Evidence tables:

**Author(s):** Jaaback and Johnson (2006)

**Design:** (Cochrane) Systematic Review with meta-analyses  
**Country:** N/A

**Included population:** Women of any age with a new diagnosis of primary ovarian cancer (of any FIGO stage) requiring chemotherapy following cytoreductive surgery.

**Included studies:** Randomised controlled trials (RCT) comparing chemotherapy that included a component of intraperitoneal (i.p.) administration with standard intravenous (i.v.) chemotherapy.

**Excluded studies:** RCTs of treatment with radio-labelled monoclonal antibodies, matrix metalloproteinase inhibitors, immunomodulators, vascular growth factors, radio isotopes, biologic therapy, gene therapy or radio colloids. Trials in which the participants had recurrent disease.

**Population:** N=1,819 (no patient demographics reported)

**Interventions and comparators in included studies:**

- **Kirmani et al., 1994 (N=62) Stage: IIc-IV**  
  Intraperitoneal: Cisplatin 200 mg per m$^2$ i.p; etoposide 350 mg per m$^2$ i.p. q 4 wks x 6  
  Intravenous: Cisplatin 100 mg per m$^2$ i.v; cyclophosphamide 600 mg per m$^2$ q 3 wks x 6

- **Alberts et al., 1996 (SWOG 8501 per GOG 104 (N=546) Stage: III, <2 cm residual**  
  Intraperitoneal: Cisplatin 100 mg per m$^2$ i.p; cyclophosphamide 600 mg per m$^2$ i.v. q 3 wks x 6  
  Intravenous: Cisplatin 100 mg per m$^2$ i.v; cyclophosphamide 600 mg per m$^2$ i.v. q 3 wks x 6

- **Polyzos et al., 1999 (N=90) Stage: III**  
  Intraperitoneal: Carboplatin 350 mg per m$^2$ i.p; cyclophosphamide 600 mg per m$^2$ i.v. q 3 wks x 6  
  Intravenous: Carboplatin 350 mg per m$^2$ i.v; cyclophosphamide 600 mg per m$^2$ i.v. q 3 wks x 6

- **Gadducci et al., 2000 (N=113) Stage: I-IV, <2 cm residual**  
  Intraperitoneal: Cisplatin 50 mg per m$^2$ i.p; cyclophosphamide 600 mg per m$^2$ i.v; epidoxorubicin 60mg per m$^2$ i.v. q 4 wks x 6  
  Intravenous: Cisplatin 50 mg per m$^2$ i.v; cyclophosphamide 600 mg per m$^2$ i.v; epidoxorubicin 60 mg per m$^2$ i.v. q 4 wks x 6

- **Markman et al., 2001 GOG 114 per SWOG 9227 (N=462) Stage: III, <1cm residual**  
  Intraperitoneal: Carboplatin (AUC9) i.v. q 28 days x 2; cisplatin 100 mg per m$^2$ i.p; paclitaxel 135 mg per m$^2$ (24 hr) i.v. q 3 wks x 6  
  Intravenous: Cisplatin 75 mg per m$^2$; i.v. paclitaxel 135 mg per m$^2$ (24 hr) i.v. q 3 wks x 6

- **Yen et al., 2001 (N=118) Stage: III, <1cm residual**  
  Intraperitoneal: Cisplatin 100 mg per m$^2$; i.p. cyclophosphamide 500mg per m$^2$ i.v; epidoxorubicin or doxorubicin 50 mg per m$^2$ i.v. q 3 wks x 6  
  Intravenous: Cisplatin 50 mg per m$^2$ i.v; cyclophosphamide 50mg per m$^2$ i.v; epidoxorubicin or doxorubicin 50 mg per m$^2$ i.v. q 3 wks x 6

- **Armstrong et al., 2002. GOG 172 (N=415) Stage: III, <1cm residual**  
  Intraperitoneal: Paclitaxel 135 mg per m$^2$ (24 hr) i.v; cisplatin 100 mg per m$^2$ i.p; paclitaxel 60
mg per m² i.p. on day 8 q 3 wks x 6
Intravenous: Cisplatin 75 mg per m² i.v; paclitaxel 135 mg per m² (24 hr) i.v. q 3 wks x 6

- Zylberberg et al., 1986. (N=20) Stage: III
  Intraperitoneal: Cisplatin i.v; doxorubicin i.v; fluorouracil i.v; bleomycin i.v; vinorelbine i.v;
  ifosfamide i.v; cisplatin i.p; doxorubicin i.p; fluorouracil i.p; bleomycin i.p; vinorelbine i.p. q 4 wks x10
  Intravenous: Cisplatin i.v; doxorubicin i.v; fluorouracil i.v; bleomycin i.v; vinorelbine i.v;
  ifosfamide i.v. q 4 wks x10

1Abbreviations: SWOG - Southwest Oncology Group; GOG - Gynecologic Oncology Group; i.p. - intraperitoneal; i.v. - intravenous

**Outcomes:**

Primary outcomes: Time to death, time to relapse.
Secondary outcome: Adverse effects.

**Results:**

Time-to event outcomes (time to death or relapse) were reported as hazard ratios (HR) and dichotomous outcomes (adverse effects) as relative risk (RR). Where no significant heterogeneity existed between combined studies, data were analysed using a fixed effects model but where heterogeneity exceeded I² > 25%, data were analysed by a random effects model. All analyses compared intraperitoneal therapy with intravenous therapy hence HR <1 favour intraperitoneal therapy but RR (adverse effects) >1 favour intravenous therapy.

- **Time to death (reported in 7 trials (5 high quality))** See GRADE profile
- **Time to relapse (reported in 4 trials (3 high quality))** See GRADE profile
- **Grade 3 or 4 adverse effects (reported in up to 7 trials)** See GRADE profile

**Follow-up:**

Follow-up periods ranged between 46 and 74 months with the majority >60 months.

**Notes:**

This moderate quality paper reviewed eight RCTs of intraperitoneal vs. intravenous chemotherapy for women with newly diagnosed ovarian cancer who had undergone cytoreductive surgery. Only two of the trials were conducted in a single centre whereas the remainder involved from two to forty participating centres each. The majority of studies were from the USA. Two authors searched The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, TRIP, the Gynaecological Cancer Review Groups Specialised Registers and others for relevant studies. Details of the search strategy were presented. Hand searching of gynaecological journals was also conducted and journal authors contacted for elaboration where required. Papers were selected, reviewed and data were extracted by two independent researchers and disagreements were resolved by discussion. Each trial was assessed for bias with respect to methods of randomisation, allocation, blinding (of the outcome assessors) loss to follow-up and intention-to-treat analyses. Overall quality was then judged on these parameters and five studies were found to be of high quality whilst three were judged to be of low quality.
Most study participants had stage III disease but some (N=200) were eligible for inclusion if staged II-IV. Only three from eight RCTs compared the same drug regimes between arms such that any observed differences in outcomes in those studies could be fairly said to be due to the delivery route. The remainder of the studies used different regimes with respect to drug, dose or both thus frustrating a true comparison between arms. In addition, the drug combinations have changed over time and only two of the more recent studies have used platins with a taxane, albeit in different doses.

The review authors did not present a comprehensive summary of treatment withdrawals but presented data that were not available from six of the included studies. Using these it is possible to show that the probability of trial participants receiving all the scheduled treatment cycles was significantly higher for patients assigned to intravenous therapy compared with those on intraperitoneal chemotherapy: OR 2.0 (95% C.I: 1.6-2.4) P<0.0001. Loss to follow-up was not reported and, as this is an important consideration in assessing study quality, all studies were downgraded for GRADE evaluation.

Meta-analyses were conducted, pooling data from two or more of the included trials to assess all outcomes with the exception of quality of life which was reported by only one study. With regard to many of the adverse effects outcomes, it was noted that the data may have been unsuitable for pooling due to the variable treatment regimes used by different studies. The resultant high between-studies heterogeneity resulted in wide confidence intervals around point estimates of effect size. In addition, many patients receiving intraperitoneal chemotherapy had been given relatively high drug doses and therefore might be expected to have experienced more serious side effects which may explain the large effect sizes for some outcomes. The combination of low event rates with large effect sizes but wide confidence intervals (that crossed both the line of ‘no effect’ and a point that could be considered as indicating ‘appreciable harm’ or ‘appreciable benefit’) render these results statistically and clinically of little value.

**Included studies**


**Author(s):** Elit et al. (2007)

**Design:** Systematic Review with meta-analyses  
**Country:** Canada

**Included population:** Women of any age with stage III ovarian cancer.

**Included studies:** Randomised controlled trials (RCT) comparing first line intraperitoneal-containing chemotherapy with first line intravenous chemotherapy.

**Excluded studies:** RCTs of treatment involving immunomodulators, intraperitoneal radioactive phosphorus or hypothermia. Trials reported in non-English language or those from which data could not be extracted.

**Population:** N=1,806 (no patient demographics reported)

**Intervention(s) and comparator(s):**


**Outcomes:**

Primary outcomes: Overall survival (5yrs), progression-free survival (5yrs).  
Secondary outcomes: Toxicity, catheter-related complications, quality of life (QOL).

**Results:**

Dichotomous outcomes (survival, progression-free survival at 5 years) were reported as relative risk (RR). Data were analysed using a random effects model regardless of the presence or absence of between studies heterogeneity ($I^2$). All analyses compared intraperitoneal therapy with intravenous therapy where RR <1 favours intraperitoneal therapy and RR >1 favour intravenous therapy. Five trials reported intention-to-treat analyses either on eligible patients or on the whole study population.

- **Overall survival at 5 years (reported in 6 trials):** See GRADE profile
• **Progression-free survival at 5 years (reported in 3 trials):** See GRADE profile

• **Toxicity:** Reported in Jaaback and Johnson (2006).

• **Catheter-related complications:** The type of catheters used were described in six studies as: ‘implantable’ (N=1) Tenckhoff (N=2) Port-A-Cath (N=2) or ‘temporary’ (N=1). Across the six studies, 24% to 75% of patients did not complete the scheduled program of intraperitoneal-containing therapy. In one study (Armstrong *et al.*, 2006) 34% of the 119 patients discontinuing intraperitoneal chemotherapy did so primarily due to catheter-related complications and for a further 8% of women it was a contributory factor. Complications included abdominal pain, bleeding, infection, peritonitis, catheter blockage, leakage, movement, malfunction and/or access problems. This specific outcome was not reported in the remainder of the trials.

• **Quality of life (QOL) (reported in 1 trial):** Only one trial (GOG-172) monitored QOL. The outcomes were reported in detail by Wenzel *et al.* (2007).

**Follow-up:**

Follow-up periods ranged between 46 and 74 months with the majority >60 months. In six out of seven trials, completeness of follow-up was reported to exceed 80%.

**Notes:**

This moderate quality paper reviewed seven RCTs of intraperitoneal vs. intravenous chemotherapy for women with stage III ovarian cancer. There is a very high overlap of studies (N=6) between this review and that of Jaaback and Johnson (2006) but since the survival outcomes are reported in a different way, the evidence may be complementary.

Only one of the trials was conducted in a single centre whereas the remainder involved from two to forty participating centres each. The majority of studies were from the USA. An unknown number of reviewers searched The Cochrane Library, MEDLINE, EMBASE, Physician Data Query Database, the Canadian Medical Association Infobase, the National Guidelines Clearinghouse and others for relevant studies. Details of the search strategy were given very briefly.

Most study participants had stage III disease but some (N=175) were eligible for inclusion if staged II-IV. Only three from eight RCTs compared the same drug regimes between arms such that any observed differences in outcomes in those studies could be fairly said to be due to the delivery route. The remainder of the studies used different regimes with respect to drug, dose or both thus frustrating a true comparison between arms. In addition, the drug combinations have changed over time and only two of the more recent studies have used platins with a taxane, albeit in different doses.

Papers were selected, reviewed and data were extracted by an unknown number of researchers. A detailed analysis of study quality was given for the included papers but there was no formal grading of studies such as is performed for a Cochrane review. However, those papers selected for GRADE reporting were assessed for quality by Jaaback and Johnson (2006) and these criteria have been used with data from this study.

**Included studies**

**Author(s):** Wenzel et al. (2007)

**Design:** Randomised controlled trial

**Country:** United States of America

**Inclusion criteria:** Women with histologically confirmed stage III epithelial ovarian cancer or primary peritoneal cancer who, after surgical debulking, had no residual disease >1cm in diameter.

**Exclusion criteria:** None stated

**Population:** N=399.

**Intervention(s) and comparator(s):**

Intraperitoneal-containing chemotherapy: Paclitaxel 135 mg per m$^2$ (24 hr) i.v.; Cisplatin 100 mg per m$^2$ i.p.; Paclitaxel 60 mg per m$^2$ i.p. on day 8 q 3 weeks x 6.

Intravenous chemotherapy: Cisplatin 75 mg per m$^2$ i.v., Paclitaxel 135 mg per m$^2$ (24 hr) i.v. q 3 weeks x 6.

**Outcomes:** Health related quality of life (HRQOL).
Quality of life assessments were completed by consenting patients at four time points: before randomisation, before chemotherapy cycle 4, between 3 to 6 weeks after all treatment and 12 months after all treatment. HRQOL was measured by means of the following scales:

Functional Assessment of Cancer Therapy–Ovarian (FACT-O) which includes a 27 item FACT-General (FACT-G) questionnaire plus 12 items targeted specifically at ovarian cancer patients (FACT-O subscale). FACT-G includes sub-scales of well-being (physical, social, emotional and functional). Two further outcomes (pain and neurotoxicity) are not reproduced here since the data were included in the above mentioned meta-analyses.

**Results:**

- **Health-related quality of life:** See GRADE profile.

**Follow-up:** N/A

**Notes:**

This paper presents data collected during the GOG-172 trial which was reported by Armstrong et al. (2006) other outcomes of which were included in the systematic reviews and meta-analyses of Jaaback and Johnson (2006) and Elit et al. (2007). This study is concerned only with the results of health-related quality of life (HRQOL) measurements. The quality of the trial itself was considered to be high with respect to design and reporting (see Jaaback and Johnson, 2006).

Compared with those on conventional, lower dose, intravenous chemotherapy, women receiving high drug doses of intraperitoneal chemotherapy reported worse QOL both at baseline before randomisation, before the 4th chemotherapy cycle and three to six weeks after completion of chemotherapy. However, one year post-treatment there were no differences in QOL measurements between study groups.