# International Collaborative Ovarian Neoplasm Trial 1: A Randomized Trial of Adjuvant Chemotherapy in Women With Early-Stage Ovarian Cancer

*International Collaborative Ovarian Neoplasm (ICON1) Collaborators*[1]

***Background:*** **The question of whether platinum-based adjuvant chemotherapy can improve outcomes in patients with early-stage epithelial ovarian cancer is an important one. We carried out a multicenter, open randomized trial to determine whether adjuvant chemotherapy would improve overall survival and prolong recurrence-free survival in women with early-stage epithelial ovarian cancer.** ***Methods:*** **Between August 1991 and January 2000, 477 patients in 84 centers in five countries were randomly assigned to receive either adjuvant chemotherapy immediately following surgery (n = 241) or no adjuvant chemotherapy until clinically indicated (n = 236). Kaplan–Meier curves of overall survival and recurrence-free survival were compared using the Mantel–Cox version of the log-rank test. All statistical tests were two-sided.** ***Results:*** **Women who received adjuvant chemotherapy had better overall survival than women who did not (hazard ratio [HR] of 0.66, 95% confidence interval [CI] = 0.45 to 0.97; *P* = .03). These results translate into 5-year survival figures of 70% for women who did not receive adjuvant chemotherapy and 79% for women who did receive adjuvant chemotherapy, a difference of 9% (95% CI = 1% to 15%). Adjuvant chemotherapy also improved recurrence-free survival (HR = 0.65; 95% CI = 0.46 to 0.91; *P* = .01). These results translate into 5-year recurrence-free survival figures of 62% for women who did not receive adjuvant chemotherapy and 73% for women who did receive adjuvant chemotherapy, a difference of 11% (95% CI = 3% to 18%).** ***Conclusion:*** **These results suggest that platinum-based adjuvant chemotherapy improves survival and delays recurrence in patients with early-stage ovarian cancer. [J Natl Cancer Inst 2003;95:125–32]**

Over 165 000 women develop ovarian cancer every year, making it the sixth most common cancer in women worldwide *(1).* At diagnosis, approximately 30% of women with ovarian cancer have early-stage disease that is confined to the pelvis (International Federation of Gynecology and Obstetrics [FIGO] stage I and II). The prognosis of early-stage disease is better than that for stage III and IV disease, but approximately 50% of women with early-stage ovarian cancer develop recurrent disease after surgery and may die from ovarian cancer *(2,3).* The primary and usually the only treatment for early-stage ovarian cancer is surgery, which in theory could be curative in low-risk patients whose disease is limited to the ovaries. There is no clear consensus, however, on what is considered to be early-stage or low-risk ovarian cancer. The relative importance of prognostic factors including tumor grade, histologic cell type, presence of ascites, degree of tumor adherence, and DNA ploidy for defining individuals at low risk of recurrence is unknown. Even when these markers have been used in clinical trials to define subgroups, there have been concerns about subjectivity and lack of reproducibility. In one study, a substantial proportion of patients had their original grade of tumor changed after central pathologic review *(4).* Trials that have attempted to define a population of low-risk patients based on optimal or superoptimal staging have also had difficulties *(5).* A number of therapies have been tried to attempt to improve survival in patients with early-stage disease who have already been treated surgically, including intraperitoneal radiation therapy, systemic chemotherapy, and total abdominal and pelvic radiation therapy. However, no

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*See* "Appendix" for the full list of names and affiliations of the ICON1 collaborators.

*See* "Notes" following "References."

randomized trial has reliably demonstrated a survival advantage of any of these therapies over the others *(6–13)* or over careful observation without immediate adjuvant therapy *(4,6–9,14,15).*

The question of whether immediate adjuvant chemotherapy after surgery would prolong the time to recurrence and improve survival in patients with early-stage epithelial ovarian carcinoma was identified in 1990 by the Advanced Ovarian Cancer Trialists Group (AOCTG) as requiring investigation. In response, the International Collaborative Ovarian Neoplasm (ICON) collaborators initiated a randomized trial in 1991 of immediate adjuvant chemotherapy for early-stage ovarian cancer (ICON1). At the same time, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a similar trial on Adjuvant ChemoTherapy In Ovarian Neoplasm (ACTION), the results of which are reported in this issue *(5).* Early in the course of both trials, it was planned that a single independent data-monitoring committee would review the combined accumulating data from both the ICON1 and ACTION trials.

## Patients and Methods

### Participants

The rate of recurrence and death in early-stage ovarian cancer patients is low, and because differences in outcomes between the two treatments were likely to be modest, a large number of patients was required. Therefore, the eligibility criteria were kept as simple as possible. The ICON studies consisted of two independent trials of chemotherapy that were initiated at the same time; one for earlier stage disease (ICON1) and one for more advanced-stage disease (ICON2). The trials were designed to be complementary so that every patient with epithelial ovarian cancer could be considered for entry into one of these randomized trials.

The protocol asked the following question of clinicians: In the opinion of the responsible clinician, does the patient require immediate chemotherapy? If the clinician was uncertain, he or she was asked to consider entering the patient into ICON1, the earlier stage trial. If the clinician was certain about the need for immediate chemotherapy, he or she was asked to consider entering the patient into ICON2, the more advanced-stage trial, which compared single-agent carboplatin with a three-drug combination of cyclophosphamide + doxorubicin + cisplatin (CAP) *(16).*

The most important eligibility criteria for ICON1 were that the patient had histologically confirmed ovarian carcinoma of epithelial origin and that the clinician was uncertain as to whether to offer immediate adjuvant chemotherapy. Other criteria were that the patient was fit to receive chemotherapy, had no previous malignant disease (except nonmelanoma skin cancer), had no previous radiation therapy or chemotherapy, and had given her written informed consent to enter the trial. Approval by the ethics committee of the local institution was required before any patient could be entered in the trial.

### Surgery

All visible tumor had to be removed. Thorough surgical staging, where possible, with total hysterectomy and bilateral salpingo-oophorectomy, where appropriate, and omentectomy was recommended as the minimum procedures.

### Randomization and Data Collection

ICON1 was run as three parallel trials through the Istituto Mario Negri in Milan, Italy; the Swiss Group for Clinical Cancer Research (SAKK) in Bern, Switzerland; and the Clinical Trials Unit of the Medical Research Council (MRC CTU), Cancer Division London, U.K. (formerly Cancer Trials Office, Cambridge, UK). Random assignment was performed in Italy for all Italian patients and in the United Kingdom for all other patients. The randomization procedure used a method of minimization stratified by center, FIGO stage *(17),* and degree of tumor differentiation. The same stratification factors were used in both randomization centers. The allocation sequence for randomization was generated on a computer by the MRC CTU and Istituto Mario Negri. The trial was open in that after patients were randomly assigned to one of the trial arms there was no blinding of treatment allocation to investigators, patients, or trial center staff.

Pretreatment data collected at the time of random assignment included age, stage, histologic cell type and degree of tumor differentiation *(18),* and planned chemotherapy regimen. Treatment and initial follow-up data were collected 6 months after randomization, and further follow-up data were collected 12 months after randomization and annually thereafter. Information on the patients' vital and disease status and date of disease recurrence, if applicable, was collected at intervals of 6 months for the first year and annually thereafter. Follow-up data included information on disease and vital status and treatment for recurrence. All follow-up data were collected either by the Istituto Mario Negri (Italian centers) or by the MRC CTU (all other centers).

### Adjuvant Chemotherapy

Six cycles of chemotherapy with single-agent carboplatin or CAP at intervals of 3 weeks were recommended, although other regimens that included platinum (combination carboplatin or single-agent cisplatin) were also allowed. The recommended dose of carboplatin when used as a single agent was based on the dose required to obtain an area under the curve (AUC) of 5 mg/mL; the recommended dose of carboplatin when used in combination was 4 mg/mL using the AUC method of Calvert et al. *(19),* in which the dose required is obtained by the formula (GFR + 25) × 5, where GFR is the measured glomerular filtration rate. The recommended dose of cisplatin when used as a single agent was 70 mg/m$^2$. The recommended doses for the CAP regimen were cyclophosphamide at 500 mg/m$^2$, doxorubicin at 50 mg/m$^2$, and cisplatin at 50 mg/m$^2$. The type of planned chemotherapy regimen for an individual patient had to be registered at the randomizing center at allocation before each patient was assigned to one of the trial arms.

### Statistical Methods and Analysis

The calculation of sample size was complicated by the fact that survival was likely to vary with tumor stage and it was difficult to estimate *a priori* the proportions of patients at each stage. It was originally planned that 2000 patients would be accrued to ICON1, which would provide 90% power to detect an absolute increase in 5-year survival of 7% (a survival improvement from 60% to 67%) at a 5% statistical significance level (two-sided test of significance).

Originally, guidelines to consider stopping the trial were stated in the ICON1 protocol as using conservative statistical significance tests (i.e., if $P<.01$, consideration would be given to stopping the trial) and in the ACTION trial protocol as following the O'Brien and Fleming rule *(20).* However, before the first

analysis the investigators of both trials agreed that a single independent data-monitoring committee would monitor the combined data from both trials as it accumulated. This data-monitoring committee followed an informal guideline that they would not stop the trials unless the results were extremely positive, for example, a *P* value of less than .001.

During the accrual period, the data-monitoring committee noted that survival in the no-adjuvant-chemotherapy arm of the combined trials was better than anticipated and that accrual was slow. Therefore, in June of 1999, the investigators of the two trials agreed that the sample size combined across both trials could be reduced to 900 patients, with approximately 450 patients to be accrued in each trial. In a combined analysis, this would provide a sufficient number of events to detect an increase in absolute 3-year survival of 6% (a survival improvement from 85% to 91%), with 90% power at a 5% statistical significance level.

The primary outcome measure was overall survival, defined as time from randomization to death from any cause. Patients who were still alive at the time of analysis were censored on the date of their last follow-up. The secondary outcome measure was recurrence-free survival, defined as the time to clinically defined recurrence or death from any cause. Kaplan–Meier curves of overall survival and recurrence-free survival were compared using the Mantel–Cox version of the log-rank test *(21)*. The stratified log-rank test was used to allow for possible differences across the two randomizing centers. All the statistical tests were two-sided, and all analyses were performed on an intention-to-treat basis.

## RESULTS

### Baseline Characteristics

Between August 1991 and January 2000, 477 patients were entered into the ICON1 trial from 84 centers in five countries (U.K., Ireland, Brazil, Switzerland, and Italy; Table 1). Two hundred forty-one patients were randomly assigned to immediate platinum-based adjuvant chemotherapy and 236 to observation until chemotherapy was indicated (i.e., no immediate adjuvant chemotherapy) (Fig. 1). For the analysis presented here, all data collected to March 2001 (in Italy) and December 2001 (data held by the MRC) was included.

Fifty percent of patients were less than 55 years old. The major histologic cell types were serous (32%), mucinous (23%), endometrioid (23%), and clear-cell (15%). Pretreatment characteristics were well balanced across the two groups (Table 1) and were similar across coordinating centers (data not shown).

Ninety-three percent of patients had FIGO stage I disease, and 73% had intermediate or well-differentiated tumors (Table 1). At randomization, six patients were classified as having stage III disease with no residual bulk. However, following randomization one of these patients was found to have had lung metastases and, in fact, had stage IV disease with residual bulk of more than 2 cm. Two other patients who were classified as having stage Ic and stage IIa disease, respectively, with no residual bulk, were found on review to have had stage III disease, with one patient having residual bulk of more than 2 cm.

### Adjuvant Chemotherapy Received

Two hundred forty-one patients were allocated to the adjuvant chemotherapy arm. As Fig. 1 shows, 44 of these patients either did not receive adjuvant chemotherapy or did not have full information available. Of the 197 patients known to have received chemotherapy (i.e., who had a documented chemotherapy regimen), 171 (87%) patients were given single-agent carboplatin, 21 (11%) were given combination cisplatin, three (2%) were given combination carboplatin, one (<1%) was given single-agent cisplatin, and one (<1%) was given an unspecified regimen. A total of 168 patients (85%) received all six cycles of chemotherapy, although 65 of these patients had some treatment modification. A total of 29 of the 197 patients who received chemotherapy (15%) received fewer than six cycles of chemotherapy. Compliance with chemotherapy and reasons for modification are summarized in Table 2. Six patients who were allocated to the no-adjuvant-chemotherapy arm actually received adjuvant chemotherapy.

**Table 1.** Patient accrual by country and patient characteristics at randomization*

| Characteristics | Treatment arm: Adjuvant chemotherapy (N = 241) | Treatment arm: No adjuvant chemotherapy (N = 236) | Total No. of patients (N = 477) |
|---|---|---|---|
| Patient accrual, n (%) | | | |
| Brazil | 1 (<1) | 0 | 1 (<1) |
| Ireland | 2 (1) | 1 (<1) | 3 (1) |
| Italy | 137 (57) | 134 (57) | 271 (57) |
| Switzerland | 6 (2) | 5 (2) | 11 (2) |
| U.K. | 95 (39) | 96 (41) | 191 (40) |
| Age (y), n (%)† | | | |
| <55 | 114 (48) | 122 (52) | 236 (50) |
| 55–65 | 65 (27) | 69 (29) | 134 (28) |
| >65 | 61 (25) | 45 (19) | 106 (22) |
| Missing | 1 | 0 | 1 |
| Median age, y | 56 | 55 | 55 |
| Tumor stage‡, n (%)† | | | |
| I | 9 (4) | 4 (2) | 13 (3) |
| Ia | 89 (37) | 97 (41) | 186 (39) |
| Ib | 27 (11) | 25 (11) | 52 (11) |
| Ic | 98 (41) | 92 (39) | 190 (40) |
| II | 15 (6) | 14 (6) | 29 (6) |
| III | 2 (1) | 4 (2) | 6 (1) |
| Missing | 1 | 0 | 1 |
| Residual bulk of disease§, n (%)† | | | |
| None | 238 (99) | 235 (99) | 473 (99) |
| <2 cm | 3 (1) | 1 (<1) | 4 (1) |
| ⩾2 cm | 0 | 0 | 0 |
| Level of differentiation, n (%)† | | | |
| Poor | 61 (27) | 63 (28) | 124 (27) |
| Intermediate | 95 (42) | 89 (40) | 184 (41) |
| Well | 71 (31) | 72 (32) | 143 (32) |
| Missing | 14 | 12 | 26 |
| Histologic cell type, n (%)† | | | |
| Serous | 79 (35) | 65 (29) | 144 (32) |
| Mucinous | 48 (21) | 55 (24) | 103 (23) |
| Endometrioid | 46 (20) | 57 (25) | 103 (23) |
| Clear cell | 31 (14) | 36 (16) | 67 (15) |
| Undifferentiated | 6 (3) | 2 (1) | 8 (2) |
| Other | 16 (7) | 10 (4) | 26 (6) |
| Missing | 15 | 11 | 26 |

*Missing = information on patient was missing from dataset.

†Percentages calculated do not include missing values in denominator and may not add up to 100% because of rounding.

‡Two patients randomized as stage Ia and II, respectively, were found to have been stage III, and one patient randomized as stage III was found to have been stage IV. Staging and grading was in accordance with International Federation of Gynecology and Obstetrics (FIGO) and World Health Organization (WHO) staging and grading systems *(16,17)*.

§Two patients randomized as having no residual bulk were found to have had residual bulk ⩾2 cm after randomization.

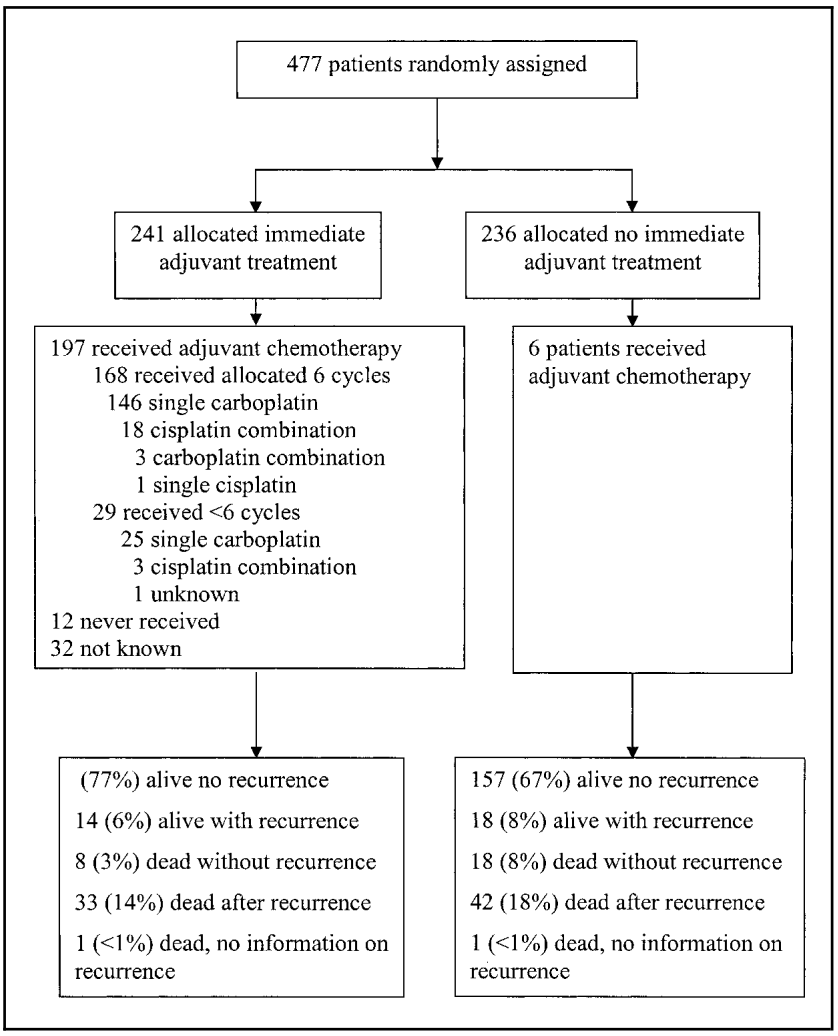


**Fig. 1.** CONSORT trial flow diagram for patients with early-stage ovarian cancer who were accrued into the International Collaborative Ovarian Neoplasm trial (ICON1). Patients were randomly assigned to either the adjuvant chemotherapy arm or to the no-adjuvant-chemotherapy arm.

## Overall Survival

After a median follow-up (for patients still alive) of 51 months, a total of 103 patients died (42 in the immediate adjuvant chemotherapy arm, 61 in the no immediate adjuvant chemotherapy arm). Patients in the adjuvant chemotherapy arm had better overall survival than patients in the no-adjuvant-chemotherapy arm (hazard ratio [HR] of 0.66, 95% CI = 0.45 to 0.97; $P = .03$). These results translate into 5-year overall survival figures of 79% for patients who received adjuvant chemotherapy and 70% for patients who did not receive adjuvant chemotherapy, a difference of 9% (95% CI = 1% to 15%) (Fig. 2). A larger number of patients died without recurrence in the no-adjuvant-chemotherapy arm than in the adjuvant chemotherapy arm (Table 3), and a greater number had missing information on cause of death. However, the numbers of patients who died for reasons not thought to be related to ovarian cancer were similar. The causes of death are consistent with the frequency of comorbid conditions in this patient population.

## Recurrence-Free Survival

Three hundred forty-four patients (72%) were alive and recurrence free at the time of this analysis. Of the other 133 (28%)

**Table 2.** Patient compliance with adjuvant chemotherapy; treatment received and reason(s) for treatment modification

| Adjuvant chemotherapy compliance | No. of patients (%) |
|---|---|
| All protocol treatment received | 103 (49) |
| Six cycles of chemotherapy received but treatment modified (dose reduced or delayed) | 65 (31) |
| Progression/death/no response | 0 |
| Toxicity | 49 |
| Patient preference | 2 |
| Other | 14 |
| Not known | 0 |
| Six cycles of chemotherapy not completed | 29 (14) |
| Progression/death/no response | 4 |
| Toxicity | 14 |
| Patient preference | 8 |
| Other | 1 |
| Not known | 2 |
| Chemotherapy never started | 12 (6) |
| Progression | 1 |
| Patient preference | 7 |
| Other | 1 |
| Not known | 3 |
| No information on chemotherapy | 32 |
| Total allocated to adjuvant chemotherapy | 241 |

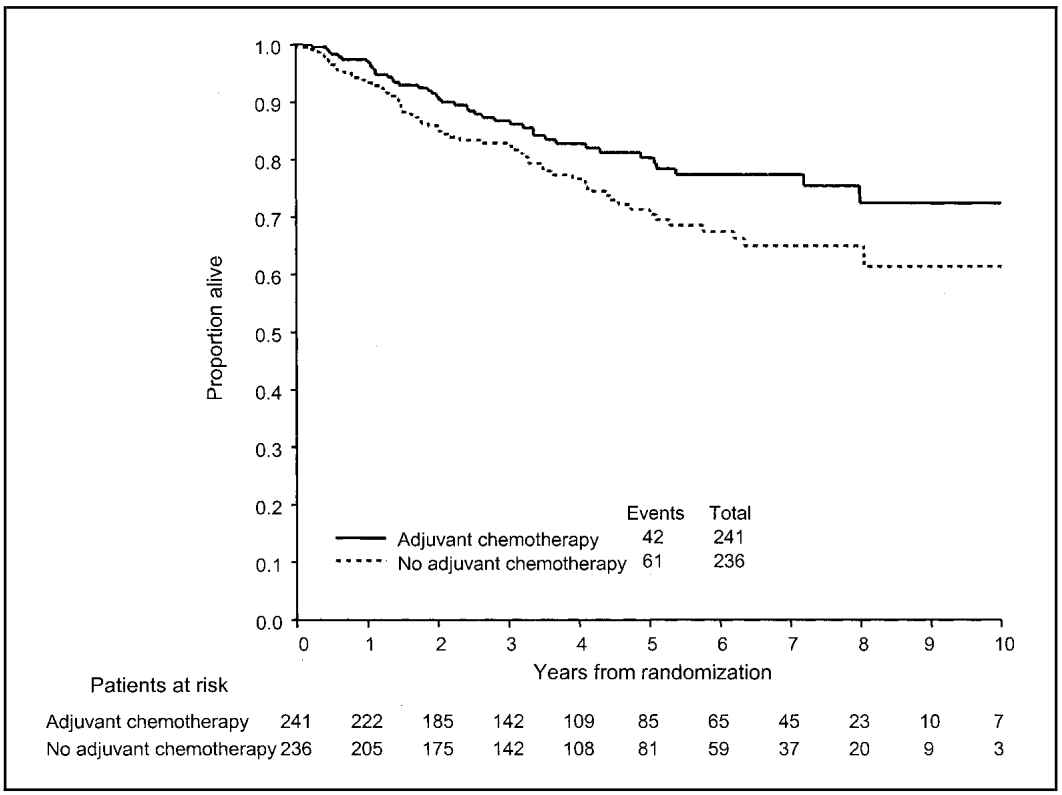


**Fig. 2.** Kaplan–Meier curves for overall survival in patients with early-stage ovarian cancer. Adjuvant chemotherapy patients (n = 241) (**solid line**) were those patients who received immediate adjuvant chemotherapy. No-adjuvant-chemotherapy patients (n = 236) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated. The hazard ratio is 0.66 (95% CI = 0.45 to 0.97, $P = .03$ using the log-rank test) in favor of adjuvant chemotherapy. These results translate into 5-year survival figures of 70% for patients who did not receive adjuvant chemotherapy and 79% for patients who did receive adjuvant chemotherapy, a difference of 9% (95% CI = 1% to 15%).

**Table 3.** Patient deaths prior to recorded recurrence

| Cause of death | Treatment arm: Adjuvant chemotherapy | Treatment arm: No adjuvant chemotherapy | Total |
|---|---|---|---|
| Ovarian cancer | 1 | 3 | 4 |
| Not thought to be related to ovarian cancer | 5* | 7† | 12 |
| Unknown cause of death | 2 | 8 | 10 |
| Total No. of deaths | 8 | 18 | 26 |

*Metastatic breast cancer (two), ischemic heart disease (one), chronic obstructive airways disease (one), and cerebral tumor (one).

†Primary lung cancer (two), cerebrovascular accident (two), ischemic heart disease (one), multiple sclerosis (one), and not specified but not related to ovarian cancer or treatment (one).

patients whose events are included in this analysis, 107 (80%) had disease recurrence (47 in the adjuvant chemotherapy arm and 60 in the no-adjuvant-chemotherapy arm) and 26 (20%) had died without recurrence (eight in the adjuvant chemotherapy arm and 18 in the no-adjuvant-chemotherapy arm). Thus the preponderance of events in the recurrence-free survival analysis was recurrences occurring sometime before death. The Kaplan–Meier curves for recurrence-free survival of both trial arms are shown in Fig. 3. Patients in the adjuvant chemotherapy arm had better recurrence-free survival than patients in the no-adjuvant-chemotherapy arm (HR = 0.65, 95% CI = 0.46 to 0.91; $P = .01$). These results translate into 5-year recurrence-free survival figures of 73% for patients who received adjuvant chemotherapy and 62% for patients in who did not receive adjuvant chemotherapy, an improvement in recurrence-free survival of 11% (95% CI = 3% to 18%).

## DISCUSSION

ICON1, the largest trial ever performed in early-stage ovarian cancer, provides evidence that adjuvant chemotherapy treatment with a platinum-based regimen improves survival and delays recurrence in a broad spectrum of patients with early-stage epithelial ovarian cancer. When ICON1 was planned, it was recognized that the low event rate would necessitate a large trial. ICON1, which accrued 477 patients over eight and a half years between August 1991 and January 2000 and ACTION, which accrued 448 patients over a similar period, were planned independently. Neither trial accrued the originally planned target number of patients (2000 and 1000, respectively). However, early on in the trials it was agreed by the trial investigators to perform a joint analysis of ICON1 and ACTION, because the larger number of patients in the combined analysis would make it possible to have a more reliable estimate of treatment size and to explore the effects of treatment in subgroups. This combined analysis *(22)* confirms the benefit of adjuvant chemotherapy on both overall survival and recurrence-free survival.

When ICON1 was launched there were only three small randomized trials in early-stage ovarian cancer comparing immediate treatment with adjuvant chemotherapy following surgery with no immediate treatment *(4,7,15)*. Two other small randomized studies comparing immediate with deferred platinum-based adjuvant chemotherapy in patients with early-stage epithelial ovarian cancer were inconclusive *(8,14)*. A full summary and formal meta-analysis of all of these trials of platinum-based adjuvant chemotherapy *(20)* lend further support to the conclusion that patients with early-stage epithelial ovarian cancer can benefit from chemotherapy and provide no evidence to support the notion that relative effects of chemotherapy vary according to patient characteristics.

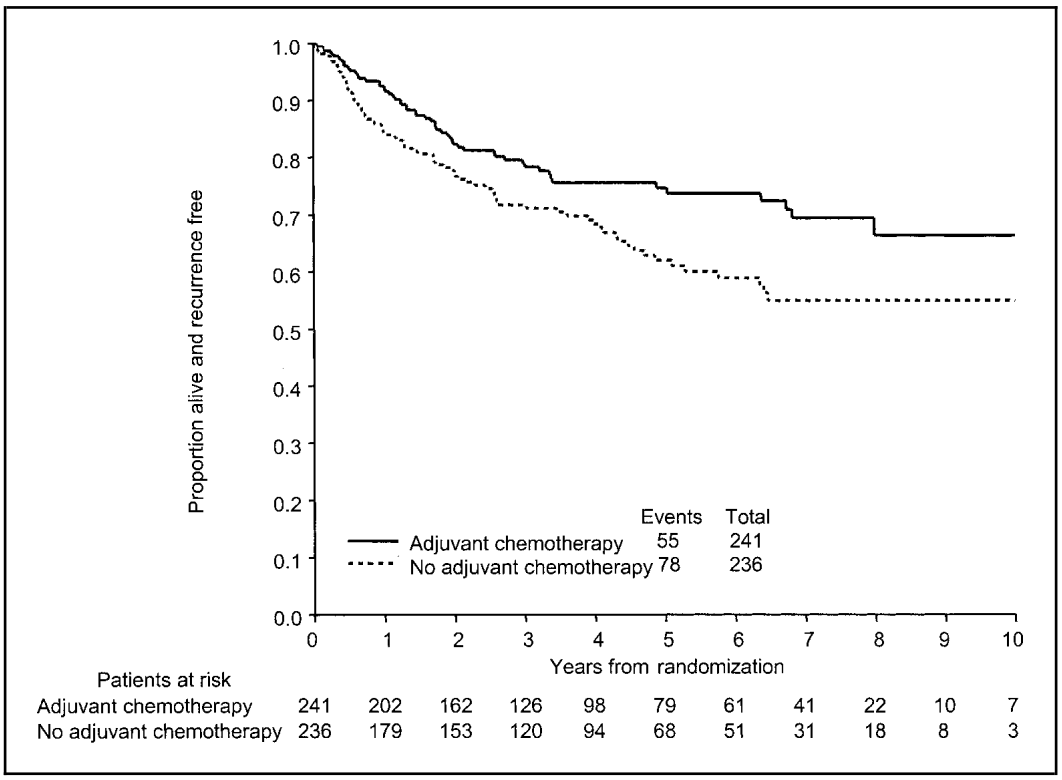


**Fig. 3.** Kaplan–Meier curves for recurrence-free survival in patients with early-stage ovarian cancer. Adjuvant chemotherapy patients (n = 241) (**solid line**) were those patients who received immediate adjuvant chemotherapy. No-adjuvant-chemotherapy patients (n = 236) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated. The hazard ratio is 0.65 (95% CI = 0.46 to 0.91, $P = .01$ using the log-rank test) in favor of adjuvant chemotherapy. These results translate into 5-year recurrence-free survival figures of 62% for patients who did not receive adjuvant chemotherapy and 73% for patients who did receive adjuvant chemotherapy, an absolute difference of 11% (95% CI = 3% to 18%).

ICON1 was a large trial, with simple entry criteria. If the clinician was uncertain whether a patient with early-stage ovarian cancer would benefit from treatment with platinum-based adjuvant chemotherapy following surgery, the patient could be entered into the trial. There was no restriction on FIGO stage or tumor grade. However, most patients were of early stage, with more than 90% of patients classified as having stages I–Ic. The results are, therefore, representative of the likely effects of chemotherapy in clinical practice.

The ICON1 trial did have some possible limitations. First, this trial was an open study. However, the main outcome—overall survival—is unlikely to have been affected by ascertainment bias. With respect to bias in ascertaining recurrence of disease, recurrence of ovarian cancer is usually symptomless and is diagnosed on clinical or radiologic examination, and all patients were followed up at the same time interval regardless of treatment arm. Therefore, such bias was also unlikely. A second possible limitation was that there was a small amount of crossover from one treatment arm to the other. However, crossover would have had the effect of reducing the estimated effect of chemotherapy that was observed between the two groups. Therefore, it is likely that the effect of immediate adjuvant chemotherapy was, if anything, underestimated in this trial.

In conclusion, the findings of this trial indicate that all patients with early-stage ovarian cancer should be considered for platinum-based adjuvant chemotherapy after removal of all visible tumor. Given that the majority of centers in this international trial chose single-agent carboplatin, this becomes, by definition, the treatment of choice. The risks and benefits of other regimens including taxanes have not been assessed in this population, and extrapolation from trials of later disease may not be appropriate. Future studies should investigate ways of further improving outcomes for women with early-stage ovarian cancer.

## Appendix: ICON1 Trial Collaborators and Affiliations

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## NOTES

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