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Evidence-Based Series 4-13 Version 3

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

# Adjuvant Care for Stage I Ovarian Cancer

*Members of the Gynecology Cancer Disease Site Group*

**An assessment conducted in November 2025 deferred the review of Evidence-based Series (EBS) 4-13 Version 3. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)**

**EBS 4-13 Version 3 is comprised of 3 sections. You can access the summary and full report here:**
**https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/646**

**Section 1: Clinical Practice Guideline (ENDORSED)**
**Section 2: Systematic Review**
**Section 3: Document Assessment and Review**

**March 15, 2022**

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## Guideline Report History

| GUIDELINE VERSION | SYSTEMATIC REVIEW | | PUBLICATIONS | NOTES and KEY CHANGES |
|---|---|---|---|---|
| | Search Dates | Data | | |
| Original 2004 | 1965 to May 2003 | Full Report | Peer review publication. Web publication. | N.A. |
| Version 2 May 2016 | 2003 to December 1 2015 | New data found in Section 3: Document Summary and Review Tool (APPENDIX A) | Updated web publication | 2004 Recommendations are ENDORSED |
| Current Version 3 March 2022 | 2015 to December 31 2021 | No new data was found. See Section 3 Document Assessment and Review | Updated web publication | 2004 Recommendations are ENDORSED |

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**Evidence-based Series 4-13 Version 3: Section 1**

# A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) Developed by the Gynecology Cancer Disease Site Group

# Adjuvant Care for Stage I Ovarian Cancer: Guideline Recommendations

*L. Elit, A. Fyles, A. Chambers, M. Fung Kee Fung, A. Covens, M. Carey, and members of the Gynecology Cancer Disease Site Group.*

**These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.**
**Please see Section 3: Document Assessment and Review for a summary of updated evidence published between 2003 and 2022, and for details on how this Clinical Practice Guideline was ENDORSED**

**Report Date: March 15, 2022**

**Guideline Questions**

1. What is the role of adjuvant care in women with completely surgically staged stage I ovarian cancer?
2. What is the role of adjuvant care in women who receive incomplete or no surgical staging of ovarian cancer?
3. What is the optimal strategy for adjuvant care in women with ovarian cancer?

**Target Population**

These recommendations apply to women with newly diagnosed stage I ovarian cancer.

**Recommendations**

- The stage of ovarian cancer is an important prognostic factor that influences survival and the choice of therapy. The quality of the surgical staging is a key determinant of treatment recommendations (*Draft Evidence Summary "#4-15 Management of an Ovarian Mass" will further describe optimal surgical staging*).
- Women who have undergone optimal surgical staging, including pelvic and para-aortic lymph node sampling, and have stage I disease may or may not benefit from adjuvant platinum-based chemotherapy (see Qualifying Statements section below).
- Women who have not undergone optimal surgical staging can be offered two options. The first option is that they undergo re-operation to optimally define the tumour stage and then be offered adjuvant therapy based on the findings. The other option is that they be offered platinum-based chemotherapy to decrease the risk of recurrence and improve survival.

- There is insufficient evidence to make a recommendation on the role of adjuvant pelvic radiation, whole abdominal-pelvic radiotherapy, or intraperitoneal radioactive chromic phosphate.

**Qualifying Statements**

- Accurate staging and tumour histology information is essential for developing recommendations on the management of ovarian cancer. A tumour pathology causing doubt should be reviewed by an expert.
- The standard of care for stage IA and IB grade I ovarian cancer in Ontario has been surgical resection with optimal staging and no adjuvant therapy. This standard is based on the work by Young et al[1] involving non-optimally staged, stage I cancer and the prognostic studies by Vergote et al[2] that reported an extremely low probability of recurrence in this population.
- The results of the largest trial comparing adjuvant chemotherapy to no chemotherapy in women with early stage ovarian cancer (International Collaborative Ovarian Neoplasm Study/Adjuvant ChemoTherapy In Ovarian Neoplasm [ICON/ACTION] Trial) are controversial because:
  - A subgroup analysis of the ACTION Trial showed no benefit from adjuvant chemotherapy in women who underwent optimal surgical staging, but that analysis was underpowered.
  - The entry criteria for the ICON Trial were vague and did not reflect the standard of surgical care offered in Canadian centres.
  - The meta-analysis included in this practice guideline demonstrates that stage I patients have an improved outcome with adjuvant chemotherapy. However, an estimated 90% of women undergoing surgical resection for ovarian cancer do not undergo optimal surgical staging. If the restaging of a sub-optimally staged patient reveals a more advanced disease, chemotherapy is the preferred treatment option. If reoperation confirms stage I disease, there is insufficient evidence for or against adjuvant chemotherapy. The treatment decision must be based on a discussion with the patient about potential benefits and risks.

**Methods**

Entries to MEDLINE (1965 through May 2003), CANCERLIT (1975 through October 2002), and Cochrane Library (2003, Issue 1) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2003) were systematically searched for evidence relevant to this practice guideline report.

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

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

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

**Key Evidence**

- Twenty-five randomized controlled trials were identified that compare treatments for stage I ovarian cancer. Eight of the studies reported results for stage I patients only.
- The randomized trials compared a variety of adjuvant therapies (chemotherapy, radiotherapy, and surgery), making it difficult to form recommendations on the optimal adjuvant therapy.
- Eleven randomized controlled trials reported at least minimal surgical staging.
- The majority of patients in the five randomized controlled trials comparing adjuvant chemotherapy to no chemotherapy did not receive lymphadenectomy as part of their surgical staging. The pooled results for stage I patients indicated a survival benefit with the addition of chemotherapy (relative risk, 0.71; 95% confidence interval, 0.56 to 0.90; p=0.005), and there was a benefit in terms of reduced recurrence favouring adjuvant chemotherapy (relative risk, 0.62; 95% confidence interval, 0.47 to 0.80; p=0.0003).
- A subgroup analysis of one randomized controlled trial demonstrated that if lymph node sampling is not conducted as part of the staging surgery then adjuvant chemotherapy is favoured in terms of overall survival (relative risk, 0.71; 95% confidence interval, 0.54 to 0.92).
- The largest trial to date randomized 925 women with stage I ovarian cancer to receive either adjuvant chemotherapy or no adjuvant chemotherapy. Platinum-based adjuvant chemotherapy was reported to improve overall five-year survival (absolute survival difference,8%; 95% confidence interval, 2% to 12%; hazard ratio, 0.67; 95% confidence interval 0.50 to 0.90; p=0.008).
- The most frequently reported adverse effects associated with chemotherapy were grade 3 or 4 vomiting/nausea and grade 3 or 4 leukopenia.

**Future Research**

Future research needs to evaluate the implementation of surgical staging as a means of avoiding the use of chemotherapy in women who may not require toxic therapy. The role of adjuvant therapy in women with poor prognostic factors who are optimally staged needs to be assessed. The optimal chemotherapy regimen in terms of agents, dose, and duration has yet to be defined.

**Related Guidelines**

1. Practice Guidelines Initiative Practice Guideline Report #4-1-2: *First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer*.
2. Practice Guidelines Initiative Evidence Summary Report #4-3: *Chemotherapy for Recurrent Epithelial Ovarian Cancer Previously Treated with Platinum*.
3. Practice Guidelines Initiative Draft Evidence Summary Report #4-15: *Management of an ovarian mass (in progress)*.

**References**


1. Young RC, Walton LA, Ellenberg SS, Homesley HD, Wilbanks GD, Decker DG, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. *N Engl J Med* 1990;322:1021-7. [31]
2. Vergote I, Vergote-De Vos LN, Abeler VM, Aas M, Lindegaard MW, Kjorstad KE, et al. Randomized trial comparing cisplatin with radioactive phosphorus or whole-abdomen irradiation as adjuvant treatment of ovarian cancer. *Cancer* 1992;69:741-9. [43]

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*The Practice Guidelines Initiative is sponsored by:*
*Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.*
*Visit http://www.cancercare.on.ca/access_PEBC.htm for all additional Practice Guidelines Initiative reports.*

## PREAMBLE: About our Practice Guideline Reports

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

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

Reference

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

**For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:**
**http://www.cancercare.on.ca/access_PEBC.htm**
**For more information, contact our office at:**
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Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

**Evidence-based Series 4-13 Version 3: Section 2**

# A quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) Developed by the Gynecology Cancer Disease Site Group

# Adjuvant Care for Stage I Ovarian Cancer: Systematic Review

*L. Elit, A. Fyles, A. Chambers, M. Fung Kee Fung, A. Covens, M. Carey, and members of the Gynecology Cancer Disease Site Group.*

**These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.**
**Please see Section 3: Document Assessment and Review for a summary of updated evidence published between 2003 and 2022, and for details on how this Clinical Practice Guideline was ENDORSED**

**Report Date: May 3, 2004**

## I. QUESTIONS

1. What is the role of adjuvant care in women with completely surgically staged stage I ovarian cancer?
2. What is the role of adjuvant care in women with ovarian cancer who receive incomplete or no surgical staging?
3. What is the optimal strategy for adjuvant care in women with ovarian cancer?

## II. CHOICE OF TOPIC AND RATIONALE

Ovarian cancer is the fifth leading cause of death from cancer in Canadian women (1). There will be an estimated 1,050 new cases of ovarian cancer diagnosed in Ontario in 2003 (1). Approximately 50% of women diagnosed with ovarian cancer will die of their disease (2). Most of these high grade serous tumours probably originate in the fallopian tube (3). Currently, the standard of care for malignant epithelial ovarian cancer (EOC) is surgery followed by adjuvant chemotherapy (4). Approximately 27% of women present with cancer confined to the ovary (stage I), and their five-year survival is 85% (5).

There is controversy concerning the benefits of adjuvant therapy in women with stage I disease because the most effective treatment for early stage ovarian cancer has not been established. The concern is that women may be overtreated, thus having to manage the adverse effects of potentially unnecessary treatments.

Surgery is necessary for diagnosis (including determining the origin of the disease), identifying the histologic type of disease, and defining the extent of intra-abdominal disease (i.e., staging). The disease stage at diagnosis is a major determinant of prognosis. Unfortunately, there is evidence that some women are not being appropriately staged and optimally debulked, which impacts their survival (6-8).

**Surgical Staging**

The elements of surgical staging have been discussed in eight consensus statements or practice guidelines (9-16). The National Institutes of Health (NIH) surgical consensus statement (15) is the most widely endorsed guideline in the gynecologic and gynecologic oncology communities. The NIH statement is based on a critical review of the literature, a process of consensus by 25 experts in the field, and consumer feedback. All the guidelines or consensus statements recommend a standard surgical procedure for women with EOC. The European Organization for Research and Treatment of Cancer (EORTC) has recently outlined four categories describing the quality of the surgery (9) (Table 1). This terminology will be used when describing the surgery for the studies discussed in this document.

**Table 1. EORTC staging data (9).**

| | | |
|---|---|---|
| 1 | Optimal | Complete staging (European Guidelines for Staging Ovarian Cancer); lymph node sampling instead of radical lymphadenectomy |
| 2 | Modified | Everything between 1 and 3 |
| 3 | Minimal | Careful inspection and palpation of all peritoneal surfaces and biopsies of suspected lesions and washings and omentectomy |
| 4 | Inadequate | Careful inspection and palpation of all peritoneal surfaces and biopsies of suspected lesions |

The pivotal issue for making a treatment decision with a patient who has stage I ovarian cancer involves whether or not she has had complete surgical staging. In an assessment of the NIH guidelines, Munoz et al (17) reported that only 10% of women with presumptive stage I disease had the recommended staging of the 785 women with ovarian cancer selected from the 1991 National Cancer Institute's Surveillance, Epidemiology and End Results (NCI SEER) Program. Young et al (18) reported the implications of incomplete surgical staging in an Ovarian Cancer Study Group project. Only 25 of 100 women with stage Ia to IIb ovarian cancer had an adequate surgical incision to completely assess the abdomen. Systematic restaging surgery revealed that 31% of the women had more advanced disease. Thus, those patients who do not have systematic surgery in early stage ovarian cancer may be understaged.

To determine the optimal management of women with early stage ovarian cancer, one first needs to assess whether the study population is stratified by completeness of surgical staging or not. Given that only 10% of women have had complete surgical staging, 90% of stage I women have had incomplete surgical staging. Therefore, the physician must determine whether a repeat operation is warranted (19). That decision is usually based on the patient's age and other co-morbidities (such as cardiac or respiratory status, performance status, etc.). In the situation where a repeat operation is not done, radiological investigations (ultrasound, computed tomography scan, and/or positron emission tomography scan) are used as a surrogate to assess the risk of residual disease. Other factors that have been used to assign a poor prognosis include: degree of differentiation* (20,21), clear cell histology*, large volume ascites*, ascites that is positive for malignancy (22), vegetations, dense adhesions*, International Federation of Gynecology and Obstetrics (FIGO) substage rupture before surgery (22), bilaterality (22), aneuploidy (20), CA125 greater than 65 u/ml, mitosis, necrosis, anisocaryosis, Bax negative (23), p53 positive, Ki67 positive, HER2 (human epidermal growth factor receptor 2) positive (24), high microvessel density (25), and Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor Receptor (EGFR), or Cox-2 positive (26). Some of these prognostic factors* have significant shortcomings, due to their subjectivity, lack of reproducibility, and low prognostic power (27). Vergote et al (22) have addressed the prognostic importance of the classic clinical and pathologic features of 1,545 stage I patients and have

found that the only factors that were strong and independent predictors of disease-free survival were degree of differentiation, rupture before or during surgery, FIGO stage, and age. In cases of incomplete surgery, Vergote et al's (22) list of poor prognostic factors may help guide the surgeon concerning re-operation versus chemotherapy.

This practice guideline was developed concurrently with a Gynecology Cancer Disease Site Group (DSG) evidence summary on the management of women presenting with an ovarian mass. The goal of these two documents is to provide practitioners with guidance and information, from diagnosis to treatment, on the optimal management of a woman with an ovarian mass. The aims of this practice guideline are to describe the adjuvant therapies available to women with early stage ovarian cancer and to offer guidance on the optimal adjuvant therapy available.

## III. METHODS

### Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (28). Evidence was selected and reviewed by three members of the PGI's Gynecology Cancer DSG and methodologists. Members of the Gynecology Cancer DSG disclosed potential conflict of interest information.

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

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

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

### Literature Search Strategy

MEDLINE (1965 through May 2003), CANCERLIT (1975 through October 2002), and the Cochrane Library (2003, Issue 1) databases were searched. "Neoplasms, ovarian" (Medical subject heading (MeSH)) was combined with each of the following terms: "early stage" or "stage I", "chemotherapy" (MeSH), "surgery" (MeSH), and "radiotherapy" (MeSH). These terms were then combined with the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized controlled trials (RCTs) comparing two or more adjuvant setting treatments (chemotherapy, radiotherapy, and/or surgery) in women with stage I ovarian cancer.

**Synthesizing the Evidence**

The practice guideline outlines RCTs that included stage I patients. There have been major methodological concerns with some of these studies, and attention will be drawn to those areas (i.e., inclusion of patients in stage II and III with minimal residual disease). Only those studies where the information on outcome of stage I patients can be determined will be included in the final analysis.

To estimate the overall effect on survival of the treatments for early stage ovarian cancer, mortality data (the number of patients who had died during the study and the number of patients included in the survival analysis by the investigators) were abstracted from the published reports of individual RCTs and pooled using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview © Update Software). Only stage I results were pooled in the analysis; thus, only studies that separated the results for stage I patients were included in the analysis. Combining data in this manner assumes a constant hazard ratio of risks for the groups being compared. Results are expressed as relative risks (also known as risk ratios) with 95% confidence intervals (CI), where a relative risk (RR) for mortality less than one indicates that the experimental treatment improved survival compared with the control treatment. Conversely, a relative risk greater than one suggests that patients in the control group experienced lower mortality. The relative risk is calculated by taking the ratio of the proportion of patients who have died in the experimental treatment group to the proportion of patients who have died in the control group. The random-effects model was used for comparative testing of the pooled results across studies in preference to the fixed-effects model, as the more conservative estimate of effect (29).

## IV. RESULTS

### Literature Search Results

#### *Practice Guidelines/Consensus Statements*

Eight existing practice guidelines or consensus statements were identified that provided recommendations for the management of early stage ovarian cancer (9-16). None of the eight guidelines or consensus statements was explicitly evidence-based, although all were presumably informed by the evidence. Table 2 outlines the recommendations of the guidelines and consensus statements.

**Table 2. Existing guideline and consensus statement recommendations regarding adjuvant therapy for women with early stage ovarian cancer.**

| Guideline/ Consensus | Recommendation for adjuvant therapy | |
|---|---|---|
| | Adjuvant therapy **not** recommended | Adjuvant therapy recommended |
| EORTC, 2003 (9) | Did not specify which patients should receive adjuvant therapy | |
| ESMO, 2001 (10) | Did not specify when adjuvant therapy would not be recommended. | • Poorly differentiated stage Ia, Ib (consider chemotherapy)<br>• Stage Ic (chemotherapy regimen not specified) |

| | | |
|---|---|---|
| SOR, 2001 (11) | Stage Ia, grade 1 | • Stage Ia, grade 2,3, Ib, Ic, IIa (no standard treatment, options include platinum-based chemotherapy, external beam radiation, or no adjuvant therapy) |
| SOGC, 2000 (12) | Did not specify which patients should receive adjuvant therapy | |
| SSO, 1997 (13) | Did not specify which patients should receive adjuvant therapy | |
| NCCN, 1996 (14) | Stage Ia, Ib, grade 1 | • Stage Ia, Ib, grade 2, 3 (paclitaxel + cisplatin or carboplatin)<br>• Stage Ic (paclitaxel + cisplatin or carboplatin) |
| NIH, 1994 (15) | Stage Ia, Ib, grade 1 | • All grade 3<br>• Clear cell histology<br>• Most stage Ic (chemotherapy regimen not specified) |
| ACOG, 1991 (16) | Stage I, borderline | • Poorly differentiated<br>• Stage Ia, Ib, grade 2, 3, stage Ic (single or multiagent)<br>• Stage I, grade 3 (multiagent) |

Note: ACOG, American College of Obstetricians and Gynecologists; EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NIH, National Institutes of Health; SGO, Society of Gynecologic Oncologists; SOGC, Society of Obstetricians and Gynaecologists of Canada; SOR, Standards, Options & Recommendations; SSO, Society of Surgical Oncology.

### *Randomized Controlled Trials*

Twenty-five published RCTs were identified that compared treatments for early stage ovarian cancer. Two publications each reported two separate randomized trials (30,31). Another four RCTs had three treatment arms (32-35). One RCT compared conservative with more extensive surgery (36). Two RCTs compared radiotherapy with no adjuvant treatment (32,37). Seven RCTs compared an adjuvant chemotherapy regimen with no adjuvant chemotherapy (9,20,30-33,38). Another five RCTs compared adjuvant chemotherapy with radiotherapy (32,33,39-41). Four RCTs were identified that compared an adjuvant chemotherapy regimen with intraperitoneal (IP) radioactive chromic phosphate ($^{32}P$) (30,31,42,43). Four RCTs compared two different forms of adjuvant chemotherapy (44-47). The remaining four RCTs compared various treatments (48-51). Table 3 outlines the RCTs included in the practice guideline.

**Table 3. Randomized controlled trials comparing treatments for early stage ovarian cancer.**

| Study | FIGO Stage | # Patients | Treatment A | Treatment B | Median Follow-up (months) |
|---|---|---|---|---|---|
| ***Comparison of surgical procedures*** | | | | | |
| Benedetti-Panici, 1996 (abstract) (36) | early stage | 94 | node sampling | pelvic and para-aortic node dissection | NR |
| ***Adjuvant radiotherapy versus no radiotherapy*** | | | | | |
| Dembo, 1979 (37) | stage Ia | 41 | pelvic RT | no treatment | NR |
| Hreshchyshyn, 1980 (32) | stage I | 52 | pelvic RT | no treatment | 36 |
| ***Adjuvant chemotherapy versus no chemotherapy*** | | | | | |

| Study | FIGO Stage | # Patients | Treatment A | Treatment B | Median Follow-up (months) |
|---|---|---|---|---|---|
| ACTION, 2003 (9) | stage Ia,Ib grade 2,3<br>stage Ic, IIa<br>stage I, IIa with clear cell cancer | 448 | platinum-based chemotherapy | no treatment | 59 |
| ICON1, 2003 (38) | stage I, II, III | 477 | platinum-based chemotherapy | no treatment | 51 |
| Trope, 2000 (20) | stage I, grade 2-3, grade 1 aneuploid or clear cell | 162 | carboplatin | no treatment | 46 |
| Bolis, 1995 (30) | stage Ia, Ib, grade 2-3 | 83 | cisplatin | no treatment | 76 |
| Young, 1990 (31) | stage Ia, Ib gr 1,2 | 81 | melphalan | no treatment | > 72 |
| Gronroos, 1984 (33) | stage I | 75 | CT | no treatment | (overall 36 months) |
| Hreshchyshyn, 1980 (32) | stage Ia, Ib | 63 | melphalan | no treatment | 36 |
| ***Adjuvant chemotherapy versus radiotherapy*** | | | | | |
| Chiara, 1994 (39) | stage I-II | 69 | cisplatin | WAR | 60 |
| Redman, 1993 (40) | stage Ic-III | 40 | cisplatin | WAR | 84 |
| Gronroos, 1984 (33) | stage I | 65 | CT | pelvic RT | (overall 36 months) |
| Hreshchyshyn, 1980 (32) | stage I | 57 | melphalan | pelvic RT | 36 |
| Smith, 1975 (41) | stage I-III | 149 | melphalan | WAR | NR |

Note: ACTION, Adjuvant ChemoTherapy In Ovarian Neoplasm; CT, chemotherapy; ICON, International Collaborative Ovarian Neoplasm Study; NR, not reported; RT, radiotherapy; WAR, whole abdominal radiation.

**Table 3 continued. Randomized controlled trials comparing treatments for early stage ovarian cancer.**

| Study | FIGO Stage | # Patients | Treatment A | Treatment B | Median Follow-up (months) |
|---|---|---|---|---|---|
| ***Adjuvant chemotherapy versus IP $^{32}P$*** | | | | | |
| Young, 1999 (abstract) (42) | high risk, stage I-II | 205 | cyclophosphamide+ cisplatin | $^{32}P$ | 72 |
| Bolis, 1995 (30) | stage Ia2, Ib2, Ic | 152 | cisplatin | $^{32}P$ | 76 |
| Vergote, 1992 (43) | stage Ia-III | 340 | cisplatin | $^{32}P$ | 62 |
| Young, 1990 (31) | stage I, grade 2-3, stage II, grade 2-3 | 141 | melphalan | $^{32}P$ | > 72 |
| ***WAR versus pelvic radiation and chemotherapy*** | | | | | |
| Sell, 1990 (52) | stage Ib, Ic, IIa, IIb | 118 | cyclophosphamide + pelvic RT | WAR | NR |
| Klaassen, 1988 (34) | stage Ia-IIb | 257 | melphalan + pelvic RT | $^{32}P$ + pelvic RT / WAR | 96 |
| Dembo, 1979 (35) | stage Ib, II, III | 190 | chlorambucil + pelvic RT + | pelvic RT / WAR | NR |
| ***Two different forms of adjuvant chemotherapy*** | | | | | |
| Bell, 2003 (abstract) (45) | stage Ia, Ib, grade 3 stage Ic clear cell stage II (completely resected) | 321 | three cycles of paclitaxel + carboplatin | six cycles of paclitaxel + carboplatin | 54 |
| Marth, 2000 (44) (abstract) | stage Ic-IIIc | 148 | cyclophosphamide+ cisplatin + interferon | cyclophosphamide+ cisplatin | NR |
| Hatae, 1998 (abstract) (46) | stage Ia | 96 | IV CT | oral CT | 19 |
| Murphy, 1993 (47) | stage Ic, II, III, IV | 99 | 6 cycles CT | 12 cycles CT | 26 |
| ***Other RCT comparisons*** | | | | | |
| Fyles, 1998 (51) | stage I-III | 125 | RT 22.5 Gy | RT 27.5 Gy | 78 |
| Davy, 1985 (50) | stage I-II | 301 | Thiotepa + IP radiation | IP radiation | NR |
| Khoo, 1984 (48) | stage I-IV | 140 | levamisole + RT + melphalan | placebo + RT + melphalan | (overall 48 months) |
| Kolstad, 1977 (49) | stage I-III | 418 | RT | $Au^{198}$ | NR |

Note: $^{32}P$, radioactive chromic phosphate; $Au^{198}$, radioactive gold; CT, chemotherapy; IP, intraperitoneal; IV, intravenous; NR, not reported; RT, radiotherapy; WAR, whole abdominal radiation.

Table 4 outlines the surgical procedures that the study participants underwent prior to randomization. Only RCTs that indicated their surgical procedures are included in the table. Of the nineteen RCTs that included details of surgical staging, eleven met at least the minimum requirements identified by EORTC for surgical staging.

**Table 4. Details of surgery prior to randomization of patients.**

| Study | Treatment | Stage I Patients (%) | TAH + BSO, omenectomy | Laparotomy (vertical incision) | Tumour capsule examined | Peritoneal washings | Biopsies of suspicious lesions | Pelvic & para-aortic node sampling | EORTC Staging Classification |
|---|---|---|---|---|---|---|---|---|---|
| ACTION, 2003 (9) | CT vs no CT | 415 (92%) | ✓[a] | - | ✓ | ✓[a] | ✓ | ✓[a] | Optimal |
| ICON1, 2003 (38) | CT vs no CT | 441 (92%) | ✓ | - | - | - | - | - | Inadequate |
| Trope, 2000 (20) | CT vs no CT | 162 (100%) | ✓ | ✓ | ✓ | ✓ | ✓ | - | Modified |
| Fyles, 1998 (51) | RT vs RT | 43 (34%) | ✓ | - | - | - | - | - | Modified |
| Bolis, 1995 (30) | CT vs no CT | 235 (100%) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | Modified |
| Chiara, 1994 (39) | CT vs WAR | 47 (68%) | ✓[a] | - | - | - | ✓[a] | - | Modified[a] |
| Murphy, 1993 (47) | CT vs CT | 13 (13%) | ✓[b] | - | - | - | - | - | Inadequate |
| Redman, 1993 (40) | CT vs RT | 7 (18%) | ✓ | - | - | - | - | - | Minimal |
| Vergote, 1992 (43) | CT vs $^{32}$P | 265 (78%) | ✓ | ✓ | - | - | ✓ | - | Minimal |
| Sell, 1990 (52) | RT + CT vs WAR | 49 (42%) | ✓ | - | - | - | - | - | Minimal |
| Young, 1990 (31) | CT vs no CT | 223 (78%) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | Modified |
| Klaassen, 1988 (34) | CT + RT vs $^{32}$P + RT vs WAR | 127 (49%) | ✓ | - | - | - | - | - | Inadequate |
| Davy, 1985 (50) | RT vs RT + CT | NR | ✓ | - | - | - | - | - | Minimal |
| Gronroos, 1984 (33) | CT vs no CT | 65 (100%) | ✓ | - | - | - | - | - | Inadequate |
| Hreshchyshyn, 1980 (32) | CT vs no CT | 86 (100%) | ✓ | - | - | - | - | - | Inadequate |
| Dembo, 1979 (35) | RT vs WAR vs RT + CT | NR | ✓ | - | - | - | - | - | Inadequate |
| Kolstad, 1977 (49) | RT vs Au$^{198}$ | 258 (62%) | ✓ | - | - | - | - | - | Modified |
| Smith, 1975 (41) | CT vs WAR | 42 (28%) | ✓ | - | - | - | - | - | Inadequate |

Note: $^{32}$P, radioactive chromic phosphate; ACTION, Adjuvant ChemoTherapy In Ovarian Neoplasm; Au$^{198}$, radioactive gold ; BSO, bilateral salpingo-oophorectomy; CT, chemotherapy; ICON, International Collaborative Ovarian Neoplasm Study; BSO, bilateral salpingo-oophorectomy; NR, not reported; RT, radiotherapy; TAH, total abdominal hysterectomy; vs, versus; WAR, whole abdominal radiation.

[a]Procedures were recommended, not required.

[b]BSO or biopsy or BSO + omenectomy

*Comparison of surgical procedures*

Only one RCT was identified that compared two forms of surgery, which have been assessed for therapeutic value (36). Benedetti-Panici (36) published an abstract of a multicentre randomized Italian study comparing systematic versus selective lymphadenectomy from 1992 to 1996. The systematic staging arm included extensive para-aortic and pelvic lymphadenectomy. The interim analysis suggested no difference in terms of relapse rate, disease-free survival (DFS), and crude survival between the treatment groups. The Gynecology Cancer DSG was unable to locate a full publication of the results of that 1996 abstract.

*Adjuvant radiotherapy versus no adjuvant radiotherapy*

Two RCTs compared adjuvant radiotherapy to no adjuvant radiotherapy in women with stage I ovarian cancer (32,37) (Table 5). In a small RCT, Dembo et al (37) compared 27 women who received no adjuvant radiotherapy (observation) to 27 women who received pelvic radiation at 45 cGy in 20 fractions. There was no benefit in terms of relapse; however, its small size meant the study was not sufficiently powered to detect a clinically meaningful difference between treatment groups. Hreshchshyn et al's (32) RCT compared three treatment arms: adjuvant chemotherapy, adjuvant radiotherapy, and no adjuvant therapy. Seventeen percent of the patients receiving no adjuvant therapy had a recurrence compared to 30% of the patients receiving adjuvant radiotherapy ($p<0.05$). A study limitation was that, although 168 patients were recruited for the study, 82 patients were excluded (49%) because they were judged to have a tumour of low malignant potential, they refused the prescribed treatment, or they were removed by their physician. When those patients were removed from the analysis, the treatment arms were no longer matched with respect to prognostic factors; therefore, the results were not internally valid (32). Also, that study was conducted prior to the development of guidelines on surgical staging; thus, patients may have been understaged, as the upper abdomen and retroperitoneum were not formally assessed for disease.

**Table 5. Survival of patients in RCTs comparing adjuvant radiotherapy to no radiotherapy.**

| Study | Treatment | # of patients | Survival | |
|---|---|---|---|---|
| Dembo, 1979 (37) | Pelvic RT | 41 | Overall survival 87%. There is no difference between treatment groups. | |
| | No treatment | | | |
| Hreshchyshyn, 1980 (32) | Pelvic RT | 23 | Recurrence rate 30% | p<0.05 |
| | No treatment | 29 | Recurrence rate 17% | |

Note: RT, radiotherapy.

*Adjuvant chemotherapy versus no adjuvant chemotherapy*

Seven RCTs compared adjuvant chemotherapy to no adjuvant chemotherapy in women with stage I ovarian cancer (Table 6). All seven RCTs that compared adjuvant chemotherapy to no adjuvant therapy reported surgical staging details (9,20,30-33,38).

**Table 6. Survival of patients in RCTs comparing adjuvant chemotherapy to no treatment.**

| Study | Treatment | # of patients | Overall survival (5 yr) | | Disease-free survival (5 yr) | |
|---|---|---|---|---|---|---|
| ACTION, 2003 (9) | Platinum-based CT | 224 | 85% | HR 0.69 95% CI 0.44-1.08 p=0.10 | RFS 68% | HR 0.63 95% CI 0.43-0.92 p=0.02 |
| | No treatment | 224 | 78% | | RFS 76% | |
| ICON1, 2003 (38) | Platinum-based CT | 241 | 79%r | HR 0.66 95% CI 0.45-0.97 p=0.03 | RFS 73% | HR 0.65 95% CI 0.46-0.91 p=0.01 |
| | No treatment | 236 | 70% | | RFS 62% | |
| Trope, 2000 (20) | Carboplatin | 81 | DSS 86% | HR 0.94 95% CI 0.37-2.36 | 70% | HR 0.98 95% CI 0.52-1.83 |
| | No treatment | 81 | DSS 85% | | 71% | |
| Bolis, 1995 (30) | Cisplatin | 41 | 88% | p=NS | NR | |
| | No treatment | 44 | 82% | | | |
| Young, 1990 (31) | Melphalan | 38 | 98% | p=0.43 | 98% | p=0.41 |
| | No treatment | 43 | 94% | | 91% | |
| Gronroos, 1984 (33) | CT | 38 | 74.1% 2 yr | p=0.02 | NR | |
| | No treatment | 37 | 95.8% 2 yr | | | |
| Hreshchyshyn, 1980 (32) | Melphalan | 34 | Recurrence rate 6% | | | p<0.05 |
| | No treatment | 29 | Recurrence rate 17% | | | |

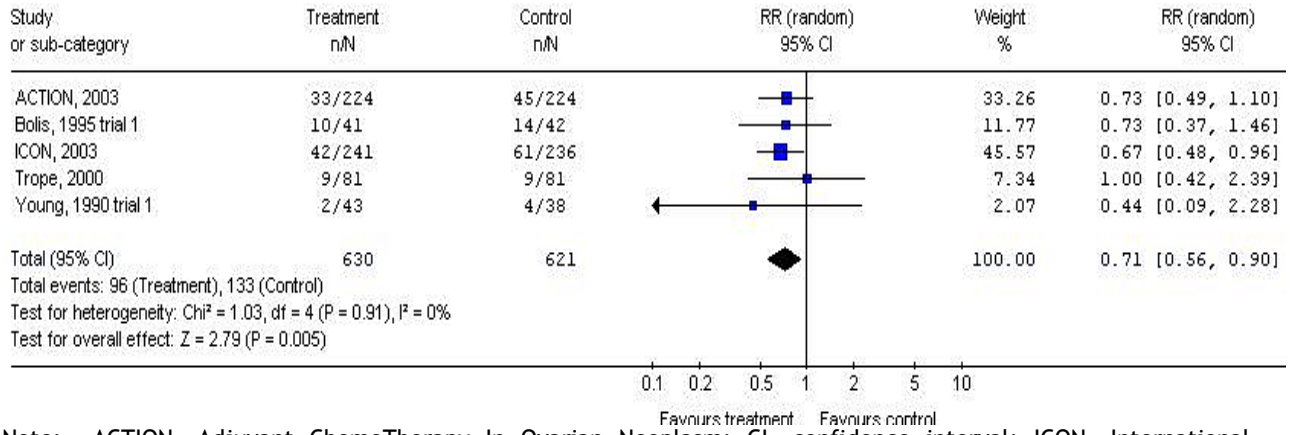
Note: ACTION, Adjuvant ChemoTherapy In Ovarian Neoplasm; CI, confidence interval; CT, chemotherapy; DSS, disease specific survival; HR, hazard ratio; ICON, International Collaborative Ovarian Neoplasm Study; NR, not reported; NS, not statistically significant; RFS, recurrence-free survival; yr, year.

*Survival*

The Gynecology Cancer DSG performed a meta-analysis of the RCTs that compared adjuvant chemotherapy to no chemotherapy on survival. The RCT by Hreshchyshyn et al (32) was omitted from the analysis because 49% of the randomized patients did not receive the management to which they were randomized, due to patient refusal and physician preference for treatment. When these patients were removed from the analysis, the treatment arms were no longer matched with respect to prognostic factors; therefore, the results were biased. The RCT by Gronroos et al (33) was also excluded because the RCT had three treatment arms, the chemotherapy regimens described are not the standard of care today, and patients with all stages of disease were included in randomization.

The results of the remaining five RCTs were pooled for mortality (9,20,30,31,38). The pooled analysis of the five RCTs that compared adjuvant chemotherapy to no adjuvant chemotherapy detected a significant difference in mortality (RR, 0.71, 95% CI, 0.56 to 0.90; p=0.005) (Figure 1). A meta-analysis of RCTs comparing adjuvant chemotherapy to no adjuvant chemotherapy in women with early stage ovarian cancer, conducted by International Collaborative Ovarian Neoplasm Study/Adjuvant ChemoTherapy In Ovarian Neoplasm (ICON/ACTION) groups, excluded the Young et al (31) RCT from the analysis (53). The RCT was excluded because the treatment group was given melphalan, which is no longer used in the treatment of ovarian cancer because of the availability of more effective chemotherapy regimens. Also, as mentioned previously, about a third of the patients in the Young et al study had borderline histologies. The ICON/ACTION meta-analysis detected a significant overall benefit for both overall survival (hazard ratio [HR], 0.72; 95% CI, 0.55 to .0.94; p=0.017) and recurrence-free survival (HR, 0.66; 95% CI, 0.53 to 0.83; p<0.02) in women treated with chemotherapy compared to women treated with no adjuvant therapy.

**Figure 1. Pooled analysis of mortality of five randomized controlled trials of adjuvant chemotherapy versus no adjuvant chemotherapy.**




Note: ACTION, Adjuvant ChemoTherapy In Ovarian Neoplasm; CI, confidence interval; ICON, International Collaborative Ovarian Neoplasm Study; RR, relative risk.

The individual RCTs detected varying results. Three RCTs did not detect a significant survival difference between the treatment and control groups (20,30,31). However, one of those studies, by Young et al (31), included a large number of patients with borderline histology (39% in the observation arm and 28% in the melphalan arm). Young et al reported no progression-free interval (p=0.41) or survival advantage for patients receiving melphalan (p=0.43) compared to patients receiving no treatment. Similarly, Bolis et al (30) did not detect a statistically significant survival benefit in the adjuvant chemotherapy group (83% versus 64%, p=0.09). The small sample size may have limited the study's power to detect a statistically significant difference in survival. There was a statistically significant difference in relapse rate (p=0.028) in favour of cisplatin. Trope et al (20) compared adjuvant carboplatin to no adjuvant chemotherapy in high risk stage I patients and did not detect a significant survival difference between groups.

One of the largest RCTs to date (N=477), ICON1, was the only trial to detect an overall survival advantage with platinum-based adjuvant chemotherapy compared to no adjuvant therapy (p=0.03) (38). ICON1 began in 1992 and was sponsored by the British Medical Research Council. Entry into the trial was based on physician uncertainty about the need for chemotherapy, and thus not all eligible stage I patients were randomized.

Another recent large RCT (N=448), the ACTION trial, detected a survival advantage for non-optimally surgically staged women (modified, minimal, and inadequate) who received platinum-based adjuvant chemotherapy compared with women who did not receive adjuvant chemotherapy (HR, 1.75; 95% CI, 1.04 to 2.95; p=0.03) (9). The group with optimal surgical staging and chemotherapy fared as well as the group with surgical staging alone (HR, 0.81; 95% CI, 0.32 to 2.05). The subgroup analysis of the ACTION trial failed to detect an improvement in survival in the optimally surgically staged group (n=151) with the addition of chemotherapy. However, that analysis comparing optimally staged women to non-optimally staged women was not included in the original study design and was underpowered to detect a clinically significant difference in outcome. The information is therefore hypothesis generating rather than definitive. The ACTION trial failed to detect an overall survival difference between adjuvant chemotherapy and no adjuvant chemotherapy when the results were analyzed for optimally and non-optimally surgically staged women together.

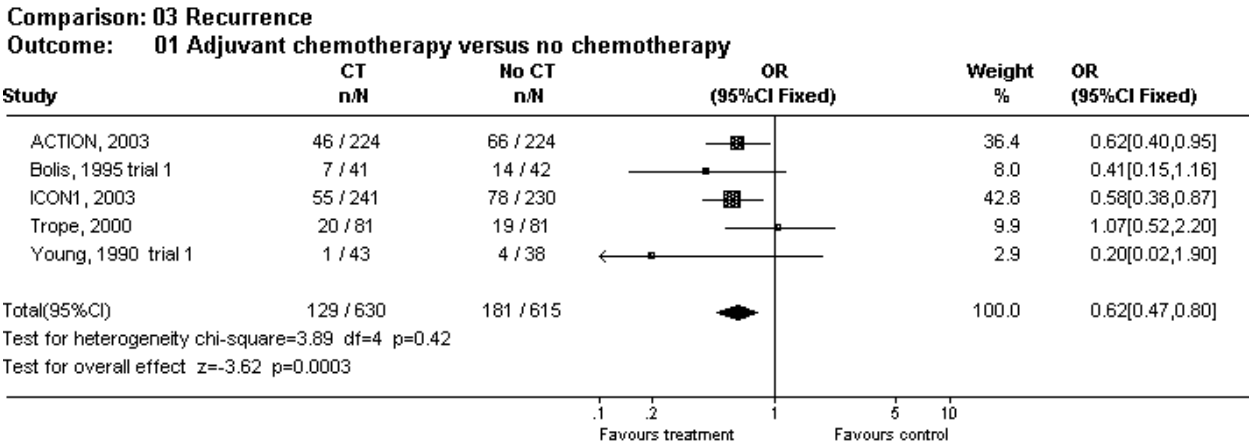
The results of the ICON1 trial and the ACTION trial have been combined to report overall results for both RCTs (53). When combined, the two trials, involving a total of 925 patients, detected a survival advantage among the women treated with adjuvant chemotherapy

compared with the women who did not receive adjuvant therapy (HR, 0.67; 95% CI, 0.50 to 0.90; p=0.008).

Recurrence

The results of five RCTs that compared adjuvant chemotherapy to no adjuvant chemotherapy were pooled for recurrence. The RCTs by Young et al (31) and Trope et al (20) did not detect a significant difference in recurrence between women who received adjuvant chemotherapy and those who did not. In contrast, three of the five RCTs detected a significant difference in recurrence in favour of adjuvant chemotherapy (9,30,38). The ICON1 trial (38) and the ACTION trial (9) both reported that recurrence-free survival is significantly improved for women who receive adjuvant chemotherapy (p<0.02) (Level 1 evidence). Alternatively, the non-optimally surgically staged women who received adjuvant chemotherapy had longer recurrence-free survival than the non-optimally staged women who did not receive adjuvant chemotherapy (p=0.008). Bolis et al's (30) RCT detected a statistically significant difference in recurrence (p=0.028) in favour of cisplatin over no adjuvant chemotherapy (83% versus 64%, p=0.09). When the results for recurrence from the five trials are pooled, there is a significant difference favouring chemotherapy (RR, 0.62; 95% CI, 0.47 to 0.80; p=0.0003) (Figure 2).

**Figure 2. Pooled analysis of recurrence of five randomized controlled trials of adjuvant chemotherapy versus no adjuvant chemotherapy.**




Note: ACTION, Adjuvant ChemoTherapy In Ovarian Neoplasm; CI, confidence interval; CT, chemotherapy; ICON, International Collaborative Ovarian Neoplasm Study; OR, odds ratio.

*Adjuvant chemotherapy versus pelvic or whole abdomino-pelvic radiotherapy*

Five RCTs were identified that compared adjuvant chemotherapy to radiotherapy (32,33,39-41) (Table 7). None of the RCTs detected a significant survival difference between treatment groups.

The results were not pooled because all the RCTs suffer from broad inclusion criteria including patients with early and advanced staged disease. The survival and recurrence rates were not reported individually for stage I patients. In addition, there are treatment delivery concerns in the application of whole abdominal radiation (WAR) in the Smith et al (41) RCT. Some methodologic concerns include an imbalance by disease stage in the treatment arms (more stage IIb patients in the WAR arm and more stage Ia patients in the chemotherapy arm), and liver shielding, meaning that the diaphragms were not treated, leaving that area as a possible tumour sanctuary site. Also, due to the age of the RCTs by Smith et al (41) and

Gronroos et al (33), the chemotherapy regimens described are not the standard of care seen today.

Of the five RCTs identified, the best-quality study is that conducted by Chiara et al (39). However, the RCT is not without flaws: the analysis is by treatment received rather than intent, and there were only 47 stage I patients included in the trial. They concluded that relapse-free survival (74% versus 50%) and overall survival (71% versus 53%) were improved in the chemotherapy arm compared to the radiotherapy arm but did not reach statistical significance.

**Table 7. Survival of patients in RCTs comparing adjuvant chemotherapy to radiotherapy.**

| Study | Treatment | # of patients | Overall survival (5 yr) | | Disease-free survival (5 yr) | |
|---|---|---|---|---|---|---|
| Chiara, 1994 (39) | Cisplatin | 36 | 71% | p=0.16 | RFS 74% | p=0.07 |
| | WAR | 34 | 53% | | RFS 50% | |
| Redman, 1993 (40) | Cisplatin | 19 | 62% | p=NS | NR | |
| | WAR | 21 | 58% | | | |
| Gronroos, 1984 (33) | CT | 38 | 74% | p=NS | NR | |
| | Pelvic RT | 27 | 87% | | | |
| Hreshchyshyn, 1980 (32) | Melphalan | 34 | Recurrence rate 6% | | | p<0.05 |
| | Pelvic RT | 23 | Recurrence rate 30% | | | |
| Smith, 1975 (41) | Melphalan | 79 | NR | | 63%[a] | NR |
| | WAR | 70 | | | 45%[a] | |

Note: CT, chemotherapy; NR, not reported; NS, not significant; RFS, recurrence-free survival; RT, radiotherapy; yr, year; WAR, whole abdominal radiation.
[a] Projected five-year survival.

*Adjuvant chemotherapy versus radioactive chromic phosphate ($^{32}P$)*

Four RCTs compared adjuvant chemotherapy to intraperitoneal (IP) radioactive chromic phosphate ($^{32}P$) (30,31,42,43) (Table 8). None of the studies detected a significant difference in survival between groups. However, only the RCTs by Bolis et al (30) and Vergote et al (43) reported results for stage I patients only. In addition, a limitation of the Young et al (31) RCT was that 17% of the population had borderline ovarian cancer.

Three of the four RCTs failed to detect a significant difference in the rates of recurrence between chemotherapy and IP $^{32}P$. The RCT by Bolis et al (30) was the only one to detect a 61% reduction in the number of relapses in women treated with chemotherapy compared with women treated with IP $^{32}P$ (p=0.007). Young et al (42) observed a somewhat lower, but not significant, recurrence rate for the chemotherapy arm (p=0.075).

**Table 8. Survival of patients in RCTs comparing adjuvant chemotherapy to IP $^{32}P$.**

| Study | Treatment | # of patients | Overall survival (5 yr) | | Disease-free survival (5 yr) | |
|---|---|---|---|---|---|---|
| Young, 1999 (abstract) (42) | Cyclophosphamide + cisplatin | 205 | 84% | NR | RFS 66% | RR 0.693 p=0.07 90% CI 0.454-1.06 |
| | $^{32}P$ | | 76% | | RFS 77% | |
| Bolis, 1995 (30) | Cisplatin | 82 | 81% | p=NS | NR | |
| | $^{32}P$ | 79 | 79% | | | |
| Vergote, 1992 (43)[a] | Cisplatin | 171 | NR | | 79% | p=NS |
| | $^{32}P$ | 169 | | | 82% | |
| Young, 1990 (31) | Melphalan | 68 | 81% | p=0.48 | 80% | p=NS |
| | $^{32}P$ | 73 | 78% | | 80% | |

Note: $^{32}P$, radioactive chromic phosphate; CI, confidence interval; NR, not reported; NS, not significant; RFS, recurrence-free survival; RR, relative risk; yr, year.
[a] The results exclude patients with borderline tumours.

*Whole abdominal radiation (WAR) versus pelvic radiation with chemotherapy*

Three RCTs were identified that compared WAR to pelvic radiation with chemotherapy (34,35,52) (Table 9). None of the studies reported results for stage I patients individually and so pooling of the results was not possible for that subgroup of interest.

Dembo et al (35) compared three treatments: pelvic radiation, pelvic radiation and chlorambucil for 2 years, and pelvic radiation with abdominal strip radiation. The pelvic radiation-only arm was discontinued because it was found to be inferior to the other two arms. In the whole sample (n=199), there was no statistically significant survival advantage between any of the treatment arms. A subanalysis showed that if the total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) could not be completed, patient survival was statistically significantly worse ($p<0.0005$). When the data were reanalyzed for survival excluding the incomplete surgery group, WAR was the superior management arm ($p=0.019$). However, concerns about the study include the suboptimal dose of chlorambucil, the lack of surgical staging, and the unusual classification of patients into risk categories by stage, grade, and residual disease, which prevented the identification of outcome information for stage I patients.

Klaassen et al (34) also compared three treatments: WAR, oral melphalan after pelvic radiation, and radioactive $^{32}P$ after pelvic radiation in poor-prognosis, early-stage ovarian cancer. In the whole study group (n=257), there was no survival advantage between treatment arms; however, the outcomes for the stage I patients were not reported separately. There were problems with compliance in all treatment arms, which makes the interpretation of outcomes difficult because the number of patients in each treatment group who completed was uneven in the end. Only 29 patients completed the full radioactive $^{32}P$ and pelvic radiation treatment compared to 101 patients who completed the full melphalan and pelvic radiation treatment. In the $^{32}P$ group, the problems with compliance were due to patient refusal and technical difficulty.

Sell et al's (52) RCT compared WAR to pelvic radiation and cyclophosphamide in women with stage Ib, Ic, IIa, IIb, or IIc ovarian cancer. Disease-free and overall survival did not differ between the two arms. The data were reanalyzed according to the Dembo et al (54) definition of intermediate risk and still no survival difference was detected. Unfortunately, the outcomes for the stage I patients were not reported separately.

**Table 9. Survival of patients in RCTs comparing WAR versus pelvic radiation and chemotherapy.**

| Study | Treatment | # of patients | Overall survival (5 yr) | | Disease-free survival (5 yr) | |
|---|---|---|---|---|---|---|
| Sell, 1990 (52) | Cyclophosphamide + pelvic RT | 58 | 55% 4 yr | p=NS | RFS 48% 4 yr | p=NS |
| | WAR | 60 | 63% 4 yr | | RFS 60% 4 yr | |
| Klaassen, 1988 (34) | Melphalan + pelvic RT | 106 | 61% | p=NS | 66% | p=0.01 (CT vs WAR) |
| | $^{32}P$ + pelvic RT | 44 | 66% | | 64% | |
| | WAR | 107 | 62% | | 56% | |
| Dembo, 1979 (35)[a] | CT + pelvic RT | 51 | 52% | CT + pelvic RT vs WAR, p=0.02 | RFS 45% | NR |
| | Pelvic RT | 31 | 50% | | RFS 47% | |
| | WAR | 50 | 82% | | RFS 78% | |

Note: $^{32}P$, radioactive chromic phosphate; CT, chemotherapy; NR, not reported; NS, not significant; RFS, recurrence-free survival; RT, radiotherapy; vs, versus; WAR, whole abdominal radiotherapy; yr, year.

[a] The results presented only include the 132 women who received complete bilateral salpingo-oophrectomy and hysterectomy.

*Two different forms of chemotherapy*

Four RCTs were identified that compared two different forms of chemotherapy in early stage ovarian cancer (44-47) (Table 10). Murphy et al (47) randomized patients with stage Ic to IV ovarian cancer to carboplatin (300 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) alternating with ifosphamide (5 g/m$^2$) and adriamycin (50mg/m$^2$) for six cycles or half the dose of each agent monthly for 12 cycles. The overall response rate was better in the six-cycle group (p=0.0009), but there was no significant difference in overall survival between the groups. Similarly, Bell et al (45) recently reported results of an RCT that compared three cycles of paclitaxel and carboplatin with six cycles of paclitaxel and carboplatin (same dosages). They reported that six cycles did not offer a significant overall or recurrence-free survival advantage over three courses of chemotherapy (p>1.0).

Hatae et al's (46) RCT compared the role of intravenous cisplatin (75 mg/m$^2$) with either intravenous cyproterone acetate (CPA) (500mg/m$^2$) or oral CPA (500mg/m$^2$) in stage Ia patients. There was no significant difference detected in response rate or overall survival.

Marth et al's (44) RCT compared cisplatin (100 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) with or without interferon (INF) gamma (0.1 mg sc) in women with stage Ic to III ovarian cancer. The progression-free interval at three years was improved in the INF-gamma group (51% versus 38%; p=0.031; RR, 0.48; 95% CI, 0.28 to 0.82). The effect on survival at three years did not reach significance. The results are not reported for stage I patients only.

**Table 10. Survival of patients in RCTs comparing two different forms of adjuvant chemotherapy.**

| Study | Treatment | # of patients | Overall survival (5 yr) | | Disease-free survival (5 yr) | |
|---|---|---|---|---|---|---|
| Bell, 2003 (abstract) (45) | 3 cycles paclitaxel + carboplatin | 321 | Probability of recurrence within 5 yr 27% | | | p=NS |
| | 6 cycles paclitaxel + carboplatin | | Probability of recurrence within 5 yr 19% | | | |
| Marth, 2000 (44) (abstract) | Cyclophosphamide + cisplatin + interferon | 148 | 78% 3 yr | p=NS | 51% | NR |
| | Cyclophosphamide + cisplatin | | 58% 3 yr | | 38% | |
| Hatae, 1998 (abstract) (46) | IV CT | 96 | No significant differences in overall or progression-free survival | | | |
| | Oral CT | | | | | |
| Murphy, 1993 (47) | 6 cycles CT | 49 | 52% 3 yr | p=0.09 | PFS 51% 3yr | p=0.06 |
| | 12 cycles CT | 50 | 35% 3 yr | | PFS 32% 3 yr | |

Note: CT, chemotherapy; NR, not reported; NS, not significant; PFS, progression-free survival; yr, year.

*Other RCT comparisons*

There were four additional RCTs identified that compared treatments for stage I ovarian cancer patients (48-51) (Table 11). Kolstad et al (49) compared adjuvant $Au^{198}$ to pelvic radiation in a randomized study of stage I and II ovarian cancer patients. They did not detect any significant differences between groups in terms of recurrence or survival.

Khoo et al (48) compared levamisole to a placebo in women with all stages of ovarian cancer. In addition to the levamisole or placebo, all patients were treated with pelvic radiation and melphalan. Khoo et al detected a higher recurrence rate in the placebo group (5%, p=0.009), but there was no difference in overall survival at four years.

Davy et al (50) compared adjuvant thiotepa to no chemotherapy in women with stage I and II ovarian cancer. All patients received isotope instillation unless adhesions prevented the procedure. The rate of recurrence, time to recurrence, or survival did not differ between the two groups. Thus, thiotepa had no added protective effect over surgery with radiotherapy.

Fyles et al (51) compared two different doses of radiation in women with stage I ovarian cancer. There was no significant difference in overall survival at five years (83% versus

72%;p=0.3) and disease-free survival (74% versus 67%; p=0.5) between the high and low dose groups.

**Table 11. Survival of patients in RCTs comparing various treatments.**

| Study | Treatment | # of patients | Overall survival (5 yr) | | Disease-free survival (5 yr) | |
|---|---|---|---|---|---|---|
| Fyles, 1998 (51) | RT 22.5 Gy | 67 | 83% | p=0.3 | 74% | p=0.5 |
| | RT 27.5 Gy | 58 | 72% | | 67% | |
| Davy, 1985 (50) | Thiopeta + IP radiation | 151 | Time to recurrence 26.5 months | | | p=NS |
| | IP radiation | 150 | Time to recurrence 23 months | | | |
| Khoo, 1984 (48) | Levamisole + RT + melphalan | 69 | Duration of survival NS | | | |
| | Placebo + RT + melphalan | 71 | | | | |
| Kolstad, 1977 (49) | RT | 220 | 75% | p=NS | NR | |
| | $Au^{198}$ | 198 | 78% | | | |

Note: $Au^{198}$, radioactive gold; IP, intraperitoneal; NR, not reported; NS, not significant; RT, radiotherapy; yr, year.

**Table 12. Overview of randomized controlled trials comparing treatments for early stage ovarian cancer.**

| Study | Stage of disease—number of patients (% of total patients) | | | Treatment A | Treatment B |
|---|---|---|---|---|---|
| | IA | IB | IC | | |
| ***Comparison of surgical procedures*** | | | | | |
| Benedetti-Panici, 1996 (abstract) (36) | 94 early stage | | | systematic pelvic and aortic lymphadenetomy | no lymphadenectomy or sampling of suspicious nodes |
| ***Adjuvant radiotherapy versus no adjuvant radiotherapy*** | | | | | |
| Dembo, 1979 (37) | 41 | - | - | 4500 in 20 fractions | no adjuvant treatment |
| Hreshchyshyn, 1980 (32) | 48 (92%) | 4 (8%) | - | 5,000 rad over 5-6 weeks | no adjuvant treatment |
| ***Adjuvant chemotherapy versus no chemotherapy*** | | | | | |
| ACTION, 2003 (9) | 155 (35%) | 37 (8%) | 223 (50%) | 75mg/m$^2$ cisplatin or 50mg/m$^2$ carboplatin | no adjuvant treatment |
| ICON1, 2003 (38) | 199 (42%) | 52 (11%) | 190 (40%) | 75mg/m$^2$ cisplatin or 500mg/m$^2$ cyclophosphamide + 50mg/m$^2$ doxorubicin + 50mg/m$^2$ cisplatin | no adjuvant treatment |
| Trope, 2000 (20) | 66 (41%) | 9 (5%) | 87 (54%) | carboplatin in 500mL 5% glucose, dosed at AUC 7 every 4 weeks for 6 courses | no adjuvant treatment |
| Bolis, 1995 (30) | 83 (100%) | - | - | 50mg/m$^2$ cisplatin every 4 weeks for 6 courses | no adjuvant treatment |
| Young, 1990 (31) | 76 (94%) | 5 (6%) | - | oral 0.2mg/kg/day melphalan for 5 days every 4 weeks for 12 courses | no adjuvant treatment |
| Gronroos, 1984 (33) | 75 (100%) | | | cyclophosphamide-vincristine or 5-fluorouracil-dactinomycin-vincristine | no adjuvant treatment |
| Hreshchyshyn, 1980 (32) | 57 (90%) | 6 (10%) | - | oral 0.2mg/kg/day melphalan for 5 days every 4 weeks for 18 months | no adjuvant treatment |
| ***Adjuvant chemotherapy versus radiotherapy*** | | | | | |
| Chiara, 1994 (39) | 2 (3%) | 1 (1%) | 44 (64%) | 50mg/m$^2$ cisplatin + 600mg/m$^2$ cyclophosphamide every 4 weeks for 6 courses | 43.2 Gy in 24 fractions to the pelvis and 30.2 Gy to the upper abdomen |
| Redman, 1993 (40) | - | - | 7 (18%) | 100 mg/m$^2$ IV cisplatin every 3 weeks for 5 courses | total dose 4500 cGy |
| Gronroos, 1984 (33) | 65 (100%) | | | cyclophosphamide-vincristine or 5-fluorouracil-dactinomycin-vincristine | weekly dose of 10 Gy in 5 fractions, up to 46-50 Gy |
| Hreshchyshyn, 1980 (32) | 47 (82%) | 10 (18%) | - | oral 0.2mg/kg/day melphalan for 5 days every 4 weeks for 12 courses | 50 Gy over 5-6 weeks |
| Smith, 1975 (55) | 29 (69%) | 10 (24%) | 3 (7%) | 0.2mg/kg/day melphalan for 5 days, every 4 weeks for 12 courses | 26-28 Gy in 2.5 weeks. |

Note: AUC, area under curve; IV, intravenous.

**Table 12 continued. Overview of randomized controlled trials comparing treatments for early stage ovarian cancer.**

| Study | Stage of disease—number of patients (% of total patients) | | | Treatment A | Treatment B |
|---|---|---|---|---|---|
| | IA | IB | IC | | |
| ***Adjuvant chemotherapy versus radioactive chromic phosphate*** | | | | | |
| Young, 1999 (42) | 142 (69%) | - | - | IV 1 gm/m$^2$ cyclophosphamide + 100 mg/m$^2$ cisplatin 3 weeks for 3 courses | 15 mCi IP$^{32}$P |
| Bolis, 1995 (30) | 152 (100%) | | | 50mg/m$^2$ cisplatin every 4 weeks for 6 courses | $^{32}$P (7-10 mCi-260-370MBq) |
| Vergote, 1992 (43) | 83 (24%) | 12 (4%) | 170 (50%) | 50 mg/m$^2$ cisplatin for 6 courses | IP$^{32}$P (7-10 mCi-260-370MBq) |
| Young, 1990 (31) | 32 (22%) | 5 (4%) | 15 (11%) | oral 0.2mg/kg/day melphalan for 5 days every 4 weeks for 12 courses | 15 mCi IP$^{32}$P |
| ***WAR versus pelvic radiation and chemotherapy*** | | | | | |
| Sell, 1990 (52) | - | 25 (21%) | 14 (12%) | abdominal 22.5 Gy in 10 fractions | pelvic 45 Gy in 20 fractions + oral 200 mg/m$^2$ cyclophosphamide for 5 days every 4 weeks for 12 courses |
| Klaassen, 1988 (34) | 103 (40%) | 24 (9%) | - | 22.5 Gy in 20 fractions | 8mg/m$^2$/day melphalan for 4 days every 4 weeks for 18 courses + 45 Gy in 20 fractions |
| Dembo, 1979 (35) | - | 12 (12%) | - | abdominopelvic 22.5 Gy in 10 fractions | pelvic 45 Gy in 20 fractions + 6 mg chlorambucil/day for 2 years |
| ***Two different forms of adjuvant chemotherapy*** | | | | | |
| Bell, 2003 (45) (abstract) | NR | | | 175 mg/m$^2$ paclitaxel + 7.5 AUC carboplatin for 3 courses | 175 mg/m$^2$ paclitaxel + 7.5 AUC carboplatin for 6 courses |
| Marth, 2000 (44) (abstract) | NR | | | 0.1 mg sc 3 times/week every other week IFN- + IV 100mg /m$^2$ cyclophosphamide + 600 mg/m$^2$ cisplatin every 4 weeks for 6 courses | IV 100mg /m$^2$ cyclophosphamide + 600 mg/m$^2$ cisplatin every 4 weeks for 6 courses |
| Hatae, 1998 (46) | 96 (100%) | - | - | IV cisplatin 75mg/m$^2$ + cyclophosphamide 500mg/m$^2$ every 4 weeks for 3 courses | Oral cyclophosphamide 50mg/m$^2$ daily for 3 months |
| Murphy, 1993 (47) | - | - | 13 | 600 mg/m$^2$ cyclophosphamide + 300 mg/m$^2$ carboplatin alternating 50 mg/m$^2$ adriamycin with ifosfamide 5 g/m$^2$ every 4 weeks for 6 courses | 300 mg/m$^2$ cyclophosphamide + 150 mg/m$^2$ carboplatin alternating 25 mg/m$^2$ adriamycin with ifosfamide 2.5 g/m$^2$ every 4 weeks for 12 courses |
| ***Other RCT comparisons*** | | | | | |
| Fyles, 1998 (51) | 43 (34%) | | | RT 22.5 Gy in 22 fractions | RT 27.5 Gy in 27 fractions |
| Davy, 1985 (50) | NR | | | 60 mg/m$^2$ thiotepa every 2 weeks for 2 courses, then 15 mg/m$^2$ thiotepa every 2 weeks for 6 months+ 40 Gy in 20 fractions | 40 Gy in 20 daily fractions |
| Khoo, 1984 (48) | 41 (29%) | | | 150 mg oral levamisole 1$^{st}$ 3 days of week + 30-35 Gy with IV melphalan (0.6 mg/kg) | placebo for the 1$^{st}$ 3 days of week + 30-35 Gy with IV melphalan (0.6 mg/kg) |
| Kolstad, 1977 (49) | 191 (46%) | 45 (11%) | 22 (5%) | Au$^{198}$ 100mCi + 30 Gy pelvic irradiation | 50 Gy pelvic irradiation |

Note: $^{32}$P, radioactive chromic phosphate; Au$^{198}$, radioactive gold; AUC, area under the curve; IFN, interferon; IP, intraperitoneal; IV, intravenous; NR, not reported; RT, radiation therapy; WAR, whole abdominal radiation.

***Adverse events***

The results presented below are a cumulative report of adverse events from all patients in the trial and not just patients with stage I disease. The fact that none of the RCTs reported which scale they used to measure adverse effects caused difficulty when trying to compare adverse event rates across studies. Complications related to chemotherapy are reported in Table 13.

Comparison of surgical procedures

The abstract by Benedetti-Panici et al (36) reported that the pelvic and para-aortic lymphadenectomy was associated with distinct risks and morbidity, long operating time, and long hospital stay.

Adjuvant radiotherapy versus no radiotherapy

There was no complication information provided in the RCT by Hreshchyshyn et al (32). Dembo et al (35) reported that the WAR group (n=75) had one death as a result of surgery, due to bowel complications. The most frequently reported acute adverse events of radiotherapy were myelosuppression (66%), bowel cramps or diarrhea (64%), nausea or vomiting (54%), and neutropenia (45%).

Adjuvant chemotherapy versus no adjuvant chemotherapy

Of the seven RCTs that compared adjuvant chemotherapy to no adjuvant chemotherapy, the only studies that provided details of complications were Gronroos et al (33), who reported no lethal complications, and Young et al (31). Young et al reported that the hematological and gastrointestinal toxicities were mild to moderate in the melphalan group (n=43). .Some degree of myelosuppression occurred in 79% of cases, with seven patients having severe thrombocytopenia, and there was one case of aplastic anemia. The concern raised by the study involves the long-term sequelae of alkylating agents.

Adjuvant chemotherapy versus radiotherapy

Of the five RCTs identified that compared adjuvant chemotherapy to radiotherapy, three studies reported complication rates. Gronroos et al (33) reported that there were no lethal complications and that nausea, vomiting, gastrointestinal, and hematologic toxicities were of anticipated severity but provided no further details. Smith et al (41) reported that complications with melphalan included myelosuppression (50%) (n=79). In the WAR group (n=70), treatment delays occurred due to myelosuppression or gastrointestinal toxicity. Radiation enteritis occurred in four patients and necessitated a treatment delay of one week or longer. Also, 10% of the patients in the WAR group required surgery for small bowel injury. Chiara et al (39) reported that the complications with WAR (n=25) included one death from severe enteritis and grade 3-4 diarrhea in 28% of patients. One patient had a laparotomy for bowel obstruction. In the cisplatin-cyclophosphamide group (n=44), 71% of the patients experienced grade 3 emesis, and 37% experienced grade 1 to 2 myelosuppression. The concerns raised by those trials included the long-term bowel complications from WAR and the short-term gastrointestinal side effects from cisplatin-cyclophosphamide.

Adjuvant chemotherapy versus radioactive chromic phosphate ($^{32}P$)

All four RCTs identified that compared adjuvant chemotherapy with $^{32}P$ reported complication rates. Young et al (31) reported that, in the $^{32}P$ arm (n=68), 7% of the patients did not receive therapy due to catheter complications, 6% developed bowel obstruction and required surgery, 21% had mild to moderate abdominal pain, 6% had severe pain, one patient had chemical peritonitis, and one had infectious peritonitis. In the melphalan group (n=68),

acute melphalan complications included hematogenous and gastrointestinal side effects. Myelosuppression occurred in 74% of the group and in 20% was considered severe. Mild to moderate gastrointestinal toxicity occurred in 16% of the patients. Two patients died of leukemia.

Vergote et al (43) reported that one patient in the $^{32}P$ arm had a pulmonary embolism (n=136). In the WAR group (n=28), one patient had treatment interrupted for one week due to grade 2 thrombocytopenia. Treatment delays occurred more often in the WAR and $^{32}P$ groups. In the cisplatin group (n=171), toxicity leading to the discontinuation of cisplatin included gastrointestinal and peripheral neuropathy. Treatment was discontinued in 12 chemotherapy patients (four with grade 1 peripheral neurotoxicity, three with skin rash, and five with nausea and vomiting).

Bolis et al (30) reported that 20% of patients were not able to get their catheter implanted, and one patient developed bowel obstruction in the $^{32}P$ arm (n=79). Toxicity for the cisplatin group (n=82) included severe nausea and vomiting (10%), severe myelosuppression (1%), greater than grade 2 neurologic complications (1%), and greater than grade 2 renal toxicity (1%). In 1999 Young et al (42) reported that the major toxicity in the $^{32}P$ arm (n=98) included bowel perforation in two patients during catheter placement. In the chemotherapy arm (n=107), 67% of the patients experienced grade 3 or 4 myelosuppression. There was one treatment death in each arm (in the $^{32}P$ due to bowel perforation and in the chemotherapy arm due to pancytopenia and cardiac arrest). The $^{32}P$ complications included the inability to place the catheter and long-term bowel complications. A concern was that the use of alkylating agents might lead to leukemia. Cisplatin had tolerable but significant neuropathy, gastrointestinal toxicity, and myelosuppression.

<u>WAR versus pelvic radiation and chemotherapy</u>

All three RCTs that compared WAR with pelvic radiation and chemotherapy reported complications. Dembo et al (35) reported that the WAR group (n=75) had one death as a result of surgery for bowel complications. The most frequently reported adverse effects were myelosuppression (66%), bowel cramps or diarrhea (64%), nausea or vomiting (54%), and neutropenia (45%). In the chemotherapy group (n=71), toxicity attributable to chlorambucil included varicella zoster (10%), major sepsis (4%), nausea (6%), neutropenia/thrombocytopenia (81%), and leukemia (3%).

Klaassen et al (34) reported that in the WAR group (n=107) three patients had WAR interrupted due to toxicity and eight had premature termination of WAR. In the melphalan group (n=106), Klaassen et al reported acute leukemia and myelodysplasia. Most patients on melphalan required some delay due to myelosuppression, but only 16 discontinued treatment due to prolonged myelosuppression. Pelvic radiation in the melphalan arm was discontinued prematurely in four patients, due to severe gastrointestinal toxicity, while 13 had pelvic radiation interrupted due to toxicity in the melphalan arm. Sell et al (52) reported higher toxicities in the WAR group (n=59) compared to the pelvic radiation and chemotherapy group (n=58). Significantly more nausea and vomiting occurred in the WAR group, where three patients stopped treatment due to gastrointestinal side effects. Approximately a third of patients in each arm reported myelosuppression. Ten chemotherapy patients developed hemorrhagic cystitis. Three to five percent of patients in both arms developed bowel obstruction that required surgery. Klaassen et al observed more late toxicities in patients receiving WAR than in those receiving chemotherapy or chromic phosphate The most commonly reported long-term adverse effects in patients treated with WAR, melphalan, or chromic phosphate were chronic diarrhea, bowel obstruction (surgically treated), and second malignancy.

Two different forms of adjuvant chemotherapy

Hatae et al (46) reported higher toxicities in the intravenous group, including myelosuppression, gastrointestinal sequelae, and hair loss. Given the side effect profile and the lack of difference in outcomes, Hatae et al concluded that oral adjuvant therapy was superior.

Murphy et al (47) reported that nausea and vomiting were the same in both treatment arms (low- versus high-dose chemotherapy). The frequency of grade 3 and 4 toxicity was higher in the low-dose arm. All patients had grade 3 hair loss. Hematologic effects were more severe in the high-dose arm. Two patients were withdrawn from the standard-dose-intensity arm, due to persistent neutropenia. No sepsis was reported, but eight patients required antibiotics for infection. In the high-dose arm, four patients required blood transfusions, and six needed platelet transfusion. One patient in the high-dose arm was withdrawn for deteriorating renal function due to disease progression.

As expected, Bell et al (45) reported that patients receiving six cycles of paclitaxel and carboplatin experienced significantly more adverse effects (anemia, granulocytopenia, neurotoxicity) compared with patients receiving only three cycles.

Other RCT comparisons

Fyles et al (51) reported that the frequency of leukopenia (five patients in the low-dose arm and seven in the high dose), thrombocytopenia (three in each arm), and radiation cystitis (one in each arm) was the same in both groups. In the low-dose arm, there were two severe bowel toxicities (one serious radiation enteritis and one bowel obstruction not requiring surgery), and in the high-dose arm, there was one patient with jaundice.

Kolstad et al (49) reported that four patients died of complications in the $Au^{198}$ group (n=124), despite being disease free. No patients in the radiation-alone group (n=134) died of complications. For the whole study population, there was a higher rate of complications in the $Au^{198}$ group, including peritonitis, stricture, subacute obstruction, obstruction, and fistula.

**Table 13. Grade 3 and 4 toxicities reported in the chemotherapy studies.**

| Study | # of patients | Treatment | Leuko-penia | Thrombo-cytopenia | Nausea/ vomiting | Diarrhea | Anemia | Renal | Neuro-toxicity |
|---|---|---|---|---|---|---|---|---|---|
| Bolis, 1995 (30) | 123 | 50 mg/m$^2$ cisplatin every 4 weeks for 6 courses | 1% | | <10% | NR | NR | 1% | 1% |
| Chiara, 1994 (39) | 44 | 50 mg/m$^2$ cisplatin + 600 mg/m$^2$ cyclophosphamide every 4 weeks for 6 courses | NR | NR | 71% | NR | NR | NR | NR |
| Murphy, 1993 (47) | 49 high dose | 600 mg/m$^2$ cyclophosphamide + 300 mg/m$^2$ carboplatin alternating 50 mg/m$^2$ adriamycin with ifosfamide 5 g/m$^2$ every 4 weeks for 6 courses | 86% | 28% | 100% | NR | 14% | NR | NR |
| | 50 low dose | 300 mg/m$^2$ cyclophosphamide + 150 mg/m$^2$ carboplatin alternating 25 mg/m$^2$ adriamycin with ifosfamide 2.5 g/m$^2$ every 4 weeks for 12 courses | 32% | 4% | 100% | NR | 4% | NR | NR |
| Redman, 1993 (40) | 19 | 100 mg/m$^2$ IV cisplatin every 3 weeks for 5 courses | 32% | NR | 84% | 16% | 26% | NR | NR |
| Young, 1990 (31) | 111 | oral 0.2 mg/kg/day melphalan for 5 days every 4 weeks for 12 courses | 20% | | NR | NR | NR | NR | NR |
| Khoo, 1984 (48) | 69 | 150 mg oral levamisole 1$^{st}$ 3 days of week + 3000-3500 rad with IV melphalan (0.6 mg/kg) | 7% | | NR | NR | NR | NR | NR |
| Smith, 1975 (41) | 79 | 0.2 mg/kg/day melphalan for 5 days, every 4 weeks for 12 courses | 1% | NR | NR | NR | NR | NR | NR |

Note: IV, intravenous; NR, not reported.

## V. INTERPRETIVE SUMMARY

### Comparison of Surgical Procedures

One abstract that reported an interim analysis addressing radical pelvic and para-aortic lymphadenectomy versus lymph node sampling suggested no difference in terms of relapse rate, disease-free survival, and crude survival. A full publication of this RCT was not identified in the literature search.

### Adjuvant Radiotherapy versus No Adjuvant Radiotherapy

The two RCTs comparing adjuvant pelvic radiotherapy with no radiotherapy are small and were conducted in an era prior to the understanding of the importance of surgical staging (32,37). Although radiation may decrease the risk of recurrence in the pelvis, the upper abdomen was never assessed for the presence of disease, and so disease occurrence at this site could be related to understaging.

### Adjuvant Chemotherapy versus No Adjuvant Chemotherapy

There were seven RCTS that compared chemotherapy to no chemotherapy. The pooled results of all the eligible trials addressing adjuvant chemotherapy detected a mortality benefit (RR 0.71, 95% CI 0.56-0.90, p=0.005) (Level 1) (Figure 1) and reduced recurrence for adjuvant chemotherapy (RR 0.62, 95% CI 0.47-0.80, p=0.0003) (Level 1) (Figure 2). The pooled results from the ACTION (9) and ICON (38) trials, which accrued simultaneously in different European countries, also detected a survival benefit for chemotherapy (p=0.008) (Level 1). This analysis could not address the role of adjuvant chemotherapy in the optimally surgically staged, stage I ovarian cancer patient with poor prognostic factors, because the RCT was not designed to compare optimally staged versus non-optimally staged patients.

The long-term follow-up of patients in the randomized study by Young et al (31) (stage Ia, Ib grade 1, 2) suggests that there are a group of patients with good prognosis tumours who are cured by well-conducted surgery alone. Since that work, most trialists have excluded this group when conducting studies on women with stage I disease, and they define a poor prognosis group as one that includes grade 3 or clear cell histology. The question that the pooled results of the ACTION/ICON trial failed to answer was "who makes up the high risk group that would most benefit from adjuvant chemotherapy?" Thus, the Gynecology Cancer DSG acknowledges that women who do not have surgical staging should have adjuvant chemotherapy as there is a survival and disease-free survival advantage in the combined results of the ACTION/ICON trial.

There are likely a group of good-prognosis, surgically staged, stage I ovarian cancer patients who do not require adjuvant chemotherapy, but the definition of this subgroup must be the focus of subsequent trials. Unfortunately, ACTION study was not powered to address the role of surgical staging in women with ovarian cancer. An appropriately powered study is required to assess whether patients with complete surgical staging require adjuvant chemotherapy.

### Adjuvant Chemotherapy versus Adjuvant Radiotherapy

None of the five RCTS that compared chemotherapy to radiotherapy found a significant difference between the groups in terms of survival. All the RCTs that compared adjuvant chemotherapy to radiotherapy are weakened by the inclusion of heterogeneous populations of patients with either early or advanced-stage disease, the lack of outcome information for the population of interest, and the inclusion of women with incomplete, surgically staged stage I disease. There are treatment delivery issues in the application of the WAR in the Smith et al (41) and Chiara et al (39) studies. The studies by Smith et al (41), Hreshchyshyn et al (32), and Gronroos et al (33) do not use the standard of chemotherapy for today. Chiara et al (39) conducted the best quality study and observed a non-significant trend toward improved survival

in the chemotherapy arm; however, the flaw in that RCT is the analysis by treatment rather than intent to treat and the small sample size. Complications identified by those RCTs include the long term bowel complications from WAR and the short-term gastrointestinal side effects from cisplatin-cyclophosphamide.

**Adjuvant Chemotherapy versus Radioactive Chromic Phosphate**

None of the four RCTs comparing chemotherapy and radioactive chromic phosphate detected a significant difference between groups in terms of survival. These studies could not be pooled because the survival and recurrence information for stage I patients was not available. In Bolis et al's (30) and Young et al's (31) work, the overall study results suggested a trend toward decreased recurrence rate and improved survival but that was not statistically significant. The complications regarding $^{32}P$ include the inability to place the catheter and long-term bowel complications. Again, the use of alkylating agents may lead to leukemia. Cisplatin has tolerable but significant neuropathy, gastrointestinal toxicity, and myelosuppression.

**Other Comparisons**

Treatment with WAR is associated with short and long-term bowel sequelae. The use of IP $^{32}P$ or $Au^{198}$ is complicated by the difficulty of actually placing the catheter and by long-term bowel problems. Alkylating agents are associated with a long-term risk of leukemia. Platinum is tolerable but associated with neuropathy, gastrointestinal side effects, and myelosuppression.

## VI. ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database on the Internet (www.cancer.gov) and conference proceedings of the American Society for Clinical Oncology (ASCO) (1997 to 2003) were searched for reports of new or ongoing trials.

| Protocol IDs | Title and details of trial |
|---|---|
| GOG-175, SWOG-G0175 | Phase III Randomized Study of Carboplatin and Paclitaxel with or without Low Dose Paclitaxel in Patients with Early Stage Ovarian Carcinoma |

## VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Gynecology Cancer DSG agreed that adjuvant chemotherapy should include a platinum-based regimen. There was no consensus concerning the use of single versus combination treatment.

*The arguments for single agent platinum chemotherapy included:*

- The 1,526 patients in ICON2 (56) (carboplatin versus CAP [cyclophosphamide, doxorubicin, and cisplatin]) and the 2,074 patients in ICON3 (38) (paclitaxel plus carboplatin versus carboplatin alone or CAP) represent all stages of ovarian cancer and showed that carboplatin is as effective as the combination therapies
- There is no adequately powered trial of carboplatin versus carboplatin/paclitaxel in stage I disease.

*The arguments for combination platinum paclitaxel are:*

- There are two well-conducted, North American-based randomized trials (GOG 111, EORTC/NCIC OV10) that show that platinum/paclitaxel provides a superior survival advantage to standard treatment in women with advanced disease. By virtue of the Goldie Hypothesis, that regimen should work even better in earlier staged ovarian cancer.
- Bell et al's (45) adequately powered RCT of three versus six cycles of carboplatin/paclitaxel in stage I disease showed no survival difference based on the number of treatment cycles.

*The arguments for considering the use of adjuvant chemotherapy in women with stage I, grade 1 and 2 ovarian cancer are:*

- The Gynecology Cancer DSG agreed that given the excellent survival in both the adjuvant treatment and no treatment arms of Young et al's study on stage I, grade 1 and 2 ovarian cancer (31), some gynecologic and medical oncologists would consider stage Ia and Ib grade 1 ovarian cancer to be low risk and not require adjuvant therapy. Of note, women with these criteria were included in the ICON1 (38) and Gronroos et al's study (33); both of these studies reported a significant survival benefit in women receiving chemotherapy compared to no adjuvant treatment. Women with stage I, grade 2 or 3 ovarian cancer were included in all the studies (see Table 3) and should be considered candidates for adjuvant chemotherapy, because when the results of the studies were pooled, there was a survival benefit in favour of chemotherapy compared to no adjuvant therapy.

## VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

### Draft Recommendations

Based on the evidence reviewed, the Gynecology Cancer DSG drafted the following recommendations:

### Target Population

These recommendations apply to women with newly diagnosed stage I ovarian cancer.

### Draft Recommendations

- Women with stage I ovarian cancer should be offered platinum-based chemotherapy to decrease their recurrence rate and increase their survival.
- There is insufficient evidence to make a recommendation addressing the role of adjuvant pelvic radiation, whole abdominal pelvic radiotherapy, or intraperitoneal radioactive chromic phosphate.

### Qualifying Statements

- A subgroup analysis suggests that there is no benefit from adjuvant chemotherapy in women with stage I epithelial ovarian cancer who have undergone optimal surgical staging as described by the European Organization for Research and Treatment of Cancer (which includes pelvic and para-aortic node sampling). Unfortunately this subgroup analysis suffers the methodological concern of being underpowered.
- Women with surgically staged stage I ovarian cancer and good prognostic factors (grade 1, non-clear cell histology) could be managed with or without adjuvant chemotherapy, as information on this subgroup is hypothesis generating and does not allow a specific recommendation.

### Future Research

Future research needs to evaluate the implementation of surgical staging as a means of avoiding the use of chemotherapy in women who may not require toxic therapy. The role of adjuvant therapy in women with poor prognostic factors who are optimally staged needs to be assessed. The optimal chemotherapy regimen in terms of agents, dose and duration has yet to be defined.

**Related Guidelines**

1. Practice Guidelines Initiative Practice Guideline Report #4-1-2: *First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer*.
2. Practice Guidelines Initiative Evidence Summary Report # 4-3: *Chemotherapy for Recurrent Epithelial Ovarian Cancer Previously Treated with Platinum*.
3. Practice Guidelines Initiative Evidence Summary Report # 4-15: *Management of an ovarian mass (in progress)*.

**Practitioner Feedback**

A draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the 'Modifications' section below.

***Methods***

Practitioner feedback was obtained through a mailed survey of 96 practitioners in Ontario (39 medical oncologists, 19 radiation oncologists, 17 surgeons, four pathologists and 17 gynecologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on September 5, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

***Results***

Forty-nine responses were received out of the 96 surveys sent (51% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 29 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 14. The Gynecology Cancer DSG was curious as to why 12 (41%) respondents indicated that they would be unlikely to make use of this guideline in their own practice, even though they indicated that the guideline was relevant to their practice. Ten of the 12 respondents agreed with the recommendations and thought they were suitable for the patient population. Eleven of the 12 indicated that they would be comfortable if their patients received the care recommended in the guideline. Unfortunately, the survey was not able to assess why the 12 respondents would be unlikely to use the guideline in their practice.

**Table 14. Practitioner responses to eight items on the practitioner feedback survey.**

| Item | Number (%) | | |
|---|---|---|---|
| | **Strongly agree or agree** | **Neither agree nor disagree** | **Strongly disagree or disagree** |
| The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear. | 28 (97%) | 0 | 1 (3%) |
| There is a need for a clinical practice guideline on this topic. | 25 (86%) | 4 (14%) | 0 |
| The literature search is relevant and complete. | 25 (86%) | 4 (14%) | 0 |
| The results of the trials described in the report are interpreted according to my understanding of the data. | 28 (100%) | 0 | 0 |
| The draft recommendations in this report are clear. | 26 (90%) | 2 (7%) | 1 (3%) |
| I agree with the draft recommendations as stated. | 22 (76%) | 4 (14%) | 3 (10%) |
| This report should be approved as a practice guideline. | 21 (72%) | 6 (21%) | 2 (7%) |
| If this report were to become a practice guideline, how likely would you be to make use of it in your own practice? | **Very likely or likely** | **Unsure** | **Not at all likely or unlikely** |
| | 13 (45%) | 4 (14%) | 12 (41%) |

***Summary of Written Comments***

Eight respondents (29%) provided written comments. The main points contained in the written comments were regarding the recommendations. One practitioner suggested that all patients need proper surgical staging. Another practitioner thought that properly staged patients with lesions such as grade 1 serous carcinoma would benefit from platinum-based chemotherapy; however, poorly staged patients should have adjunctive chemotherapy. A third practitioner indicated that the draft recommendation to offer women with stage I ovarian cancer platinum-based chemotherapy conflicted with the qualifying statement and thought it should be clarified to say that all women with stage I ovarian cancer should receive chemotherapy regardless of staging completeness. That practitioner also thought that a recommendation should be added regarding the need for re-operation to assess nodes if that was not done as part of staging, instead of just offering chemotherapy.

***Modifications/Actions***

The practice guideline recommendations and qualifying statements were clarified to address the concerns from practitioner feedback. A paragraph was also added to the DSG Consensus section to clarify the rationale for the recommendations.

***Practice Guidelines Coordinating Committee Approval Process***

The practice guideline report was circulated to members of the PGCC for review and approval. Seven of 12 members of the PGCC returned ballots. Five PGCC members approved the practice guideline report as written, and two members approved the guideline conditional on the Gynecology Cancer DSG addressing specific concerns. One PGCC member thought that the recommendations were somewhat confusing, and offered suggestions as to how to clarify the recommendations. The other PGCC member noticed an inconsistency between Figure 1 (meta-analysis of survival for patients receiving adjuvant chemotherapy versus no

chemotherapy) and the text regarding the results of the Bolis et al study (30). The member also mentioned the importance of acknowledging that the Bolis et al study did not detect a *statistical* significant difference between treatments, although the results may have clinical relevance.

***Modifications/Actions***

The Gynecology Cancer DSG revised the recommendations, based on the suggestions offered by the PGCC member. The inconsistency between Figure 1 and the text regarding the results in the Bolis et al study was corrected. The overall result of the meta-analysis of survival for patients receiving adjuvant chemotherapy versus no chemotherapy did not change when the data for the Bolis et al study were corrected. The description of the Bolis et al study was revised to indicate that the results of their trial were not statistically significant, and a qualifier was added to indicate that the trial was not powered to detect a statistically significant difference.

## IX. PRACTICE GUIDELINE

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

### Target Population

These recommendations apply to women with newly diagnosed stage I ovarian cancer.

### Recommendations

- The stage of ovarian cancer is an important prognostic factor that influences survival and the choice of therapy. The quality of the surgical staging is a key determinant of treatment recommendations (*Draft Evidence Summary "#4-15 Management of an Ovarian Mass" will further describe optimal surgical staging*).
- Women who have undergone optimal surgical staging, including pelvic and para-aortic lymph node sampling and have stage I disease, may or may not benefit from adjuvant platinum-based chemotherapy (see Qualifying Statements below).
- Women who have not undergone optimal surgical staging can be offered two options. The first option is that they undergo re-operation to optimally define the tumour stage and then be offered adjuvant therapy based on the findings. The other option is that they be offered platinum-based chemotherapy to decrease the risk of recurrence and improve survival.
- There is insufficient evidence to make a recommendation on the role of adjuvant pelvic radiation, whole abdominal-pelvic radiotherapy, or intraperitoneal radioactive chromic phosphate.

### Qualifying Statements

- Accurate staging and tumour histology information is essential for developing recommendations on the management of ovarian cancer. When there is doubt about the tumour pathology, it should be reviewed by an expert.
- The standard of care for stage IA and IB grade I ovarian cancer in Ontario has been surgical resection with optimal staging and no adjuvant therapy. This is based on work by Young et al in non-optimally staged, stage I cancer, and the prognostic studies by Vergote et al that reported an extremely low probability of recurrence in this population.
- The results of the largest trial comparing adjuvant chemotherapy to no chemotherapy in women with early stage ovarian cancer (ICON/ACTION Trial) are controversial because:

- A subgroup analysis of the ACTION Trial showed no benefit from adjuvant chemotherapy in women who underwent optimal surgical staging, but this analysis was under-powered.
- The entry criteria for the ICON Trial were vague and did not reflect the standard of surgical care offered in Canadian centers.
- The meta-analysis included in this practice guideline demonstrates that stage I patients have an improved outcome with adjuvant chemotherapy. However, an estimated 90% of women undergoing surgical resection for ovarian cancer do not undergo optimal surgical staging. If the restaging of a suboptimally staged patient reveals a more advanced disease, chemotherapy is the preferred treatment option. If reoperation confirms stage I disease, there is insufficient evidence for or against adjuvant chemotherapy. The treatment decision must be based on a discussion with the patient about potential benefits and risks.

**Future Research**

Future research needs to evaluate the implementation of surgical staging as a means of avoiding the use of chemotherapy in women who may not require toxic therapy. The role of adjuvant therapy in women with poor prognostic factors who are optimally staged needs to be assessed. The optimal chemotherapy regimen in terms of agents, dose, and duration has yet to be defined.

**Related Guidelines**

1. Practice Guidelines Initiative Practice Guideline Report #4-1-2: *First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer*.
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3. Practice Guidelines Initiative Draft Evidence Summary Report #4-15: *Management of an ovarian mass (in progress)*.

## X. JOURNAL REFERENCE

This material has been published as "Elit L, Chambers A, Fyles A, Covens A, Carey M, Fung Kee Fung M. Systematic review of adjuvant care for women with stage I ovarian carcinoma. *Cancer* 2004;101(9):1926-35." © 2004 American Cancer Society; Publisher: Wiley-Liss, Inc. DOI: 10.1002/cncr.20595.

## XI. ACKNOWLEDGEMENTS

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

## REFERENCES


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**Appendix 1. Guidelines and reviews providing recommendations for the surgical management of a suspicious ovarian mass.**

| Article | TAH + BSO | Laparotomy | Inspection of peritoneal surfaces | Peritoneal washings | Biopsies of suspicious lesions | Pelvic & para-aortic node sampling | Omentec-tomy | Appendec-tomy | Debulking |
|---|---|---|---|---|---|---|---|---|---|
| *Guidelines* | | | | | | | | | |
| EORTC, 2003 (9) | - | - | ✓ | ✓ | ✓ | ✓ | ✓ | - | - |
| ESMO, 2001 (10) | ✓ | ✓ | - | ✓ | ✓ | ✓ | ✓ | - | - |
| SOR, 2001 (11) | ✓ | - | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓-- advanced |
| SGO, 2000* (57) | - | - | - | - | - | - | - | - | - |
| SOGC, 2000 (12) | ✓ | - | ✓ | ✓ | ✓ | ✓ | ✓ | - | ✓-- advanced |
| NCCN, 1997 (58), 1996 (14) | ✓ | ✓ | - | - | - | - | - | - | ✓ |
| SSO, 1997 (13) | ✓ | - | - | ✓ | ✓ | ✓ | ✓ | - | - |
| NIH, 1994 (15) | ✓ | ✓ | - | ✓ | ✓ | ✓ | ✓ | - | ✓ |
| ACOG, 1991 (16) | ✓ | - | ✓ | ✓ | ✓ | ✓ | ✓ | - | - |
| *Reviews* | | | | | | | | | |
| Gibbs, 2001** (59) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | - | - | - |
| Leblanc, 2000 (60) | ✓ | - | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | - |
| Williams, 1996*** (61) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | - | - |
| Hoskins, 1993 (62) | ✓ | - | - | ✓ | ✓ | ✓ | - | - | - |

Note: ACOG, American College of Obstetricians and Gynecologists; BSO, bilateral salpingo-oophorectomy; EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NIH, National Institutes of Health; SGO, Society of Gynecologic Oncologists; SOGC, Society of Obstetricians and Gynaecologists of Canada; SOR, Standards, Options & Recommendations; SSO, Society of Surgical Oncology; TAH, total abdominal hysterectomy.

*SGO stressed the importance of surgical staging in their guideline but did not provide specific recommendations for procedures.
**TAH + BSO is optional in early stage patients—dependent upon fertility.
***Suspected early stage recommendations.

**Evidence-based Series 4-13 Version 3: Section 3**

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

# Adjuvant Care for Stage I Ovarian Cancer

# Document Review Summary

*L. Hogan, C. Arinze, and the members the Gynecology Cancer Disease Site Group.*

**Review Date: March 15, 2022**

**The 2004 guideline recommendations are**

## ENDORSED

**This means that the recommendations are still current and relevant for decision making.**

**OVERVIEW**

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2004 and updated in 2016. In November 2020, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. The results of the literature search were discussed with the clinical expert and it was determined that the existing recommendations could be endorsed.

**DOCUMENT ASSESSMENT AND REVIEW RESULTS**

**Questions Considered**

1. What is the role of adjuvant care in women with completely surgically staged stage I ovarian cancer?
2. What is the role of adjuvant care in women who receive incomplete or no surgical staging of ovarian cancer?
3. What is the optimal strategy for adjuvant care in women with ovarian cancer?

**Literature Search and New Evidence**

The new search (January 2017 to December 2021) of Medline, Embase, and the Cochrane Database for systematic reviews, yielded 210 publications. Out of the 210 publications, the full text of 23 articles were retrieved and reviewed. No new publications of RCTs or systematic review of RCTs were identified that investigated the role of adjuvant care in women who

received incomplete or no surgical staging or women with completely surgically staged stage I ovarian cancer. An additional search for ongoing studies on Clinicaltrials.gov did not yield any potential study on stage 1 ovarian cancer.

**Impact on the Guideline and Its Recommendations**
Although no new evidence was identified in the updated search, the Gynecology Cancer DSG considered that the questions were still relevant and ENDORSED the 2004 recommendations on adjuvant care for stage I ovarian cancer.

# Document Review Tool

| | |
|---|---|
| **Number and Title of Document under Review** | 4-13 Adjuvant Care for Stage I Ovarian Cancer |
| **Original Report Date** | May 4, 2016 |
| **Date Assessed (by DSG or Clinical Program Chairs)** | November 17, 2020 |
| **Health Research Methodologist** | Chika Arinze |
| **Clinical Expert** | Liat Hogen |
| **Approval Date and Review Outcome (once completed)** | February 8, 2022 |

Original Question(s):

1. What is the role of adjuvant care in women with completely surgically staged stage I ovarian cancer?
2. What is the role of adjuvant care in women who receive incomplete or no surgical staging of ovarian cancer?
3. What is the optimal strategy for adjuvant care in women with ovarian cancer?

Target Population:

These recommendations apply to women with newly diagnosed stage I ovarian cancer.

Study Selection Criteria:

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized controlled trials (RCTs) comparing two or

more adjuvant setting treatments (chemotherapy, radiotherapy, and/or surgery) in women with stage I ovarian cancer.

Search Details:

- January 2017 to October 2021 Cochrane (Database of Systematic Reviews)
- January 2015 to December 2021 (Medline and Embase)
- January 2015 to December 2021 (Clinicaltrial.org for ongoing trials)

Summary of new evidence:

Out of 210 hits from the search of Medline, Embase, and the Cochrane Database for systematic reviews, no new publications of RCTs or systematic review of RCTs investigating the role of adjuvant care in women who received incomplete or no surgical staging and women with completely surgically staged stage I ovarian cancer. Search of ongoing trials did not yield studies on stage 1 ovarian cancer.

Clinical Expert Interest Declaration:

The clinical expert (LH) and Health Research Methodologist (CA) declared no conflict.

| | |
|---|---|
| 1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed) | NA - No new evidence was found |
| 2. Does the newly identified evidence support the existing recommendations? | NA - No new evidence was found |
| 3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary) | NA - No new evidence was found |
| **Review Outcome as recommended by the Clinical Expert** | ENDORSE |
| ***If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?*** | |

| | |
|---|---|
| **DSG/Expert Panel Commentary** | Although no new evidence was identified in the updated search, the review is still important because the questions are relevant. |

**Literature Search strategy:**
Database(s): Ovid MEDLINE(R) 1996 to December 10, 2021, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2017 to October 27, 2021

1. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
2. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
3. random allocation/ or double blind method/ or single blind method/
4. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
5. or/1-4
6. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
7. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
8. (6 or 7) and random$.tw.
9. (clinic$ adj trial$1).tw.
10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
11. placebos/
12. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
13. (allocated adj2 random).tw.
14. or/9-13
15. 5 or 8 or 14
16. (comment or letter or editorial or news or newspaper article or patient education handout or case reports or historical article).pt.
17. 15 not 16
18. exp animals/ not humans/
19. 17 not 18
20. (systematic adj (review: or overview:)).mp.
21. (meta-analy: or metaanaly:).mp.
22. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
23. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
24. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
25. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
26. or/20-25
27. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
28. (stud: adj1 select:).ab.
29. (27 or 28) and review.pt.
30. 26 or 29
31. (guideline or practice guideline).pt.
32. exp consensus development conference/

33. consensus/
34. (guideline: or recommend: or consensus or standards).ti.
35. 31 or 32 or 33 or 34
36. 30 or 35
37. (comment or letter or editorial or news or newspaper article or case reports or historical article).pt.
38. 36 not 37
39. 19 or 38
40. Neoplasms, ovarian.mp
41. ovarian cancer.mp.
42. cancer, ovary.mp.
43. 40 or 41 or 41
44. early stage.mp
45. stage I.mp.
46. 44 or 45
47. 43 and 45
48. chemotherapy.mp.
49. surgery.mp.
50. radiotherapy.mp.
51. 48 or 49 or 50
52. 47 and 51
53. 39 and 52
54. (201509$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$ or 2021$).ed.
55. 53 and 54
56. limit 55 to english language

**Database(s): Embase 1996 to 2021 October 27**

1. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
3. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4. or/1-3
5. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6. 5 and random$.tw.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9. placebo/
10. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11. (allocated adj2 random).tw.
12. or/7-11
13. 4 or 6 or 12
14. (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
15. 13 not 14
16. animal/ not human/
17. 15 not 16
18. (systematic adj (review: or overview:)).mp.
19. (meta-analy: or metaanaly:).mp.

20. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
21. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
22. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
23. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
24. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
25. (stud: adj1 select:).ab.
26. (24 or 25) and review.pt.
27. or/18-23
28. 26 or 27
29. (27 or 28) and review.pt.
30. consensus development conference/
31. practice guideline/
32. *consensus development/ or *consensus/
33. *standard/
34. (guideline: or recommend: or consensus or standards).kw.
35. (guideline: or recommend: or consensus or standards).ti.
36. or/30-35
37. (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
38. (28 or 36) not 37
39. 17 or 38
40. Neoplasms, ovarian.mp.
41. ovarian cancer.mp.
42. cancer, ovary.mp.
43. 40 or 41 or 42
44. early stage.mp.
45. stage I.mp.
46. 44 or 45
47. 43 and 45
48. chemotherapy.mp.
49. surgery.mp.
50. radiotherapy.mp.
51. 48 or 49 or 50
52. 47 and 51
53. 39 and 52
54. (201509$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$ or "2021").ew.
55. 53 and 54

## DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel 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. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic 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 Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

**APPENDIX A: DOCUMENT ASSESSMENT AND REVIEW CONDUCTED IN 2016**

**Evidence-based Series 4-13 Version 3: Section 3**

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

# Adjuvant Care for Stage I Ovarian Cancer

# Guideline Summary Review

*L. Elit, N. Coakley, and the members the Gynecology Cancer Disease Site Group.*

**Review Date: May 4, 2016**

**The 2004 guideline recommendations are**

## ENDORSED

**This means that the recommendations are still current and relevant for decision making.**

**OVERVIEW**

**Evidence-based Series History**

This guidance document was originally released by Cancer Care Ontario's Program in Evidence-based Care in 2004. In December 2015, the PEBC guideline update strategy was applied and the new document to be updated released in February 2016. The recommendations and the systematic review in this version are the same as May 2004 version. One change was made in the document. In the original document in section 2 in the introduction, it is stated that the most common form of ovarian cancer originates in the epithelial surface cells of the ovary. We now know that most of these high grade serous tumours probably originate in the fallopian tube rather than the ovary and the document has been changed to reflect this new evidence.

**Update Strategy**

Using the Document Review Tool, the PEBC update strategy includes an updated search of the literature review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

**DOCUMENT ASSESSMENT AND REVIEW RESULTS**

**Questions Considered**

1. What is the role of adjuvant care in women with completely surgically staged stage I ovarian cancer?

2. What is the role of adjuvant care in women who receive incomplete or no surgical staging of ovarian cancer?
3. What is the optimal strategy for adjuvant care in women with ovarian cancer?

**Literature Search and New Evidence**

Medline, EMBASE and the Cochrane Database of Systematic reviews were searched from June 2003 to December 1, 2015. The search strategy can be found at the end of this document section. The American Society Clinical Oncology, and National Guidelines Clearing House using the terms, early-stage ovarian cancer were also searched. The search yielded 15 references representing 4 practice guidelines, 2, meta-analyses, 3 Cochrane Reviews and 5 RCTs (of which 1 is an abstract). Brief results of these publications are shown in the Document Review Tool at the end of this report.

**Impact on Guidelines and Its Recommendations**
The new data supports existing recommendations. Hence, the Gynecology DSG ENDORSED the 2004 recommendations for adjuvant care for stage 1 ovarian cancer.

**DOCUMENT REVIEW TOOL**

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|---|---|
| **Number and title of document under review** | **4-13** Adjuvant Care for Stage 1 Ovarian Cancer |
| **Current Report Date** | May 3, 2004 |
| **Clinical Expert** | Dr. L. Elit |
| **Research Coordinator** | Nadia Coakley |
| **Date Assessed** | 19 Jan 2016 |
| **Approval Date and Review Outcome (once completed)** | January 20, 2016 - ENDORSED |

Original Question(s):
1. What is the role of adjuvant care in women with completely surgically staged stage I ovarian cancer?
2. What is the role of adjuvant care in women who receive incomplete or no surgical staging of ovarian cancer?
3. What is the optimal strategy for adjuvant care in women with ovarian cancer?

Target Population:
These recommendations apply to women with newly diagnosed stage I ovarian cancer.
Study Section Criteria:
Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized controlled trials (RCTs) comparing two or more adjuvant setting treatments (chemotherapy, radiotherapy, and/or surgery) in women with stage I ovarian cancer.

Search Details:
Medline, MEBASE and Cochrane June 2003- December 1, 2015

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| Also searched: American Society Clinical Oncology (Past 5 years only), and National Guidelines Clearing House using the terms, ovarian cancer and early stage<br>Brief Summary/Discussion of New Evidence:<br>330 total hits from Medline, Cochrane and EMBASE + 1 hit from clinicaltrials.gov.<br><br>Fifteen references representing 4 practice guidelines, 2, meta analyses, 3 Cochrane reviews and 5 RCTs (of which 1 is an abstracts).<br><br>Clinical Expert Interest Declaration:<br>None | |
| **Instructions. Instructions.** For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary. | |
| 4. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? | no |
| 5. On initial review,<br>a. Does the newly identified evidence support the existing recommendations?<br>b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? | a. Yes<br>b. Yes |
| 6. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary: | No |
| 7. Do the PEBC and the DSG/GDG responsible for this document have the | Not applicable |

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| resources available to write a full update of this document within the next year? | |
| **Review Outcome** | ENDORSE |
| **DSG/GDG Approval Date** | April 26, 2016 |
| **DSG/GDG Commentary** | The updated search has provided more detail on agents, duration of use, lack of benefit of maintenance therapy, Bev, Rupture, Not in package but there is new staging from FIGO that has some effect. |

| Reference | Disease type and population | Intervention | Results |
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| **Guideline** | | | |
| Alberta Health Services Guideline 2013 | The recommendations outlined in this guideline apply to adults over the age of 18 years with epithelial ovarian cancer | The guideline was originally developed in 2011 and then updated in 2012 and 2013. The literature was reviewed prior to each update, using the search strategy described above. The 2012 and 2013 reviews included a total of 35 studies and eight studies, respectively. | Stage I/IIA<br>• Young patient: fertility preserving staging<br>• Older patient: total hysterectomy, bilateral salpingoophorectomy and staging<br>o Stage IA / IB, Grade 1:Observation<br>o Stage IA / IB, Grade 2<br>-Observation depending on histologic type and individual case selection.<br>-Chemotherapy depending on histologic type and individual case selection.<br>o Stage IC / IIA, Grades 1-3<br>- Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles dependent on histological type, grade, and individual case selection<br>o Clear cell carcinoma: Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles<br>o Papillary serous carcinoma:<br>-Grade 1: Observation<br>-Grade 2/3: Chemotherapy with carboplatin and paclitaxel × 6 cycles<br>o Endometrioid tumours:<br>- Grade 1/2: Observation<br>- Grade 3: Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles<br>o Mucinous tumours:<br>-Grade 1/2: Observation<br>-Grade 3: Chemotherapy with carboplatin and paclitaxel × 3 cycles<br>o Undifferentiated tumors: Chemotherapy with carboplatin and paclitaxel X 6 cycles<br>o If incomplete staging, consider:<br>-Completion of surgical staging if medically fit patient +/- chemotherapy as indicated |

| Reference | Disease type and population | Intervention | Results |
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| | | | - OR chemotherapy |
| SIGN (Scottish intercollegiate guidelines network)<br>3013<br>Epithelial ovarian cancer | This guideline provides recommendations based on current evidence for best practice in the management of epithelial ovarian cancer. It excludes the management of borderline tumours. | The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane<br>Library. The year range covered was 2003-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated<br>by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence | -All women with high grade early stage (1a-1b) ovarian cancer should be considered for adjuvant chemotherapy<br>-Patients with low-grade serous, clear cell and mucinous histological subtypes should be considered for clinical trials<br>-Routine systematic lymphadenectomy in early stage epithelial ovarian cancer is not recommended.<br>-Retroperitoneal lymph node sampling should be considered as part of surgical staging for apparent early stage disease<br>-First line chemotherapy treatment of epe;litheial ovarian caner should include a platinum agent either in combination or as a single agent, unless specifically contraindicated<br>-Carboplatin is a the platinum drug of choice in both single and combination therapy<br>- Paclitaxcel is recommended in combination therapy with platinum in the first line post-surgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy. In those unable to tolerate paclitaxel, peglated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative.<br>- Patients who are unfit for combination therapy should be offered single agent carboplatin.<br>-A third cytotoxic agent should not be added to carboplatin and paclitaxel.<br>- Carboplatin AuC 6 (day 1 q21) and paclitaxel 80 mg/m2 (day 1, 8, 15 q21) may be considered for the treatment of first line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient |
| NCCN guideline (National Comprehensive Cancer Network (US)<br>2015 | Comprehensive Ovarian cancer Guideline | This is more of a disease management pathway and is difficult to sum up. Please have a look at the guideline. | http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf |

| Reference | Disease type and population | Intervention | Results |
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| NICE (National Institute for Health and Care Excellence) UK<br><br>Ovarian cancer: recognition and initial management (CG122)<br><br>2011 | The guideline recommendations are applicable to women with epithelial ovarian cancer (the most common type of ovarian cancer), as well as women with fallopian tube carcinoma, primary peritoneal carcinoma or borderline ovarian cancer | NICE commissioned the National Collaborating Centre for Cancer to develop this guideline. The Centre established a Guideline Development Group (see appendix A), which reviewed the evidence and developed the recommendations. An independent Guideline Review Panel oversaw the development of the guideline (see appendix B). | ***Section 1.3 Management of suspected early (stage I) ovarian cancer***<br><br>***The role of systematic retroperitoneal lymphadenectomy***<br>*-Perform retroperitoneal lymph node assessment as part of optimal surgical staging in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).*<br>-Do not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).<br>**Adjuvant systemic chemotherapy for stage I disease**<br>-Do not offer adjuvant chemotherapy to women who have had optimal surgical staging and have low-risk stage I disease (grade 1 or 2, stage Ia or Ib).<br>-Offer women with high-risk stage I disease (grade 3 or stage Ic) adjuvant chemotherapy consisting of six cycles of carboplatin. Discuss the possible benefits and side effects of adjuvant chemotherapy with women who have had suboptimal surgical staging and appear to have stage I disease. |
| **Chemotherapy** | | | |
| Winter-Roach BA 2012 Cochrane Review | Epithelial | An electronic search was performed using the Cochrane Gynaecological Cancer Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2 2008), MEDLINE (1966 to 2008), EMBASE (1980 to 2008) and CancerLit. The search | Meta-analysis of 3 trials with adequate data, assessing 1008 women, indicated that women who received adjuvant platinum-based chemotherapy had better OS than those who did not (HR 0.71; 95% CI 0.53 to 0.93). Likewise, meta-analysis of four trials with adequate data, assessing 1170 women, indicated that women who received adjuvant chemotherapy had better progression-free survival (PFS) than those who did not (HR 0.67; 95% CI 0.53 to 0.84). The trials included in these meta-analyses gave consistent estimates of the effects of chemotherapy. |

| Reference | Disease type and population | Intervention | Results |
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| | | strategy was developed using free text and MeSH key words<br><br>Five randomized controlled trials (RCTs), enrolling 1277 women, with 46 to 110 months follow-up, met our inclusion criteria. These trials had low risk of bias. | Sub-group analysis suggested that women who had optimal surgical staging of their disease were unlikely to benefit from adjuvant chemotherapy (HR for OS 1.22;95% CI 0.63 to 2.37) whereas those who had sub-optimal staging did (HR for OS 0.63; 95% CI 0.46 to 0.85). One trial showed a benefit from adjuvant chemotherapy among women at high risk (HR for OS 0.48; 95% CI 0.32 to 0.72) but not among those at low risk (HR for OS 0.95; 95% CI 0.54 to 1.66). However, these sub-group findings could be due to chance.<br>AUTHORS' CONCLUSION:<br>Adjuvant platinum based chemotherapy is effective in prolonging the survival of the majority of patients who are assessed as having early stage epithelial ovarian cancer. However, even given the limits of sub-group analyses, there is strong evidence that optimal surgical staging identifies patients who have either little or nothing to gain from adjuvant chemotherapy. Taken together with the lack of a survival advantage seen in patients with "low-risk" cancers in the ICON1 trial, it appears safe to withhold adjuvant chemotherapy from optimally staged patients with well differentiated tumors |
| Collinson F. 2014<br>RCT | Patients with histologically confirmed epithelial OC were eligible if, in the opinion of the treating physician, there was uncertainty as to whether the patient required immediate adjuvant chemotherapy. Patients had to be fit to receive chemotherapy, with no previous malignant disease | Patients were randomly assigned with a 1:1 ratio to receive immediate adjuvant chemotherapy (N=241) or no immediate adjuvant chemotherapy (N=236). Six cycles of chemotherapy with either single-agent carboplatin (87% of patients received) or the three-drug combination cyclophosphamide, doxorubicin and cisplatin (CAP) was recommended, | With a median follow-up of 10 years, the estimated HR for Recurrence free survival(RFS) was 0.69 [95% confidence interval (CI) 0.51–0.94, *P* = 0.02] and OS 0.71 (95% CI 0.52–0.98, *P* = 0.04) in favour of chemotherapy. In absolute terms, there was a 10% (60%–70%) improvement in RFS and a 9% (64%–73%) improvement in OS; the benefit of chemotherapy might be greater in high-risk disease (18% improvement in OS). Uncertainty remains about the optimal chemotherapy regimen. The only randomised trial data available are from a subset of 120 stage 1 patients in ICON3 where the treatment difference, comparing carboplatin with carboplatin/paclitaxel was estimated with relatively wide CIs [progression-free survival HR = 0.71 (95% CI 0.39–1.32) and OS HR = 0.98 (95% CI 0.49–1.93)] |

| Reference | Disease type and population | Intervention | Results |
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| | (excepting non-melanomatous skin cancer) and to have not received any previous chemotherapy or radiotherapy. | although alternative platinum-based regimens were also allowed. No patients received paclitaxel. The planned chemotherapy regimen for a patient was specified before individual randomisation. | |
| Perren TJ<br>2011<br>RCT | Histologically confirmed, high-risk, early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I or IIA and clear-call or grade 3 tumors) or advanced (FIGO stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (based on local histopathological findings). Additional eligibility criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 | Carboplatin (AUC 5 or 6) and paclitaxel (175 mg/$m^2$), given every 3 weeks for 6 cycles, or above regimen plus bevacizumab (7.5 mg per kg of body weight), given concurrently every 3 weeks for 5 or 6 cycles and continued for 12 additional cycles or until progression of disease. | PFS for FIGO Stage 1<br>Bevacizumab 6/54 events<br>Standard Chemo 9/65 events<br>HR 0.73; 95%CI 0.27-2.02 p= 0.55<br><br>No other results were broken down by stage |
| Mannel RS<br>2011<br>RCT phase III | Eligibility was limited to patients with stage IA/B (grade 3 or clear cell), all IC or II epithelial ovarian cancer. | All patients were to receive carboplatin AUC 6 and paclitaxel 175mg/$m^2$ q3 weeks×3 courses with random assignment to either observation | At least 3 cycles of treatment were administered to 524/542 (97%) of patients, and among those assigned to maintenance paclitaxel, 80% completed the regimen. The incidence of grade 2 or worse peripheral neuropathy (15.5% vs. 6%), infection/fever (19.9% vs. 8.7%), and dermatologic events (70.8% vs. 52.1%) was higher on the maintenance regimen ( $p$ <0.001). |

| Reference | Disease type and population | Intervention | Results |
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| | | or maintenance paclitaxel 40mg/m $^2$ /week×24weeks. Recurrence required clinical or radiological evidence of new tumor. | The cumulative probability of recurring within 5 years for the maintenance paclitaxel regimen is 20% vs. 23% for surveillance (HR 0.807; 95% CI: 0.565–1.15). The probability of surviving 5 years was 85.4% and 86.2%, respectively. |
| Trope C<br>2007<br>Meta Analysis | Medline and Cochrane were searched between 1970 to 2006. Additional manual searches in relevant journal indexes and reference lists of retrieved articles were performed. The search term EOC (Early Ovarian Cancer) was used in combination with AC/adjuvant radiotherapy, surgery, and prospective randomized studies. Only prognostic randomized controlled studies, other controlled studies, and meta-analyses were used | 22 randomized studies were found. Nine of these studies were of low quality because they had methodologic flaws such as the omission of a control arm, inclusion of borderline tumors, incomplete surgical staging, or the inclusion of patients with stage II and III disease with minimal residual disease. Most of these trials included too few patients for conclusive results and will not be addressed. | 22 prospective RCTs were analyzed, which included 4,626 patients. No difference between adjuvant chemotherapy (AC) and radiotherapy was found. There is agreement that patients with stage IA, grade 1 tumors have excellent survival and do not need postsurgical therapy.<br>The International Collaborative Ovarian Neoplasm 1/Adjuvant Chemotherapy in Ovarian Neoplasm trials were the first to show an effect on survival of AC, but in patients with adequate surgical staging, there was no additional effect of AC. For patients who are staged incompletely at the time of initial surgery, completion of the staging procedure with either laparoscopy or laparotomy is a reasonable approach before a final decision is made regarding the need for AC. If full staging cannot be performed due to medical contraindication or patient refusal, consideration of AC is reasonable in selected patients. Using prognostic variables such as grade, International Federation of Gynecology and Obstetrics substage, pretreatment of CA-125 _ 30 U/mL, and DNA ploidy, it is possible to divide patients into risk groups to avoid overtreatment. Gynecologic Oncology Group study 157 suggests that it may be possible to minimize chemotherapy-induced toxicity by using three instead of six cycles of AC, although it is not known fully whether this will compromise effectiveness. |
| Bell J.<br>2006<br>RCT | All eligible patients had a histological diagnosis of epithelial ovarian cancer including serous, mucinous, endometrioid, mixed, undifferentiated, | Patients were to receive either 3 (N= 232) or 6 (N=225) cycles of chemotherapy consisting of paclitaxel 175 mg/m$^2$ by 3 h infusion and carboplatin dosed at AUC 7.5 | Median follow-up is 6.8 years for 344 women alive at last contact. Grade 3 or 4 neurotoxicity occurred in 4/211 (2%) and 24/212 (11%) treated patients on the 3- and 6-cycle regimens, respectively ($p < 0.01$); 6 cycles also caused significantly more severe anemia and granulocytopenia. The recurrence rate for 6 cycles was 24% lower (hazard ratio [HR]: 0.761; 95% confidence |

| Reference | Disease type and population | Intervention | Results |
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| | Brenner, clear cell, and transitional types. Borderline or low malignant potential tumors were ineligible. After a staging operation, patients were to have completely resected stage IA grade 3 (or clear cell), stage IB grade 3 (or clear cell), stage IC, or stage II disease. | by infusion over 30 min. Treatment cycles were scheduled every 21 days. Standard preparative regimen for paclitaxel included dexamethasone, diphenhydramine, and cimetidine. | interval [CI]: 0.51–1.13, *p* = 0.18), and the estimated probability of recurrence within 5 years was 20.1% (6 cycles) versus 25.4% (3 cycles). The overall death rate was similar for these regimens (HR: 1.02; 95% CI: 0.662–1.57). |
| Herrstedt J 2009<br>RCT - Abstract | Histological verified first diagnosis of epithelial ovarian cancer, FIGO IC-IV | (TC) Paclitaxel carboplatin paclitaxel 175 mg/m$^2$ 3h iv d1 + carboplatin AUC 5 iv d1) or<br><br>(TCG) Gemcitabine, paclitaxel carboplatin (TC + gemcitabine 800 mg/m$^2$ iv d1+8) for at least 6 cycles every 21 days starting within 6 weeks post-operatively. | Final analysis has shown that addition of gemcitabine did not improve overall survival in patients with FIGO stage IIB-IV disease. Approximately 11% of the patients (n = 175) had FIGO stage I-IIA disease (stratum I). Most patients received6+ cycles (93.3% TC, 86.9% TCG). With a median follow-up of53.8 (range 0 -75) months, and using the log rank test and Cox regression analysis, no relevant differences in progression free survival (first quartile about 57 months and median 75 months in both groups, HR = 0.90 [95% CI: 0.47-1.72],p = 0.7500) and a negative trend in overall survival (first quartile 75 months in both groups, HR = 2.19 [95% CI: 0.75-6.41],p = 0.1419) were seen. Addition of G to TC did not improve efficacy in patients with stage I-IIA ovarian cancer. This was also the case for stratum II-III patients (previously reported). The addition of G to TC in patients with first diagnosis of ovarian cancer cannot be recommended. |
| **Surgery** | | | |
| Kim HS 2013<br>Meta Analysis | The impact of intraoperative rupture on prognosis is controversial in early-stage epithelial ovarian | PubMed, Embase, and the Cochrane Library were searched up to May 2011. 9 eligible studies including 2382 patients were evaluated. | Preoperative involvement decreased progression-free survival when compared with intraoperative rupture (PFS; HR, 1.47; 95% CI, 1.01–2.14), which also showed poorer PFS than no rupture (HR, 2.41; 95% CI, 1.74–3.33). Although preoperative involvement reduced PFS when compared with intraoperative |

| Reference | Disease type and population | Intervention | Results |
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| | cancer. A meta-analysis to determine its impact and to evaluate factors to increase its risk was preformed. | All patients were classified into three groups: no rupture; intraoperative rupture; preoperative involvement. | rupture (HR, 2.63; 95% CI, 1.11–6.20), there was no difference in it between intraoperative rupture and no rupture in patients who underwent complete surgical staging operation and adjuvant platinum-based chemotherapy if needed (HR, 1.49; 95% CI, 0.45–4.95). Furthermore, adhesion to adjacent tissues, grade 2 or 3 disease were more common (ORs, 2.01 and 2.47; 95% CIs, 1.20–3.37 and 1.12–5.46), whereas mucinous tumor was less frequent (OR, 0.51; 95% CI, 0.37–0.72) in intraoperative rupture than in no rupture. |
| Lawrie TA 2013 Cochrane Review | Women with stage I ovarian cancer defined by FIGO<br><br>Surgical staging via laparoscopy (experimental group) versus laparotomy (control group) for stage I ovarian cancer. | Cochrane, MEDLINE, EMBASE, LILACS, Biological Abstracts and CancerLit (1990 to December 2011. | There were no studies to include, therefore we tabulated data from non-randomised studies (NRS) for discussion. This review has found no good-quality evidence to help quantify the risks and benefits of laparoscopy for the management of early-stage ovarian cancer as routine clinical practice. No meta-analyses were performed. |
| **Combination treatment** | | | |
| Shylasree TS 2013 Cochrane Review | Women of any age with a diagnosis of ovarian carcinosarcoma (malignant mixed Mullerian tumour of the ovary) at any FIGO stage.<br>• | Cochrane, MEDLINE, and EMBASE, registers of clinical trials, abstracts of scientific meetings, reference lists of review articles were searched up to February 2012.<br>RCT's of:<br>• adjuvant chemotherapy with or without radiotherapy (surgery followed by chemotherapy with or without radiotherapy); | The search strategy identified 297 unique references of which all were excluded. Authors' conclusions, We found no evidence to inform decisions about neoadjuvant and adjuvant chemotherapy and radiotherapy regimens, or chemotherapy alone, for women with ovarian carcinosarcoma. Ideally, an RCT that is multicentre or multinational, or well designed non-randomised studies that use multivariate analysis to adjust for baseline imbalances, are needed to compare treatment modalities and improve current knowledge. Further research in genetic and molecular signalling pathways might improve understanding of this tumour subtype. |

| Reference | Disease type and population | Intervention | Results |
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| | | • adjuvant radiotherapy and combination chemotherapy;<br>• adjuvant single drug chemotherapy versus combination chemotherapy;<br>• neoadjuvant chemotherapy and radiotherapy (chemotherapy with or without radiotherapy followed by surgery).<br>• surgery alone. | |

**Results from Clinical trials.gov**

| ClinicalTrials.gov Identifier: | Title | Description |
|---|---|---|
| NCT00003644 | Carboplatin Plus Paclitaxel With or Without Continued Low-Dose Paclitaxel in Treating Patients With Early-Stage Ovarian Cancer | This randomized phase III trial is studying carboplatin and paclitaxel alone too see how well they work compared to carboplatin and paclitaxel together with continued low-dose paclitaxel in treating patients with early-stage ovarian cancer. |

## References


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13. Shylasree TS, Bryant A, Athavale R. Chemotherapy and/or radiotherapy in combination with surgery for ovarian carcinosarcoma. Cochrane Database of Systematic Reviews. 2014 (3).
14. Trope C, Kaern J. Adjuvant chemotherapy for early-stage ovarian cancer: review of the literature. J Clin Oncol. 2007;25(20):2909-20.
15. Winter Roach BA, Kitchener HC, Lawrie TA. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews. 2015 (4).

Literature Search Strategy

EMBASE
1. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
3. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4. or/1-3
5. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6. 5 and random$.tw.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9. placebo/
10. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11. (allocated adj2 random).tw.
12. or/7-11
13. 4 or 6 or 12
14. (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
15. 13 not 14
16. animal/ not human/
17. 15 not 16
18. (systematic adj (review: or overview:)).mp.
19. (meta-analy: or metaanaly:).mp.
20. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
21. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
22. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
23. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
24. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
25. (stud: adj1 select:).ab.
26. (24 or 25) and review.pt.
27. or/18-23
28. 26 or 27
30. consensus development conference/
31. practice guideline/
32. *consensus development/ or *consensus/
33. *standard/
34. (guideline: or recommend: or consensus or standards).kw.
35. (guideline: or recommend: or consensus or standards).ti.
36. or/30-35
37. (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
38. (28 or 36) not 37
39. 17 or 38
40. Neoplasms, ovarian

41, ovarian cancer.mp
42. cancer, ovary.mp
43. 40 or 41 or 42
44. early stage
45. stage I
46. chemotherapy
47. surgery
48. radiotherapy
49. 44 or 45
50. 43 and 49
51. 46 or 47 or 48
52. 50 and 51
53. 39 and 52

Medline
pebc 2015
1. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
2. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
3. random allocation/ or double blind method/ or single blind method/
4. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
5. or/1-4
6. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
7. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
8. (6 or 7) and random$.tw.
9. (clinic$ adj trial$1).tw.
10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
11. placebos/
12. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
13. (allocated adj2 random).tw.
14. or/9-13
15. 5 or 8 or 14
16. (comment or letter or editorial or news or newspaper article or patient education handout or case reports or historical article).pt.
17. 15 not 16
18. exp animals/ not humans/
19. 17 not 18
20. (systematic adj (review: or overview:)).mp.
21. (meta-analy: or metaanaly:).mp.
22. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
23. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
24. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
25. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
26. or/20-25
27. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.

28. (stud: adj1 select:).ab.
29. (27 or 28) and review.pt.
30. 26 or 29
31. (guideline or practice guideline).pt.
32. exp consensus development conference/
33. consensus/
34. (guideline: or recommend: or consensus or standards).ti.
35. 31 or 32 or 33 or 34
36. 30 or 35
37. (comment or letter or editorial or news or newspaper article or case reports or historical article).pt.
38. 36 not 37
39. 20 or 38
40. Neoplasms, ovarian
41. ovarian cancer.mp
42. cancer, ovary.mp
43. 40 or 41 or 41
44. early stage
45. stage I
46. 44 or 45
47. 43 and 45
48. chemotherapy
49. surgery
50. radiotherapy
51. 48 or 49 or 50
52. 47 and 51
53. 39 and 52.

## OUTCOMES DEFINITIONS

4. **EDUCATION AND INFORMATION** – 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 our website, each page is watermarked with the word "ARCHIVED".

5. **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.

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

7. **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.