CONTEXT AND POLICY ISSUES

In 2012, there were an estimated 2,600 new cases of ovarian cancer in Canada with an incidence rate of 11 cases per 100,000 individuals. Furthermore, the total estimated deaths caused by ovarian cancer were 1,750 with a mortality rate of 7 cases per 100,000 individuals. Given that more than half of epithelial ovarian cancer patients present with extra-pelvic metastasis, the majority of these cases are incurable. The current standard primary treatment for advanced epithelial ovarian cancer consists of surgical debulking followed by platinum and taxane based intravenous (IV) therapy.

Intraperitoneal (IP) chemotherapy, an alternate form of chemotherapy administration, entails the infusion of the chemotherapeutic agent directly into the peritoneal cavity where tumours are often localized for most of their natural history. Intraperitoneal chemotherapy allows for the administration of higher drug concentrations that directly target tumours, avoiding systemic adverse events caused by IV administration.

The limitations of IP chemotherapy include the requirement of experienced medical oncologists and nurses who possess the technical expertise and knowledge of managing IP catheter complications. Intraperitoneal chemotherapy is unable to target the lymphatic and venous system where the cancer may spread. Moreover, IP administration is limited to treating microscopic or small volume residual disease after debulking surgery as it typically only penetrates 1 to 2 millimeters of the outer surface of the tumour.

This report is an update to a CADTH Rapid Response dated August 2009 which concluded that chemotherapy regimens including an IP component improved overall survival and progression-free survival compared to IV chemotherapy in patients with advanced epithelial ovarian cancer. Since 2009, new scientific literature has been published and these will be summarized and appraised to provide policy makers with updated information on the clinical effectiveness,
RESEARCH QUESTIONS

1. What are the comparative clinical benefits and harms of intraperitoneal versus intravenous chemotherapy for the treatment of ovarian cancer?

2. What is the cost-effectiveness of intraperitoneal versus intravenous chemotherapy for the treatment of ovarian cancer?

3. What are the evidence-based guidelines regarding the use of intraperitoneal chemotherapy for patients with ovarian cancer?

KEY FINDINGS

This update concurs with the conclusions from the 2009 Rapid Review in which chemotherapy regimens that included an IP component improved overall survival and progression-free survival compared to IV chemotherapy in patients with advanced epithelial ovarian cancer. No new evidence for the cost-effectiveness of IP chemotherapy was found since the previous Rapid Review. Guidelines for the administration of IP chemotherapy were inconsistent with three recommending the use of IP chemotherapy and one recommending against its use in patients with ovarian cancer.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid Medline, PubMed, The Cochrane Library (2013, Issue 3), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and April 19, 2013.

Selection Criteria and Methods

One reviewer screened citations to identify publications that met the inclusion criteria. Potentially relevant articles were retrieved based on the review of titles and abstracts. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1. Rapid Response reports are organized so that the evidence for each research question is presented separately.
Table 1: Selection Criteria

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients with ovarian cancer who are undergoing chemotherapy</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Chemotherapy using an intraperitoneal delivery system</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Chemotherapy using an intravenous delivery system</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Q1. Patient survival, comparative effectiveness for cancer treatment,</td>
</tr>
<tr>
<td></td>
<td>comparative safety/adverse events,</td>
</tr>
<tr>
<td></td>
<td>Q2. Cost-effectiveness, cost-utility of intraperitoneal chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Q3. Guidelines for use of intraperitoneal chemotherapy</td>
</tr>
<tr>
<td><strong>Study Designs</strong></td>
<td>HTA/ Systematic review/Meta-analysis, Randomized controlled trials, Economic evaluation, Evidence based clinical practice guidelines</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, or were full text articles published prior to January 2009. Health technology assessments, meta-analyses, systematic reviews and guidelines were excluded if there was incomplete reporting of methods or if they were superseded by a more recent or more rigorous review or guideline. Randomized controlled trials (RCTs) were excluded if they were described in a systematic review included in this report. Economic evaluations were excluded if they were not cost-effectiveness or cost-utility analyses.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. The methods used when conducting the literature search, study selection, quality assessment, data extraction, and summarizing the data were appraised for systematic reviews. Systematic reviews were appraised using the AMSTAR instrument and evidence-based clinical practice guidelines were appraised using the AGREE II instrument.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 202 citations. Upon screening titles and abstracts, 191 citations were excluded and 11 potentially relevant articles were retrieved for full-text review. 10 additional potentially relevant reports were retrieved from the grey literature and by hand search. Of the 21 potentially relevant reports 16 were excluded. One systematic review and four sets of evidence-based clinical practice guidelines published after 2009 met the inclusion criteria. No economic evaluations were found. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Clinical studies

One systematic review was retrieved and is described in Appendix 2.
The systematic review by Jaaback and colleagues (2011) included nine RCTs, published between 1986 and 2009, consisting of 2119 ovarian cancer patients comparing IP to IV chemotherapy in women with advanced ovarian cancer. The reported outcomes of this systematic review included overall survival, disease-free survival, adverse events, and quality of life (QOL). This publication is an update of a previous systematic review performed in 2006 which was included in the 2009 CADTH rapid response. The update included one new trial (Yen et al. 2009).

For the purpose of this review, an overall summary of the findings of Jaaback and colleagues (2011) is provided with more emphasis placed on the updated trial.

**Economic evaluations**

No new evidence for the cost-effectiveness of IP chemotherapy was found.

**Evidence-based guidelines**

The evidence-based clinical practice guidelines were published between 2009 and 2013. One guideline was Canadian from the Alberta Provincial Gynecologic Oncology Tumour Team, while the other three were international: National Institute for Health and Care Excellence (NICE, United Kingdom), the Association of Comprehensive Cancer Centres (ACCC, Netherlands), and National Comprehensive Cancer Network (NCCN) (United States).

**Summary of Critical Appraisal**

Study strengths and limitations are presented in Appendix 3.

**Clinical studies**

The systematic review by Jaaback and colleagues was well designed and of high methodological quality. The authors used rigorous methods to search, select, appraise and synthesize the studies. An ‘a priori’ design was provided and two independent data extractors were used for the study selection. A comprehensive literature search was performed which included grey literature. A list of both included and excluded studies was provided. Of the included nine RCTs, six were rated higher quality based on the Cochrane risk of bias tool, while 3 were rated lower quality. The key limitations of the lower quality studies were the uncertainties regarding selection, detection and attrition bias.

The newly included trial by Yen and colleagues (2009) randomized 367 patients with stage III ovarian cancer and the data of 298 of these participants were analyzed. The participants were randomized to either IP versus IV cisplatin or carboplatin after giving all IV paclitaxel. A total of 146 participants in the IP group received 3 hours of paclitaxel (175mg/m²) on day one, 100 mg/m² cisplatin or 300 mg/m² of carboplatin administered by IP on day two. The regimen was continued every 3 weeks for 6 cycles. A total of 152 participants in the IV group received the same regimen but the 100 mg/m² cisplatin or 300 mg/m² carboplatin on day two was administered by IV. Mathematical modeling was used to calculate overall survival from cytoreductive surgery to the last follow-up or disease specific death. This study had an overall low risk of bias, as they were only uncertain about the trial’s allocation concealment and blinding of outcome assessment.
Evidence-based guidelines

All four included clinical practice guidelines were of high methodology quality. The guidelines for intraperitoneal chemotherapy for ovarian cancer from the Alberta Provincial Gynecologic Oncology Tumour Team\(^5\) properly identified the scope and purpose, rigour of development, applicability and editorial independence. The presentation of the guidelines was clear. However, the authors did not mention the views and preferences of the target population and the strength of evidence and grade of recommendations were not provided.

The NICE guidelines\(^2\) were of high quality and properly identified the scope, purpose and stakeholder involvement. The authors provided a clear description of the methods for formulating recommendations, identified strengths and limitations of the body of evidence, and discussed health benefits, side effects and risks of intraperitoneal chemotherapy. Different options for the management of ovarian cancer were presented and key recommendations were easily identifiable. The authors clearly described the applicability of the recommendations. The strength of evidence and grade of recommendations were both provided.

Both the ACCC\(^6\) and NCCN\(^7\) guidelines clearly described the scope, purpose, applicability and editorial independence. Both were clearly presented, but lacked detail regarding the rigour of development and stakeholder involvement. Specifically, both guidelines did not mention the views and preferences of ovarian cancer patients. The systematic methods used to search the evidence and the criteria for selecting the evidence were not clearly stated in the NCCN guidelines. Both the NCCN and ACCC guidelines did not provide the procedure for updating their respective guidelines. The strength of evidence and grade of recommendations were both provided in the ACCC\(^6\) and NCCN\(^7\) guidelines.

Summary of Findings

Clinical studies

The overall results from the meta-analysis from Jaaback and colleagues\(^3\) suggest that the administration of a component of IP chemotherapy for the initial management of epithelial ovarian cancer improved both overall survival and disease-free survival (Appendix 4). Eight of the nine RCTs provided data for the meta-analysis for overall survival (n=2026, HR 0.81, 95% confidence interval [CI]: 0.72 to 0.90), while five of the nine trials provided data for disease-free survival (n=1311, hazard ratio [HR] 0.78, 95%CI: 0.70 to 0.86). Intraperitoneal chemotherapy was associated with more adverse effects such as pain (three trials, n=1235, risk ratio [RR] 7.47, 95%CI: 4.41 to 12.67), fever (five trials, n=1797, RR 1.64, 95% CI: 1.13 to 2.38), infection (three trials, n=1171, RR 3.34, 95%CI: 2.06 to 5.43), metabolic complications (two trials, n=873, RR 4.45, 95% CI: 2.72 to 7.26), and gastrointestinal adverse effects (five trials, n=1339, RR 1.71, 95% CI: 1.28 to 2.26), when compared to IV chemotherapy. In the one RCT published since 2009\(^9\), mathematical modeling results revealed improved survival (odds ratio [OR] 2.14, 95% CI: 1.93 to 2.41, P=0.02) in favour of IP therapy.

Evidence-based guidelines

Four evidence-based clinical practice guidelines were retrieved and are summarized in Appendix 5.
The NCCN guidelines recommend IP chemotherapy for patients with stage III optimally debulked (<1 cm residual) disease. They also state that IP chemotherapy can be used for stage II patients, although there is no published randomized evidence. The following IP regimen is recommended: day 1: paclitaxel (135 mg/m² of continuous IV infusion over 24 hours); day 2: cisplatin (75-100 mg/m² IP) after IV paclitaxel; day 8: paclitaxel (60mg/m² IP); repeat every 3 weeks times 6 cycles. The authors recommend 6 to 8 cycles for stage II to IV patients, and 3 to 6 cycles for earlier-stage patients. Patients should have normal renal function prior to starting IP or IP/IV treatment with no previous medical conditions that could worsen during chemotherapy. IV hydration prior to IP chemotherapy may also prevent renal toxicity.7

The Alberta Provincial Gynecologic Oncology Tumour Team5 guidelines identify IP chemotherapy as a preferred option for advanced ovarian cancer (stage III/IV). They recommend optimal debulking with an adjuvant IP chemotherapy regimen: day 1: cisplatin (75 mg/m² IP) + paclitaxel (135 mg/m² IV); day 8: paclitaxel (60 mg/m² IP), repeat every 3 weeks times 6 cycles. The authors state that if patients are hypersensitive to paclitaxel, docetaxel (75 mg/m² IV) can be used as a substitute. Single agent carboplatin [dose at area under the curve (AUC) 5 or 6 IV] and/or dose reduction is strongly recommended if toxicity develops.5

The NICE guidelines clearly state that patients with stage II to IV ovarian cancer should not be offered IP chemotherapy, except as part of a clinical trial. The authors believe that although recent evidence has confirmed the feasibility of administering paclitaxel by the IP route, significant immediate toxicities have been reported and further research is needed.2

The ACCC guidelines state that for patients with stage III ovarian carcinoma who have had a complete or optimal debulking (residual IP residual lesions, <1 cm), it is plausible to advise the IP regimen used by Armstrong and colleagues.10 These guidelines highlight that IP treatment should be performed in a centre with expertise in IP chemotherapy. Since IP chemotherapy is associated with substantial toxicity, treatment should be restrained if there is an increased risk of anastomotic leakage.6

Limitations

Six of the nine included RCTs were of high quality in the systematic review. The meta-analyses revealed heterogeneity for the differences between interventions for haematological adverse events, anaemia, thrombocytopenia, leukopenia, renal, neurological and pulmonary adverse events. Furthermore, the chemotherapy regimens that were compared among the IP and IV groups were not equivalent in most of the included RCTs. The results of survival and adverse effects should therefore be interpreted with caution. There was also uncertainty regarding blinding of outcome assessment in six of the nine included trials.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The conclusions of this update are in concordance with those from the 2009 Rapid Response.4 Limited evidence suggests that the use of IP chemotherapy increases overall survival and progression-free survival among advanced ovarian cancer patients. IP chemotherapy is associated additional pain, fever, infection, metabolic complications and gastrointestinal adverse effects when compared to IV chemotherapy. These adverse effects need to be considered when determining the most appropriate method of chemotherapy for the patient. It is still not evident whether the benefits seen with IP compared to IV administration are due to different routes of
administration, or if they are caused by chemotherapy doses. No conclusions can be made on the cost-effectiveness of IP versus IV chemo due to the absence of economic studies. Guidelines for the administration of IP chemotherapy revealed inconsistencies regarding its recommended use. Further research addressing IP versus IV chemotherapy may help to reduce uncertainty and provide further insight on the optimal dose, timing and mechanism of administration.

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REFERENCES


APPENDIX 1: Selection of Included Studies

202 citations identified from electronic literature search and screened

11 potentially relevant articles retrieved for scrutiny (full text, if available)

10 potentially relevant reports retrieved from other sources (grey literature, hand search)

21 potentially relevant reports

16 reports excluded:
- irrelevant study design (4)
- irrelevant comparator (1)
- irrelevant outcomes (5)
- already included in at least one of the selected systematic reviews (2)
- other (review articles, editorials) (4)

5 reports included in review
APPENDIX 2: Characteristics of Included Systematic Review

<table>
<thead>
<tr>
<th>Author, year, funding source</th>
<th>Key inclusion criteria, N studies</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Jaaback et al., 2011<sup>3</sup> | RCTs (cut-off May 2011); assessing women with a new diagnosis of primary epithelial ovarian cancer 9 RCTs (2119 patients) | • Intraperitoneal chemotherapy  
• Intravenous chemotherapy | • Overall survival  
• Disease-free survival  
• Adverse events  
• QOL |

RCT = randomized controlled trial, QOL = quality of life
## APPENDIX 3: Critical Appraisal of Systematic Reviews and Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td><strong>Systematic reviews</strong></td>
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</table>
| Jaaback et al., 2011³ | • High quality systematic review  
• Comprehensive literature search was performed  
• The scientific quality of included studies was assessed  
• Independently extracted by two reviewers  
• Appropriate methods were used to assess statistical heterogeneity in each meta-analysis | • No major limitations |
| **Clinical Practice Guidelines** | | |
| National Comprehensive Cancer Network (NCCN), 2013, United States⁷ | • Scope and purpose properly described  
• Very clear presentation  
• Applicability well described  
• Strength of evidence and grade of recommendation are provided. | • Rigour of development is not properly described and lacks detail |
| Alberta Provincial Gynecologic Oncology Tumour Team, 2013, Canada⁵ | • Strengths and limitations clearly described  
• Clearly described methods for formulation recommendations  
• Explicit links between supporting evidence and recommendations  
• Externally reviewed by experts  
• Guideline updating procedure provided  
• Very clear presentation  
• Applicability well described | • Views and preferences of ovarian cancer patients not sought  
• Strength of evidence and grade of recommendation not provided. |
| National Institute for Health and Care Excellence (NICE), 2011, United Kingdom² | • Systematic methods were used to search evidence  
• Clearly described criteria for selecting evidence  
• Strengths and limitations clearly described  
• Clearly described methods for formulation recommendations  
• Considered health benefits, side effects, and risks  
• Explicit links between supporting evidence and recommendations  
• Externally reviewed by experts  
• Guideline updating procedure provided | • No major limitations |
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td></td>
<td>provided</td>
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<tr>
<td></td>
<td>• High quality clinical practice guidelines</td>
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<td></td>
<td>• Scope and purpose properly described</td>
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<td></td>
<td>• Stakeholder involvement is properly identified</td>
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<td></td>
<td>• Very clear presentation</td>
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<tr>
<td></td>
<td>• Applicability well described</td>
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</tr>
<tr>
<td></td>
<td>• Strength of evidence and grade of recommendation are provided.</td>
<td></td>
</tr>
<tr>
<td>Association of Comprehensive Cancer Centres (ACCC), 2009, Netherlands⁶</td>
<td>• Scope and purpose properly described</td>
<td>• Uncertainty regarding stakeholder involvement</td>
</tr>
<tr>
<td></td>
<td>• Very clear presentation</td>
<td>• The procedure for updating the guideline is not transparent</td>
</tr>
<tr>
<td></td>
<td>• Applicability well described</td>
<td>• Rigour of development lacks detail</td>
</tr>
<tr>
<td></td>
<td>• Strength of evidence and grade of recommendation are provided.</td>
<td></td>
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</tbody>
</table>
APPENDIX 4. Summary of Findings from Jaaback et al., 2011

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of trials</th>
<th>Number of participants (n)</th>
<th>IP vs IV chemotherapy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>8</td>
<td>2026</td>
<td>HR 0.81 (0.72 to 0.90)</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>5</td>
<td>1311</td>
<td>HR 0.78 (0.70 to 0.86)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td>1235</td>
<td>RR 7.47 (4.41 to 12.67)</td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
<td>1797</td>
<td>RR 1.64 (1.13 to 2.38)</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>1171</td>
<td>RR 3.34 (2.06 to 5.43)</td>
</tr>
<tr>
<td>Metabolic complications</td>
<td>2</td>
<td>873</td>
<td>RR 4.45 (2.72 to 7.26)</td>
</tr>
<tr>
<td>Gastrointestinal AE’s</td>
<td>5</td>
<td>1339</td>
<td>RR 1.71 (1.28 to 2.26)</td>
</tr>
</tbody>
</table>

AE= adverse effect; CI=confidence interval; HR= hazard ratio; RR= risk ratio
### APPENDIX 5. Summary of Recommendations from Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Recommendation</th>
<th>Rating of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network (NCCN), 2013, United States</td>
<td>For patients with stage III optimally debulked (&lt;1 cm residual) disease, the following IP regimen is recommended: day 1: paclitaxel (135 mg/m² of continuous IV infusion over 24 hours); day 2: cisplatin (75-100 mg/m² IP) after IV paclitaxel; day 8: paclitaxel (60 mg/m² IP); repeat every 3 weeks × 6 cycles.</td>
<td>Strong recommendation based on high quality systematic reviews and RCTs</td>
</tr>
<tr>
<td>Alberta Provincial Gynecologic Oncology Tumour Team, 2013, Canada</td>
<td>For stage III/IV epithelial ovarian cancer, optimal debulking with an adjuvant IP chemotherapy regimen can be used: day 1: cisplatin (75 mg/m² IP) + paclitaxel (135 mg/m² IV); day 8: paclitaxel (60 mg/m² IP), every 3 weeks × 6 cycles.</td>
<td>Not provided</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (NICE), 2011, United Kingdom</td>
<td>Patients with stage II to IV ovarian cancer should not be offered IP chemotherapy, except as part of a clinical trial</td>
<td>Strong recommendation based on high quality systematic reviews and RCTs</td>
</tr>
<tr>
<td>Association of Comprehensive Cancer Centres (ACCC), 2009, Netherlands</td>
<td>For patients with stage III ovarian carcinoma who have had a complete or optimal debulking (residual IP residual lesions, &lt;1 cm), the following IP chemotherapy regimen can be applied: day 1: paclitaxel (135 mg/m² IV); day 2: cisplatin (100 mg/m² IP); day 8: paclitaxel (60 mg/m² IP), repeat every 3 weeks × 6 cycles.</td>
<td>Strong recommendation based on high quality systematic reviews and RCTs</td>
</tr>
</tbody>
</table>

IP=intraperitoneal; IV=intravenous; RCT=randomized controlled trial