0.001), type of tumour other than clear cell or mucinous
(p<0.001), and timing of enrolment after surgery (p<0.001). Size of residual tumour (≤ 0.5 cm or > 0.5 cm to 2 cm) did not significantly affect overall survival outcomes.

While the four small remaining trials reported no significant differences between treatment groups (10-12,14), one underpowered trial did report a non-statistically significant 16-month improvement in survival with intraperitoneal versus intravenous chemotherapy (11).

Five-year overall survival was not reported as a study end-point in any of the randomized trials, however there was sufficient information from six of the seven randomized trials (8-11,13,14) to extract data for pooling results across trials. The remaining trial did not report data sufficient for pooling (12). As seen in Figure 2, the relative risk of 0.88 (95% CI, 0.85-0.98; NNT = 12.5) shows that a greater treatment effect is seen with intraperitoneal chemotherapy when compared with intravenous chemotherapy alone.

**Figure 2. Pooled analysis of five-year overall survival.**

<table>
<thead>
<tr>
<th>Study of subcategory</th>
<th>Intraperitoneal</th>
<th>Intravenous</th>
<th>RR (random) 95% CI</th>
<th>RR (rational) 95% CI</th>
<th>Weight</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong, 2000 (6)</td>
<td>103/285</td>
<td>127/216</td>
<td>0.88 (0.85-0.98)</td>
<td>12.5</td>
<td>21.66</td>
<td>0.81 (0.68, 0.97)</td>
</tr>
<tr>
<td>Mehtan, 2001 (9)</td>
<td>105/235</td>
<td>124/227</td>
<td>0.88 (0.71, 1.00)</td>
<td>15.19</td>
<td>25.58</td>
<td>0.85 (0.62, 1.18)</td>
</tr>
<tr>
<td>Vani, 2002 (10)</td>
<td>51/115</td>
<td>67/125</td>
<td></td>
<td></td>
<td>4.06</td>
<td>0.75 (0.50, 1.12)</td>
</tr>
<tr>
<td>Ondrejick, 2000 (11)</td>
<td>51/115</td>
<td>67/125</td>
<td></td>
<td></td>
<td>3.76</td>
<td>0.88 (0.77, 1.02)</td>
</tr>
<tr>
<td>Alberts, 1997 (12)</td>
<td>147/267</td>
<td>174/299</td>
<td></td>
<td></td>
<td>3.79</td>
<td>0.99 (0.88, 1.16)</td>
</tr>
<tr>
<td>Hinman, 1994 (13)</td>
<td>12/33</td>
<td>29/50</td>
<td></td>
<td></td>
<td>3.79</td>
<td>0.99 (0.88, 1.16)</td>
</tr>
<tr>
<td>Total</td>
<td>856</td>
<td>936</td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.90 (1.01, 0.95)</td>
</tr>
</tbody>
</table>

**Adverse Events Associated with Chemotherapy.**

Table 3 presents the most common grade 3 or 4 adverse events reported across the seven trials identified in the search of the literature. On average, more statistically significant adverse events were detected in patients who received intraperitoneal-containing chemotherapy when compared to those who received intravenously administered chemotherapy. The most common severe adverse events reported were hematological and gastrointestinal. In two trials, approximately three quarters of patients experienced severe leucopenia with intraperitoneal chemotherapy (8,9), and in one trial almost half experienced severe gastrointestinal adverse events with intraperitoneal chemotherapy (8). In contrast, three trials reported significantly less leucopenia with cyclophosphamide and intraperitoneal cisplatin (10,13) or carboplatin (12) when compared with identical doses delivered intravenously. One trial (13) also reported significantly less tinnitus, clinical hearing loss, and neuromuscular toxic effects in patients treated with intraperitoneal chemotherapy. In two trials (12,13) grade 2 or higher abdominal pain was significantly greater in the intraperitoneal group (p<0.01). Significant transient dyspnea was also seen in patients who received intraperitoneal chemotherapy, which could be related to compression of the base of the lung by the fluid-filled intraperitoneal cavity (12,13).

Patient death due to treatment was an infrequent occurrence, and there were generally similar rates detected between treatment groups with the greatest difference being two deaths in the intraperitoneal arm and no deaths in the intravenous arm in one of the trials (13).

On average, adherence to the assigned chemotherapy regimen was greater for patients who received intravenous chemotherapy as compared to those who received intraperitoneal chemotherapy (Table 1). In the trial by Armstrong et al (8), only 42% of patients completed the assigned intraperitoneal chemotherapy regimen. In that trial, of 205 eligible patients in the intraperitoneal chemotherapy arm, 84 patients received one or more courses of intravenous chemotherapy, and 37 patients received carboplatin instead of cisplatin. Twenty-nine percent of patients discontinued intraperitoneal chemotherapy due to nausea, vomiting, dehydration, renal or metabolic adverse events (16). In another trial (9), 18% of patients received two or less courses of
intraperitoneal chemotherapy therapy primarily because of excessive bone marrow toxicity with initial
doses of intravenous carboplatin (AUC = 9). In one trial, where toxicity was roughly similar between
the two treatment arms, 20 patients (32%) switched to intravenous chemotherapy primarily because
of patient refusal and/or logistical issues (11). In that trial, 11% of patients crossed-over to
intravenous chemotherapy prior to receiving any intraperitoneal chemotherapy (11). The remaining
trials (12-14) did not report details on toxicity-related treatment discontinuation or crossover to
intravenous chemotherapy.

Table 3. Grade 3 or 4 toxicity.

<table>
<thead>
<tr>
<th>Author Year (Ref)</th>
<th>No. of pts.</th>
<th>Trt. Arm</th>
<th>Leucopenia</th>
<th>Neutropenia</th>
<th>Thromboembolism</th>
<th>Infection</th>
<th>Gastrointestinal</th>
<th>Anemia</th>
<th>Fatigue</th>
<th>Renal or Genitourinary</th>
<th>Neurotoxicity</th>
<th>Metabolic</th>
<th>Pain</th>
<th># of Treatment Related Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong 2006 (8)</td>
<td>210 IV</td>
<td>64%</td>
<td>NR</td>
<td>4%</td>
<td>6%</td>
<td>24%</td>
<td>4%</td>
<td>9%</td>
<td>2%</td>
<td>27%</td>
<td>7%</td>
<td>11%</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>201 IP</td>
<td>76%</td>
<td>NR</td>
<td>12%</td>
<td>16%</td>
<td>46%</td>
<td>NR</td>
<td>NR</td>
<td>18%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Markman 2001 (9)</td>
<td>227 IV</td>
<td>62%</td>
<td>NR</td>
<td>3%</td>
<td>&lt;2%</td>
<td>17%</td>
<td>NR</td>
<td>&lt;4%</td>
<td>5%</td>
<td>&lt;2%</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>235 IP</td>
<td>77%</td>
<td>NR</td>
<td>49%</td>
<td>&lt;4%</td>
<td>37%</td>
<td>NR</td>
<td>NR</td>
<td>1%</td>
<td>&lt;2%</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Yen 2001 (10)</td>
<td>63 IV</td>
<td>33%</td>
<td>NR</td>
<td>16%</td>
<td>NR</td>
<td>NR</td>
<td>19%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>55 IP</td>
<td>18%</td>
<td>NR</td>
<td>13%</td>
<td>NR</td>
<td>NR</td>
<td>13%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Gadducci 2000 (11)</td>
<td>56 IV</td>
<td>19%</td>
<td>NR</td>
<td>2%</td>
<td>NR</td>
<td>NR</td>
<td>6%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>57 IP</td>
<td>24%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>9%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Polyzos 1999 (12)</td>
<td>46 IV</td>
<td>39%</td>
<td>NR</td>
<td>22%</td>
<td>NR</td>
<td>NR</td>
<td>6%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>44 IP</td>
<td>11%</td>
<td>NR</td>
<td>7%</td>
<td>NR</td>
<td>NR</td>
<td>9%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Alberts 1996 (13)</td>
<td>279 IV</td>
<td>50%</td>
<td>NR</td>
<td>69%</td>
<td>9%</td>
<td>NR</td>
<td>25%</td>
<td>NR</td>
<td>25%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>267 IP</td>
<td>40%</td>
<td>NR</td>
<td>56%</td>
<td>8%</td>
<td>NR</td>
<td>25%</td>
<td>NR</td>
<td>25%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Kirmani 1994 (14)</td>
<td>33 IV</td>
<td>21%</td>
<td>NR</td>
<td>42%</td>
<td>5%</td>
<td>31%</td>
<td>7%</td>
<td>NR</td>
<td>0%</td>
<td>3%</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>29 IP</td>
<td>19%</td>
<td>NR</td>
<td>42%</td>
<td>0%</td>
<td>19%</td>
<td>3%</td>
<td>NR</td>
<td>6%</td>
<td>8%</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
</tbody>
</table>

Note. Ref, Reference; No. of Pts., number of patients; Trt, treatment; bolded figures represent statistically significant differences between treatment groups p ≤ 0.05.

a grade 4 neutropenia was significantly higher in patients treated with intraperitoneal chemotherapy, however actual data were not reported.

b toxicity ≥ grade 2.

c toxicity reported by cycle of chemotherapy.

Complications Associated with Intraperitoneal Chemotherapy

The type of catheters employed varied within and among trials, and as seen in Table 4, complications associated with intraperitoneal chemotherapy were not consistently reported. Of the 24% to 75% of patients that were not able to complete the assigned intraperitoneal chemotherapy regimen, only the authors of the GOG 172 trial explicitly reported the number of patients who discontinued treatment due to catheter-related complications (8,16). Of the 119 patients that discontinued intraperitoneal treatment, catheter-related complications were either the primary (34%) or contributing factors (8%) behind the decision to cross-over to intravenous chemotherapy (8,16). In two other trials (11,14), at least 10% and 16% of patients experienced catheter-related complications requiring treatment discontinuation. Catheter-related complications included abdominal pain, bleeding, infection, peritonitis, catheter blockage, leakage, movement, malfunction, and/or access problems.

In one trial (8,16) whether or not the intraperitoneal catheter was placed during the primary surgery did not appear to be significant. On a related note, patients with left colon or rectosigmoid resection were less likely to initiate intraperitoneal chemotherapy than those not having the procedure (16% versus 5%; p=0.012), and were also less likely to complete all six cycles of intraperitoneal chemotherapy (34% versus 44%; p=not reported).
Table 4. Complications associated with intraperitoneal treatment.

<table>
<thead>
<tr>
<th>Author Year (Ref)</th>
<th>No. of pts.</th>
<th>Trt. arm</th>
<th>Patients with &lt;6 cycles of IP Chemo&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Catheter-related Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% of Catheter related complications</td>
<td>Pain</td>
</tr>
<tr>
<td>Armstrong 2006 (8,16)</td>
<td>205</td>
<td>IP</td>
<td>58%</td>
<td>34%</td>
</tr>
<tr>
<td>Markman 2001 (9)</td>
<td>235</td>
<td>IP</td>
<td>29%</td>
<td>NR</td>
</tr>
<tr>
<td>Yen 2001 (10)</td>
<td>55</td>
<td>IP</td>
<td>75%</td>
<td>NR</td>
</tr>
<tr>
<td>Gadducci 2000 (11)</td>
<td>57</td>
<td>IP</td>
<td>36%</td>
<td>16%</td>
</tr>
<tr>
<td>Polyzos 1999 (12)</td>
<td>44</td>
<td>IP</td>
<td>NR</td>
<td>11%</td>
</tr>
<tr>
<td>Alberts 1996 (13)</td>
<td>267</td>
<td>IP</td>
<td>42%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>Kirmani 1994 (14)</td>
<td>29</td>
<td>IP</td>
<td>24%</td>
<td>≥10%</td>
</tr>
</tbody>
</table>

Note. Ref, Reference; No. of pts., number of patients; #, number; trt., treatment; NR, not reported.
<sup>a</sup> percentages reflect the 119 patients who were unable to complete cycles of intraperitoneal chemotherapy.
<sup>b</sup> Patients who received all cycles of the planned cisplatin dose.

Quality of Life
Only one of the seven trials reported quality-of-life outcomes (8). With lower FACT-O scores representing a poorer quality of life, Armstrong et al (8) reported significantly lower scores for patients in the intraperitoneal chemotherapy versus patients in the intravenous chemotherapy treatment arm prior to randomization (106.4 versus 111.9, p=0.03), before the fourth cycle (103.3 versus 114.7, p<=0.001), and at 3 to 6 weeks after the sixth cycle (110.5 versus 118.4, p=0.009). The difference in quality of life scores was not significant between treatment groups at 12 months after the completion of the sixth cycle of chemotherapy (125.5 versus 127.2, p=0.56).

Systematic Review with Meta-analyses
Jaaback and Johnson (15) reported results of a comprehensive systematic review with meta-analyses using virtually the same data identified in the present review of the evidence. That review also included a small randomized trial of 20 patients (18) that was written in French, and therefore excluded from the present review. The authors concluded that intraperitoneal-containing chemotherapy improved progression-free and overall survival when compared to intravenous chemotherapy alone, however the toxicity and complications related to catheterization needed to be considered when deciding upon the most appropriate treatment for individual patients. The authors also concluded that there was insufficient information to address the optimal dose, timing or mechanism of administration from the available data.

DISCUSSION
The results from the seven randomized trials identified have shown that deriving conclusions regarding the role of intraperitoneal chemotherapy in treating women with epithelial ovarian cancer is complex. While not ideal, the methodological quality of the randomized trials was deemed to be adequate for the purpose of deriving conclusions around the role of intraperitoneal chemotherapy. Of the three larger and four smaller trials, the baseline patient characteristics were reported to be well-balanced between treatment groups, completeness of follow-up was greater than 80%, the power
and patient accrual to detect statistically significant differences between treatment groups was sufficient in the three larger trials, the intention-to-treat principle was employed in five trials, and there were data from six of the trials sufficient for pooling a clinically relevant outcome measure, overall survival. Overall, to derive conclusions based upon the evidence, the emphasis was placed largely on the results of the three larger trials that, in spite of differences in trial designs and treatment regimens, were adequately powered to detect statistically significant differences between treatment groups. It was also important to consider the results of the entire body of evidence in the context of the historical development of intraperitoneal chemotherapy tested in the randomized setting to date.

In 1994, the randomized trial by Kirimani et al (14) showed that intraperitoneal chemotherapy with cisplatin and etoposide was feasible, but the study was closed early because of poor patient accrual with the introduction of carboplatin and the local oncologic community preference for carboplatin-based chemotherapy at the time. Alberts et al (13) went on to detect a statistically significant overall survival benefit of eight months with intravenous cyclophosphamide and intraperitoneal cisplatin; however, only a little over half of the patients in either arm were able to complete all cycles of treatment due to toxicity, and the chemotherapy in the control group is not considered relevant by current standards (cisplatin combined with cyclophosphamide). In succession, Polyzos (12), Gaducci (11), and Yen (10) then published the results of three small trials showing that intraperitoneal chemotherapy was feasible with generally acceptable toxicity; however, no superiority over intravenous chemotherapy was detected. One of the trials did report that it was unlikely that patients with large residual disease volumes in any one area would benefit from a regional approach as compared to a systemic approach (12). Markman et al (9) then published results that intraperitoneal chemotherapy presented a modest treatment advance with a significant improvement in progression-free survival and borderline significant improvement in overall survival, but at the cost of greater toxicity. The authors concluded that this regimen should not be used as standard clinical practice due to the toxicity of intravenous carboplatin followed by intraperitoneal cisplatin and intravenous paclitaxel. That study did confirm the survival advantage of cisplatin administered as intraperitoneal chemotherapy as first detected in the trial by Alberts et al (13); however, it is also possible that the survival advantage was observed because a total of eight cycles of chemotherapy were delivered in the intraperitoneal chemotherapy arm as compared to six cycles of treatment in the intravenous chemotherapy-alone arm. Finally, in 2006, results from the GOG 172 trial reported by Armstrong et al (8) clearly showed the survival benefit associated with intraperitoneal chemotherapy. Even with only 42% of 205 patients completing all six cycles of intraperitoneal-containing chemotherapy, the 16-month improvement in median overall survival over intravenous chemotherapy alone was clinically meaningful in this patient population at high risk of recurrence. The limitations of that study were that the survival differences might be related to the extra dosing of intraperitoneal paclitaxel on day 8, and the fact that fewer than half of the patients were able to tolerate the treatment arm primarily because of either increased severe toxicity or catheter-related complications. It remains to be seen whether the survival benefit with this regimen occurs mostly within the first few cycles of intraperitoneal chemotherapy or if the benefit would have been greater had more patients completed all six cycles of treatment.

The significant median survival benefits reported in three of the larger randomized trials are consistent with the pooled analyses across three trials for five-year progression-free survival and across six trials for five-year overall survival. In spite of important trial differences, there was no statistically significant heterogeneity detected among trials in the pooled analyses. These data are also consistent with the results of the systematic review with meta-analyses reported by Jaaback and Johnson (15). This consistency, coupled with current clinical understanding and sound pharmacokinetics, provides the best evidentiary support available to derive conclusions regarding the efficacy of intraperitoneal chemotherapy. While clinically and statistically significant survival advantages have been detected with the use of intraperitoneal chemotherapy, there are several important reasons for the uncertainty surrounding the use of intraperitoneal chemotherapy as a standard practice for this patient population. One reason is that the optimal intraperitoneal chemotherapy regimen has yet to be defined. In the trial with the greatest survival benefits detected to date (8), grade 3 or 4 toxicity was much more common in patients who received intraperitoneal

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chemotherapy, and most patients (58%) were unable to complete the assigned cycles of treatment. It is possible that the increase in toxicity was due to the intraperitoneal dose of paclitaxel administered on day 8 after intraperitoneal cisplatin, but, even in the control arm with fewer adverse events, the severe toxicity associated with intravenous paclitaxel and cisplatin was still considerable. The same applies to the trial by Markman et al (9), but, in that trial, the increased toxicity in the treatment arm may have arisen from the additional two cycles of carboplatin (AUC=9) administered only to patients in the intraperitoneal treatment arm. As a better-tolerated agent in place of cisplatin, intravenous carboplatin AUC 5-6 is administered as first-line treatment in this patient population, and intravenous paclitaxel at 175 mg/m$^2$ is administered over three hours instead of over 24 hours as in the Armstrong and Markman studies (8,9) in order to reduce neurotoxicity. Historically, there was a lower response rate detected with intraperitoneal carboplatin compared to intraperitoneal cisplatin for small volume residual cancer (19). However, there is more recent literature on the use of higher doses of intraperitoneal carboplatin. In one study, a combination of intraperitoneal carboplatin with intravenous paclitaxel at 175 mg/m2 had an acceptable toxicity rate at AUC of 6 to 7. (20). Another study revealed that survival rates appeared to be higher among patients who received an intraperitoneal carboplatin dose of greater than 400 mg/m$^2$ compared to less than this threshold (21). There is also some suggestion that intraperitoneal carboplatin may be more efficacious than intravenous carboplatin (22), and so the use of intraperitoneal carboplatin may be an attractive substitution for intraperitoneal cisplatin. However, there have been no randomized comparisons between intraperitoneal cisplatin and carboplatin to date. Furthermore, the three trials showing a survival advantage in the present evidence series used intraperitoneal cisplatin. Thus, the role and optimal dose of intraperitoneal carboplatin are yet to be determined.

Secondly, the optimal patient population is still up for debate given that greatest benefits were seen in patients with residual disease volumes ≤ 1 cm in any one area. For patients with residual disease volumes greater than 1 cm, it is known that there is poor tumour penetration in bulky disease with intraperitoneal chemotherapy, but it is not known how this impacts upon survival outcomes. With intraperitoneal chemotherapy, there is also less exposure to extraperitoneal disease, but again, the impact upon survival outcomes is unknown.

Thirdly, there are important catheter-related complications and difficulties with implantation associated with intraperitoneal chemotherapy that patients and clinicians might be reluctant to accept. Alberts et al (23) suggested that complications such as fibrosis-sheath formation and small bowel obstruction or perforation can be reduced with the use of the Port-A-Cath designed for intravenous injection, and Armstrong et al (8) suggested that complications might be reduced with the standardization of the catheter device as well as the technique and timing of port implantation. In spite of potential future improvements to catheterization device and implantation, in the trial by Armstrong et al (8) catheter-related complications played a large role in patient’s decisions to cross over to intravenous chemotherapy (8,16). A review by Markman and Walker (25) provides practical guidance for the delivery of intraperitoneal chemotherapy. They report that venous and intraperitoneal access devices can be placed at the time of initial surgery (resection and staging laparotomy) provided that surgery is optimal and without complications, or alternately they can also be placed several weeks after initial surgery. The drug-delivery device should be a fully implantable port attached to a large single lumen venous silicone catheter, to avoid kinks and flow obstructions. In addition, peritoneal catheters with fenestrations and Dacron cuffs should not be used as they are associated with complications and are not removed easily in the office setting under local anesthesia. Specific issues around the delivery of intraperitoneal chemotherapy such as flushing the catheter with heparin, mixing and warming the chemotherapy, dealing with pain, hydration, and the assessment of peritonitis and/or gastrointestinal injury are further detailed in that review (24).

Overall, intraperitoneal chemotherapy is obviously a more complex therapy than intravenous chemotherapy but also one that confers an improved survival benefit in a patient population at high risk for disease recurrence.

CONCLUSIONS
As front-line therapy for patients with optimally debulked stage III ovarian cancer, the intravenous administration of a platinum agent and a taxane remains a standard of care. However, intraperitoneal cisplatin-containing chemotherapy resulted in a significant improvement in progression-free and overall survival when compared with intravenous platinum-based chemotherapy alone. The increased survival benefits seen with intraperitoneal chemotherapy must be weighed against increased toxicity and complication rates related to catheterization. The optimal disease volumes for front-line therapy are still open to debate, as are the optimal intraperitoneal chemotherapy regimens for front-line therapy. The greatest survival benefits to date were detected in patients with ≤ 1 cm of residual disease in any one area with 135 mg/m² of intravenous paclitaxel over 24 hours on day 1, 100 mg/m² of intraperitoneal cisplatin on day 2, and 60 mg/m² of intraperitoneal paclitaxel on day 8, repeated every 21 days for six cycles. On that schedule, however, only 42% of patients were able to complete all six cycles of the assigned treatment.

The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer is still emerging. Future research in the randomized setting should focus on the optimal patient population to receive treatment and the optimal intraperitoneal chemotherapy regimen, including the most appropriate agents, infusate volume, schedule, and dose. The role of intraperitoneal chemotherapy in various other patient populations with ovarian cancer such as those with early-stage high-risk disease should also be explored in a prospective fashion.

CONFLICT OF INTEREST
None declared.

JOURNAL REFERENCE
This material has been published as “Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. Elit L, Oliver TK, Covens A, Kwon J, Fung MF, Hirte HW, Oza AM. Cancer. 2007 Feb 15;109:692-702” © 2007 American Cancer Society; Publisher: Wiley-Liss, Inc.
DOI 10.1002/cncr.22466

ACKNOWLEDGEMENTS
The Gynecology DSG would like to thank the members of the working groups L. Elit, T. Oliver, A. Covens, J. Kwon, M. Fung-Kee-Fung, H. Hirte, and A. Oza for taking the lead in drafting this evidence series.

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

Funding
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Contact Information
For further information about this series, please contact:

Dr. Michael Fung Kee Fung, Chair, Gynecology Cancer Disease Site Group; Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario; Telephone: 613-737-8560, FAX: 613-737-8828.

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REFERENCES


THE PROGRAM IN EVIDENCE-BASED CARE
The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines
Each Evidence-Based Series is comprised of three sections.
- Section 1: Clinical Practice Guideline. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
Section 2: Systematic Review. This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

Section 3: Guideline Development and External Review: Methods and Results. This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This evidence-based series was developed by the Gynecology Cancer DSG of Cancer Care Ontario’s Program in Evidence-Based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel
Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodology issues. The Report Approval Panel gave formal approval of the document as written but did provide minor suggestions to consider. Aside from minor editorial and formatting comments, the Report Approval Panel suggested that it would be worthwhile to include a discussion of how the factors related to trial quality and characteristics influenced the conclusions derived from the DSG. The Panel also suggested that overall survival, which was included in the text, be added to the tables to help inform the reader, and a comment on the methodological aspects pertaining to the meta-analysis be added to the Discussion. In response, a section on the methodological assessment of the trials was added to the Discussion, five-year progression free and overall survival were added to the tables, and it was reported that, while presented, five-year progression-free and overall survival data were not study endpoints but were used mainly to pool results across trials. Finally, given the subtle shift in survival presentation, a comment was added to the Discussion on the information that comprised the evidentiary basis of this series, of which the meta-analysis was part.

External Review by Ontario Clinicians
Following the review and discussion of Sections 1 and 2 of this evidence-based series and the review and approval of the report by the PEBC Report Approval Panel, the Gynecology Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations developed by the panel.

| BOX 1: |
| DRAFT RECOMMENDATIONS (approved for external review April 26, 2006) |
| **Target Population** |
| These recommendations apply to women with stage III epithelial ovarian cancer for whom first-line chemotherapy after cytoreductive surgery is being considered. |
| **Recommendations** |
| • As front-line therapy, the intravenous administration of a platinum agent and a taxane remains a standard of care for this patient population. Cisplatin-containing intraperitoneal chemotherapy should be offered to patients on the basis of significant improvements in progression-free and overall survival when compared with cisplatin-containing intravenous |
chemotherapy alone.
- The survival benefits associated with intraperitoneal chemotherapy must be weighed against the statistically significant increases in toxicity and catheter-related complications.
  - For patients with residual tumour diameter ≤ 1 cm in any one area, significant survival benefits were detected with intraperitoneal chemotherapy.
  - For patients with disease volumes > 1 cm in any one area, the role of intraperitoneal chemotherapy is yet to be defined.
- The optimal intraperitoneal chemotherapy regimen has yet to be defined. The greatest median survival benefits were detected with intraperitoneal cisplatin and paclitaxel; however, only 42% of patients were able to complete all six cycles of the assigned treatment.

Methods
Practitioner feedback was obtained through a mailed survey of 221 practitioners in Ontario (radiation oncologists, surgeons, medical oncologists, gynecologists, and general practitioners). 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. The practitioner feedback survey was mailed out on April 28, 2006. Follow-up reminders were sent at two weeks (postcard) and four weeks (complete package mailed again).

Results
Seventy-six responses were received out of the 221 surveys sent. Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, forty indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>38 (95%)</td>
<td>2 (5.0%)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>36 (90.0%)</td>
<td>3 (7.5%)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>34 (87.2%)</td>
<td>5 (12.8%)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>36 (92.3%)</td>
<td>3 (7.7%)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>34 (85.0%)</td>
<td>3 (7.5%)</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>38 (95.0%)</td>
<td>2 (5.0%)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>34 (85.0%)</td>
<td>5 (12.5%)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely</td>
<td>Unsure</td>
<td>Not at all likely or unlikely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 (66.7%)</td>
<td>9 (23.1%)</td>
<td>4 (10.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Written Comments
Fourteen respondents provided written comments; the practitioners were either supportive of the recommendations and the guideline overall, or were concerned that the body of evidence was not sufficient to endorse intraperitoneal chemotherapy as a standard treatment option.
Modifications/Actions
The concern of some practitioners over the body of evidence in this evolving treatment approach is a valid one; however, large survival benefits have been detected in the randomized setting, and almost all of the practitioners who responded to the survey (Table 1) agreed with the draft recommendations as stated. With those considerations in mind, the Gynecology Cancer DSG concluded that no changes to the document were needed.

Conclusion
This report reflects the integration of feedback obtained through the external review process with final approval given by the Gynecology Cancer DSG and the Report Approval Panel of the Program in Evidence-based Care. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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REFERENCES


Guideline review outcomes definitions.

1. ARCHIVED - An archived document 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 the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. 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.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. 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.