International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial: Two Parallel Randomized Phase III Trials of Adjuvant Chemotherapy in Patients With Early-Stage Ovarian Carcinoma

International Collaborative Ovarian Neoplasm 1 (ICON1) and European Organisation for Research and Treatment of Cancer Collaborators–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION)[1]

Background: **Adjuvant chemotherapy has been suggested as a possible strategy to improve survival in women with early-stage ovarian cancer; however, all randomized studies to date have been too small to answer this question reliably.** ***Methods:*** **We performed a preplanned combined analysis of two parallel randomized clinical trials (International Collaborative Ovarian Neoplasm 1 [ICON1] and Adjuvant ChemoTherapy In Ovarian Neoplasm [ACTION]) in early-stage ovarian cancer that compared platinum-based adjuvant chemotherapy with observation following surgery. Between November 1990 and January 2000, 925 patients (477 in ICON1 and 448 in ACTION) who had surgery for early-stage ovarian cancer were randomly assigned to receive platinum-based adjuvant chemotherapy (n = 465) or observation (n = 460) until chemotherapy was indicated. Kaplan–Meier analysis was used to compare overall and recurrence-free survival by treatment allocation. In subgroup analyses of pretreatment age, tumor stage, histologic cell type, and differentiation grade, the differences in relative size of effect were tested using a chi-square test for interaction or a chi-square test for trend. All tests of statistical significance were two-sided.** ***Results:*** **After a median follow-up of over 4 years, 245 patients had died or had a recurrence (ICON1: 133, ACTION: 112). Overall survival at 5 years was 82% in the chemotherapy arm and 74% in the observation arm (difference = 8% [95% confidence interval (CI) = 2% to 12%]; hazard ratio [HR] = 0.67, 95% CI = 0.50 to 0.90; *P* = .008). Recurrence-free survival at 5 years was also better in the adjuvant chemotherapy arm than it was in the observation arm (76% versus 65%, difference = 11% [95% CI = 5% to 16%]; HR = 0.64, 95% CI = 0.50 to 0.82; *P* = .001). Subgroup analyses provided no evidence of a difference in the size of effect of chemotherapy on survival in any pretreatment subcategory.** ***Conclusions:*** **Platinum-based adjuvant chemotherapy improved overall survival and recurrence-free survival at 5 years in this combined group of patients with early-stage ovarian cancer defined by the inclusion criteria of the ICON1 and ACTION trials. [J Natl Cancer Inst 2003;95:105–12]**

The treatment for early-stage ovarian cancer is typically surgery alone, and in patients with well or moderately differentiated early-stage ovarian cancer confined to the pelvis (International Federation of Gynecology and Obstetrics [FIGO] stage I–IIa), surgical treatment alone may be curative. Overall, however, the 5-year survival rate for patients with early-stage ovarian cancer varies from 50% to 85%, depending on stage and grade of tumor *(1).* These disappointing results have set the stage for all kinds of adjuvant treatment, of which chemotherapy is the most popular *(2).* Whole abdominal radiation with intraperitoneal radioactive chromic phosphate (^{32}P) has also been suggested as a possible adjuvant treatment *(1),* but there is no agreement about whether any of these treatments are of real benefit to the patient *(3).*

Few randomized trials have attempted to investigate the question of whether adjuvant treatment is of benefit to patients. Widely discussed randomized trials include an American study *(4)* (of observation versus melphalan), which included only 46 patients with just six events, an Italian study *(2)* (of observation versus cisplatin), which included 83 patients, and a recent Scandinavian study *(5)* (of observation versus carboplatin), which reported on 162 patients. In the Italian study, adjuvant cisplatin chemotherapy was associated with a statistically significant improvement in disease-free survival (hazard ratio [HR] for disease-free survival = 0.35 [95% confidence interval (CI) = 0.14 to 0.89]) but not in overall survival (HR = 1.15 [95% CI = 0.44

[1]*Writing Committee:* J. Baptist Trimbos, Mahesh Parmar, Ignace Vergote, David Guthrie, Giorgio Bolis, Nicoletta Colombo, Jan B. Vermorken, Valter Torri, Costantino Mangioni, Sergio Pecorelli, Andrea Lissoni, Ann Marie Swart.

Affiliations of Writing Committee: J. B. Trimbos, Leiden University Medical Center, Leiden, The Netherlands; M. Parmar, D. Guthrie, A. M. Swart, Medical Research Council Clinical Trial Unit, London, U.K.; I. Vergote, University Hospital Gasthuisberg, Leuven, Belgium; G. Bolis, Istituto Mangiagalli/Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy; N. Colombo, European Institute of Oncology, Milan; J. B. Vermorken, University Hospital Antwerp, Antwerp, Belgium; V. Torri, Istituto Mario Negri, Milan; C. Mangioni, A. Lissoni, Ospedale San Gerardo, Monza, Italy; S. Pecorelli, Universita di Brescia, Brescia, Italy.

Correspondence to: J. Baptist Trimbos, M.D., Ph.D., Department of Gynecology, Leiden University Medical Center, POB 9600, 2300 RC, Leiden, The Netherlands (J.B.M.Z.Trimbos@lumc.nl) or Mahesh Parmar, Ph.D., Medical Research Council Clinical Trials Unit Cancer Division, 222 Euston Rd., London NW1 2DA, U.K. (Mahesh.Parmar@ctu.mrc.ac.uk).

See "Appendix" for the full list of names and affiliations of the ICON1 and EORTC–ACTION collaborators.

See "Notes" following "References."

to 2.98]). In the other two trials, no differences were found between the two trial arms. However, all three trials were small and lacked the statistical power to detect realistic differences.

The question of whether the use of adjuvant chemotherapy would prolong recurrence-free survival and improve overall survival in patients with early-stage epithelial ovarian carcinoma was identified by several European research groups as requiring investigation. The European Organisation of Research and Treatment of Cancer–Adjuvant ChemoTherapy In Ovarian Neoplasm trial (EORTC–ACTION) and the International Collaborative Ovarian Neoplasm (ICON1) trial were set up as parallel, complementary randomized trials designed to compare the effect of using immediate platinum-based adjuvant chemotherapy with that of deferring adjuvant treatment (i.e., observation) until clinically indicated in patients with surgically resected early-stage ovarian cancer. The aim was to perform two trials that would each be large enough to answer the relevant questions but that could also be combined in a joint analysis.

Subjects and Methods

Trial Designs

Although the EORTC–ACTION trial and the ICON1 trial had similar designs with regard to randomly assigning patients to either adjuvant chemotherapy or no adjuvant chemotherapy (i.e., observation) and to addressing the same question, there were differences between them. Detailed information on eligibility criteria for ICON1 and ACTION is available in the companion papers *(6,7)*; only brief details are given here.

In the ACTION trial, patients were considered eligible for entry into the trial if they had high-risk early-stage ovarian cancer, defined as FIGO stage Ia and Ib with grade II or III tumor, all grades of FIGO stage Ic–IIa, and all clear-cell carcinomas *(8,9)*. Strict guidelines for comprehensive surgical staging and tumor typing and grading were given in the study protocol. In the protocol, patients in the immediate chemotherapy arm had to receive at least four courses of a platinum-based regimen, i.e., single-agent carboplatin, single-agent cisplatin, combination carboplatin, or combination cisplatin. The preferred dose and dose modification in case of morbidity were outlined in the study protocol. The chemotherapy regimen used was to be decided by each individual institution at the beginning of the trial, and patients in the no-adjuvant-chemotherapy arm who had a recurrence were to receive the same regimen as patients in the immediate chemotherapy arm. Recurrence of disease had to be confirmed cytologically or histologically.

In the ICON1 trial, by contrast, all patients with histologically confirmed ovarian carcinoma of epithelial origin were eligible for participation in the trial if, in the opinion of the responsible clinician, it was uncertain whether the patients would benefit from immediate adjuvant chemotherapy. Although patients of all stages were potentially eligible, most patients were either stage I or stage II. Guidelines for surgical staging including total hysterectomy, bilateral salpingo-oophorectomy, and, if the omentum was involved, a total supracolonic omentectomy, or, if it was not macroscopically involved, removal of the distal 2 cm or infracolic omentectomy. Patients in the chemotherapy arm had to receive six courses of platinum-based adjuvant chemotherapy, with the combination of cyclophosphamide + doxorubicin + cisplatin (CAP) or single-agent carboplatin being recommended, although other regimens that included platinum at predefined minimum doses were also allowed. Patients in the control arm were able to receive chemotherapy at the time of recurrence or after recurrence. Tumor recurrence was based on clinical, radiologic, or histologic diagnosis.

Statistical Analysis

In both studies, the primary endpoint was overall survival and the secondary endpoint was recurrence-free survival. Overall survival was defined as the time from randomization to the date of death from any cause; patients who were alive at the time of analysis were censored at the time of last follow-up. Recurrence-free survival was defined as the time from randomization to the date of the first recurrence or death from any cause; patients who were alive and without recurrence at the time of analysis were censored at the time of last follow-up.

The ACTION and ICON1 datasets were combined for this analysis. The trials were analyzed on an intention-to-treat basis. All statistical tests were two-sided. The stratified (by trial) log-rank test, which adjusted for possible differences between ACTION and ICON1, was used for comparing overall survival and recurrence-free survival in the two combined trial arms. Log-rank statistics were used to calculate hazard ratios, and the hazard ratios themselves were stratified by trial. Kaplan–Meier curves *(10)* of overall survival and recurrence-free survival by treatment allocation were compared. Subgroup analyses explored whether the effect of chemotherapy was different in different subgroups defined by pretreatment characteristics including age, tumor stage, histologic cell type, and cell differentiation. The differences in relative size of effect were tested using a chi-square test (χ^2) for interaction or, when appropriate, a χ^2 test for trend *(11)*.

A systematic review of the literature was undertaken to identify all randomized trials of the treatment of patients with early-stage ovarian cancer that included a comparison of platinum-based adjuvant chemotherapy with no adjuvant chemotherapy. Literature searches included MEDLINE® and Cancerlit®, with a modified version of the optimum strategy developed by the Cochrane Collaboration *(12)*. Abstracts were reviewed to determine the treatment groups and methods of treatment allocation. The derived log-rank of observed minus expected number of events and the variance for individual trials (back-calculated from the hazard ratios) were combined across all trials with the fixed effect model to give a pooled hazard ratio. This pooled hazard ratio represents the overall risk of an event on immediate adjuvant chemotherapy versus that of an event on no immediate adjuvant chemotherapy. The χ^2 test for heterogeneity *(13)* was used to test for statistical heterogeneity in all trials and to assess the consistency of the effect across different subsets of trials.

Results

Between November 1990 and January 2000, 448 patients were accrued to the ACTION trial, and between August 1991 and January 2000, 477 patients were accrued to the ICON1 trial. A total of 925 patients from 124 centers in 13 countries were randomly assigned to immediate platinum-based adjuvant chemotherapy (465 patients) or to observation (i.e., no adjuvant chemotherapy) until chemotherapy was indicated (460 patients). Table 1 gives the distribution of the various patient and tumor characteristics among the two trial arms for the total of 925 patients; the two trial arms appeared well-balanced.

Table 1. Patient characteristics in the combined European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION)/International Collaborative Ovarian Neoplasm 1 (ICON1) trials*

	Adjuvant chemotherapy (N = 465)	No adjuvant chemotherapy (N = 460)
Age (y), n (%)†		
<55	233 (50)	233 (51)
55–65	126 (27)	147 (32)
>65	105 (23)	80 (17)
Missing	1	0
Median age, y	55	55
Tumor stage‡, n (%)†		
I	9 (2)	4 (<1)
Ia	168 (36)	173 (38)
Ib	46 (10)	43 (9)
Ic	208 (45)	205 (45)
II	31 (7)	29 (6)
III	2 (<1)	4 (1)
Missing	1	2
Histologic cell type, n (%)†		
Serous	161 (36)	139 (31)
Mucinous	90 (20)	90 (20)
Endometrioid	94 (21)	129 (29)
Clear-cell	68 (15)	62 (13)
Undifferentiated	9 (2)	7 (2)
Other/mixed	23 (5)	19 (4)
Missing	20	14
Tumor grade, n (%)†		
I	97 (22)	100 (23)
II	210 (47)	203 (46)
III	139 (32)	141 (32)
Missing	19	16
Adjuvant chemotherapy regimen, n (%)†		
Single–agent carboplatin	242 (57)	
Combination cisplatin	115 (27)	
Allocated treatment not received	25 (6)	
Combination carboplatin	23 (6)	
Single–agent cisplatin	12 (3)	
CAP	8 (2)	
Missing	40	

*A total of 925 patients were enrolled in the combined trials of EORTC–ACTION and ICON1. Missing = information on patient was missing. CAP = cyclophosphamide + doxorubicin + cisplatin. Percentages may not add up to 100% because of rounding.

†Percentages were calculated excluding missing values from denominator.

‡Two patients who were randomly assigned as stage Ia and II, respectively, were found to have been stage III, and one patient randomly assigned as stage III was found to have been stage IV. Staging and grading were in accordance with International Federation of Gynecology and Obstetrics (FIGO) and World Health Organization (WHO) guidelines *(8,9)*.

With over 4 years median follow-up for survivors (59 months for ACTION and 51 months for ICON1), a total of 245 patients have died or experienced recurrence of disease: 112 in ACTION (25% of the ACTION trial population) and 133 in ICON1 (28% of the ICON1 trial population). A total of 181 patients have died: 78 in ACTION (17%) and 103 in ICON1 (22%). Kaplan–Meier curves for overall survival and recurrence-free survival in the combined trial population are shown in Figs. 1 and 2, respectively. For overall survival, HR = 0.67 (95% CI = 0.50 to 0.90, P = .008) in favor of adjuvant chemotherapy. These results translate into 5-year overall survival figures of 74% for women in the no-adjuvant-chemotherapy arm and 82% for women in the adjuvant chemotherapy arm, a difference of 8% (95% CI = 2% to 12%). For recurrence-free survival, HR = 0.64 (95% CI = 0.50 to 0.82, P = .001) in favor of adjuvant chemotherapy. These results translate into 5-year recurrence-free survival figures of 65% for women in the no-adjuvant-chemotherapy arm and 76% for women in the adjuvant chemotherapy arm, a difference of 11% (95% CI = 5% to 16%).

Subgroup analyses of the combined ICON1 and ACTION data within the subcategories of age, tumor stage, histologic cell type, and cell differentiation (Fig. 3) provide no evidence that the effect of adjuvant chemotherapy was different within any of the subgroups. A separate subgroup analysis of staging completeness was not done because information about surgical staging was not collected in the ICON1 trial *(6)*.

The results of both trials individually are similar to one another *(6,7)*. There is an early and sustained separation of the Kaplan–Meier curves for both overall survival and recurrence-free survival in both trials, with evidence of a benefit from adjuvant chemotherapy. The hazard ratios for overall survival are also similar: 0.66 (95% CI = 0.45 to 0.97) and 0.69 (95% CI = 0.44 to 1.08) for ICON1 and ACTION, respectively, as are the hazard ratios for recurrence-free survival, 0.65 (95% CI = 0.46 to 0.91) and 0.63 (95% CI = 0.44 to 0.92) for ICON1 and ACTION, respectively.

In a systematic review of the literature, we identified eight randomized trials of early-stage ovarian cancer that include a comparison of adjuvant chemotherapy with no further treatment. Four of these trials used melphalan or other nonplatinum-based chemotherapy as adjuvant chemotherapy *(4,14–16),* and they are, therefore, of limited relevance to current clinical practice. Four other, more recent studies (including ACTION and ICON1) used platinum-based adjuvant chemotherapy *(2,5–7)*; the results of these trials are summarized in Table 2. With data from the four trials combined, of which the ACTION and ICON1 trials provide 84% of deaths and 80% of the recurrences and/or deaths, the hazard ratio for overall survival among patients in the adjuvant chemotherapy arms compared with that among patients in the no-adjuvant-chemotherapy arms is 0.72 (95% CI = 0.55 to 0.94, P = .017), and the hazard ratio for recurrence-free survival is 0.66 (95% CI = 0.53 to 0.83, P<.001), with no evidence of heterogeneity between the trials (Fig. 4).

Discussion

These findings indicate that platinum-based adjuvant chemotherapy improves overall survival and recurrence-free survival in the spectrum of patients studied in the ICON1 and EORTC–ACTION trials. There were different eligibility criteria in the two trials, with a more precisely defined patient population in the ACTION trial than in the ICON1 trial. The ICON1 trial did not collect data on surgical staging details; thus, the results from that trial cannot contribute to the discussion on staging.

The main strength of this combined analysis is the number of patients included and the consistency of the results across the two trials. Subgroup analysis revealed no differences between the various subgroups with regard to the beneficial treatment effect of chemotherapy; however, a conclusion on this point is hampered by the small number of patients in each subgroup. The results of this analysis provide evidence that platinum-based adjuvant chemotherapy can improve the survival of women with early-stage ovarian cancer as defined in the ACTION and ICON1 trials. The better toxicity profile of single-agent carbo-

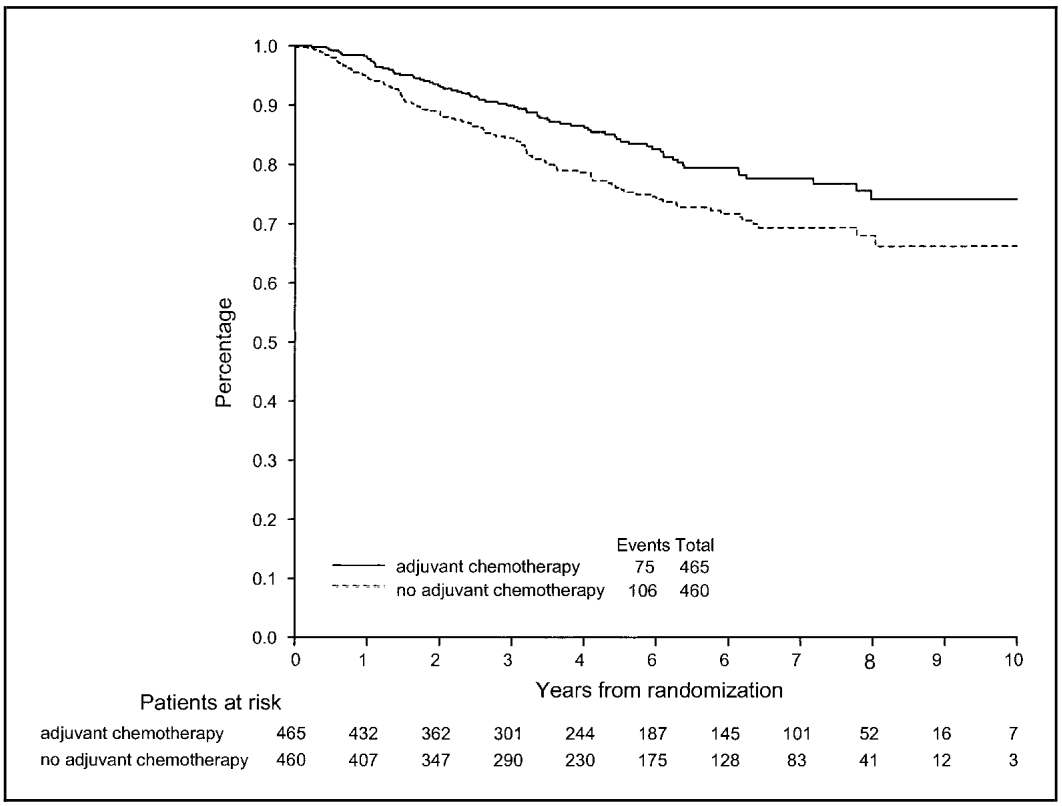

Fig. 1. Kaplan–Meier curves for overall survival in patients with early-stage ovarian carcinoma. Adjuvant chemotherapy patients (n = 465) (**solid line**) were those patients who received immediate adjuvant chemotherapy. No-adjuvant-chemotherapy patients (n = 460) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated. The hazard ratio is 0.67 (95% CI = 0.50 to 0.90, P = .008 using the log-rank test) in favor of adjuvant chemotherapy. Five-year survival figures were 74% for women in the no-adjuvant-chemotherapy group and 82% for women in the adjuvant chemotherapy group, a difference of 8% (95% CI = 2% to 12%).

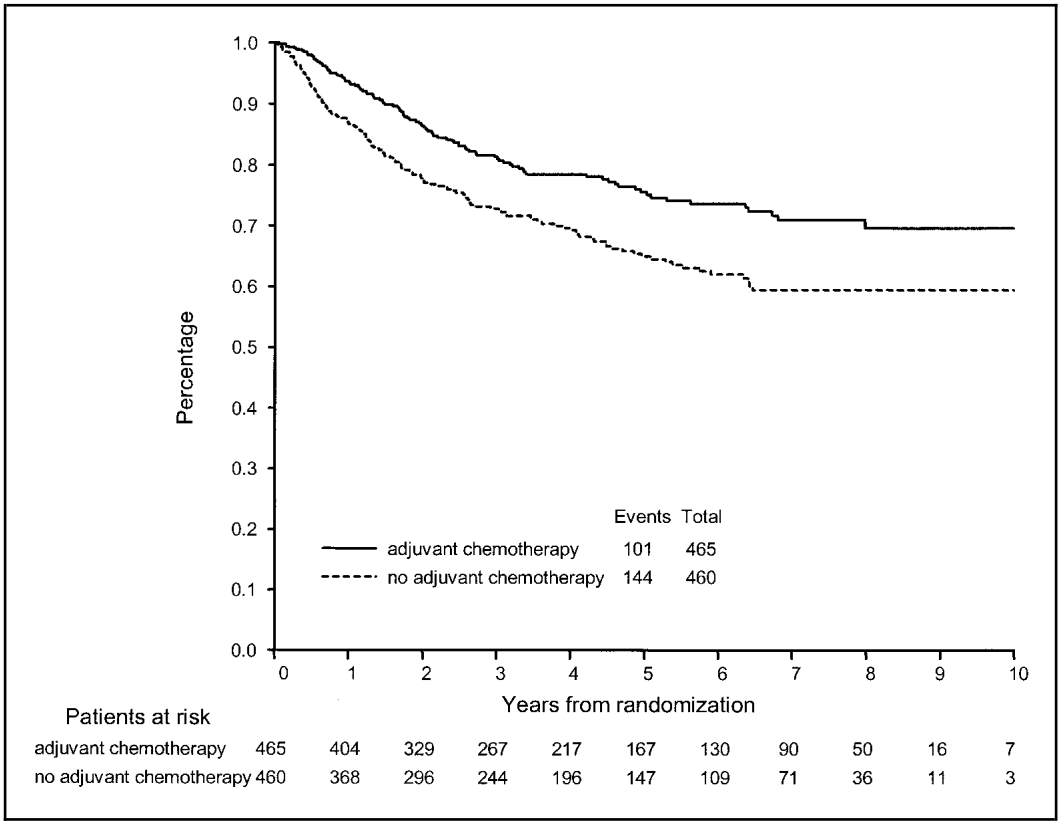

Fig. 2. Kaplan–Meier curves for recurrence-free survival in patients with early-stage ovarian carcinoma. Adjuvant chemotherapy patients (n = 465) (**solid line**) were those patients who received immediate adjuvant chemotherapy. No-adjuvant-chemotherapy patients (n = 460) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated. The hazard ratio is 0.64 (95% CI = 0.50 to 0.82, P = .001 using the log-rank test) in favor of adjuvant chemotherapy. Five-year survival figures were 65% for women in the no-adjuvant-chemotherapy group and 76% for women in the adjuvant chemotherapy group, a difference of 11% (95% CI = 5% to 16%).

platin alone suggests that it may be the treatment of choice for early-stage ovarian cancer. Other regimens, including taxanes, have not been studied in this patient population; therefore, extrapolation to different chemotherapy regimens from trials of later disease may not be appropriate *(22–25).*

However, clinical trials, especially in rarer diseases such as early-stage ovarian cancer, cannot provide answers to all of the questions regarding the optimal chemotherapy treatment for individual patients. Some clinicians may interpret the results of these trials as a basis for considering the routine offering of

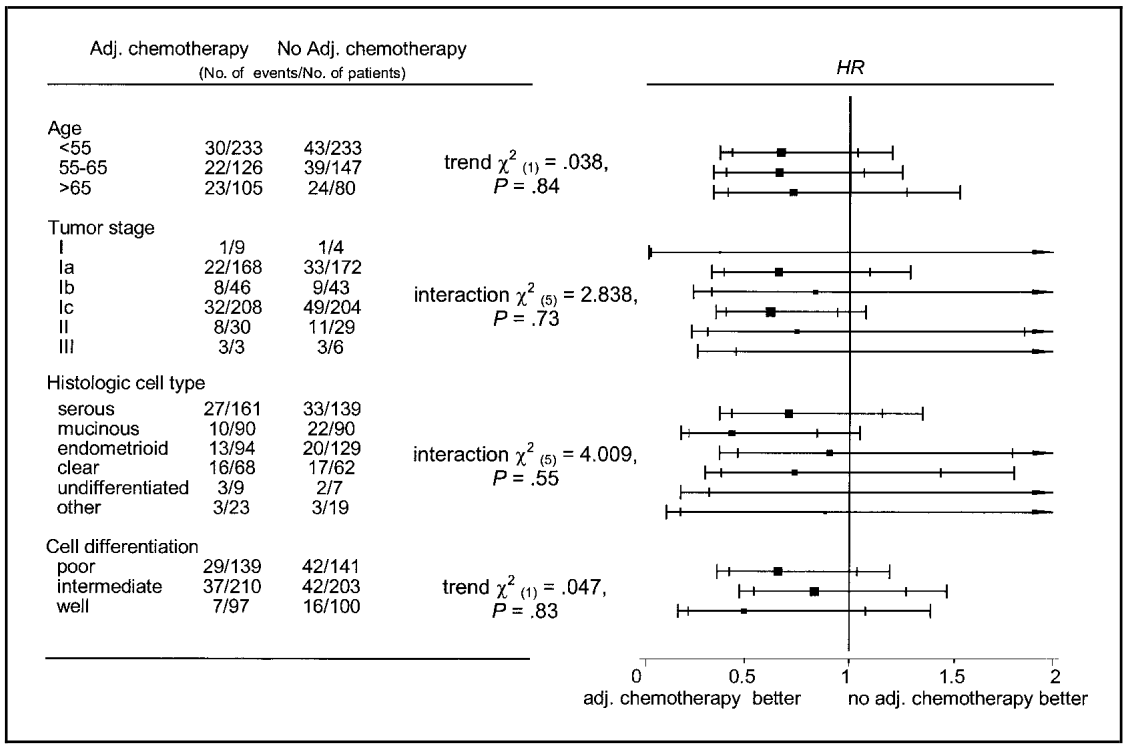

Fig. 3. Forest plots of the interaction or trend between the subgroups age, tumor stage, histologic cell type, and cell differentiation versus treatment effect (adjuvant chemotherapy better versus no-adjuvant-chemotherapy better) for overall survival. For each dataset, the hazard ratio (HR) for overall survival is plotted as a **solid square,** and the area of the square is proportional to the variance of the estimated effect. The length of the horizontal line through the square indicates the 99% confidence interval (CI), and the inner tick marks indicate the 95% CI. The **arrow** at the end of the horizontal line indicates that the CI is larger than the scale of the figure. The differences in relative size of effect were tested using a chi-square test (χ^2) for interaction, or when appropriate, a χ^2 test for trend.

Table 2. Meta-analysis of four randomized trials comparing no adjuvant chemotherapy with platinum-based adjuvant chemotherapy in early ovarian cancer*

Trial	Entry criteria	Intervention	Median follow-up, mo	Survival	No. of events/No. of patients†		HR (95% CI)	*P* value‡
					Adjuvant chemotherapy	No adjuvant chemotherapy		
Bolis et al. *(2)*	FIGO stage Ia and Ib, grade 2 or 3	Cisplatin	71	RF	7/41	14/42	0.48 (0.24 to 1.14)	.095
				O	9/41	8/42	1.15 (0.44 to 2.98)	.773
Trope et al. *(5)*	FIGO stage I, non-clear-cell aneuploid grade 1; FIGO stage I, non-clear-cell, grade 2 or 3; FIGO stage I, clear-cell	Carboplatin	46	RF	20/81	19/81	0.98 (0.52 to 1.83)	.9
				O	9/81	9/81	0.94 (0.37 to 2.36)	.9
Trimbos et al., ACTION *(7)*	FIGO stage Ia, Ib, grade 2 or 3; FIGO stage Ic, IIa, all grades; clear-cell	Platinum	59	RF	46/224	66/224	0.63 (0.43 to 0.92)	.02
				O	33/224	5/224	0.69 (0.44 to 1.08)	.104
ICON1 Collaborators, ICON1 *(6)*	FIGO stage I and II; clinician uncertain if patient would benefit from treatment	Platinum	51	RF	55/241	78/236	0.65 (0.46 to 0.91)	.01
				O	42/241	61/236	0.66 (0.45 to 0.97)	.03

*RF = recurrence free; O = overall; FIGO = International Federation of Gynecology and Obstetrics *(9);* HR = hazard ratio; CI = confidence interval.
†No. of events = number of deaths plus the number of patients with disease recurrence. No. of patients = number of patients entered into the trial.
‡*P* values were calculated using the log-rank test.

platinum-based adjuvant chemotherapy to a majority of patients with early-stage ovarian cancer. Others might highlight the fact that, of the 925 patients, only one-sixth were known to be optimally staged—that is, there was evidence that all of the disease was surgically removed. In these optimally staged patients, the clinician may consider the argument for using adjuvant chemotherapy as not strong *(7,17).* It has been shown that incompletely staged early-stage ovarian carcinoma harbors occult stage III disease in approximately one-fifth to one-fourth of patients *(18–21).* This unappreciated residual disease could be postulated as an explanation for the beneficial effect of adjuvant chemotherapy. Whichever point of view is taken, these trials show that adjuvant chemotherapy can have a distinct role in the treatment of women with early-stage ovarian cancer.

APPENDIX

ICON1 Trial Collaborators and Affiliations

U.K.: Addenbrooke's Hospital, Cambridge: H. M. Earl, N. M. Bleehen, R. J. Osborne; Belfast City Hospital, Belfast: R. J. Atkinson; Birmingham & Midland Hospital for Women, Birmingham: K. K. Chan; Charing Cross Hospital, London: G. Rustin; Cheltenham General Hospital, Cheltenham: R. Counsell, J. R. Owen; Churchill Hospital, Oxford: N. P. Rowell, C. J. Alcock, T. Ganesan; Birmingham City Hospital, Birmingham: D. M. Luesley; Clatterbridge Hospital, Wirral: J. A. Green; Derbyshire Royal Infirmary, Derbyshire: D. Guthrie; Dudley Road Hospital, Birmingham: G. R. Blackledge, R. Callender, D. M.

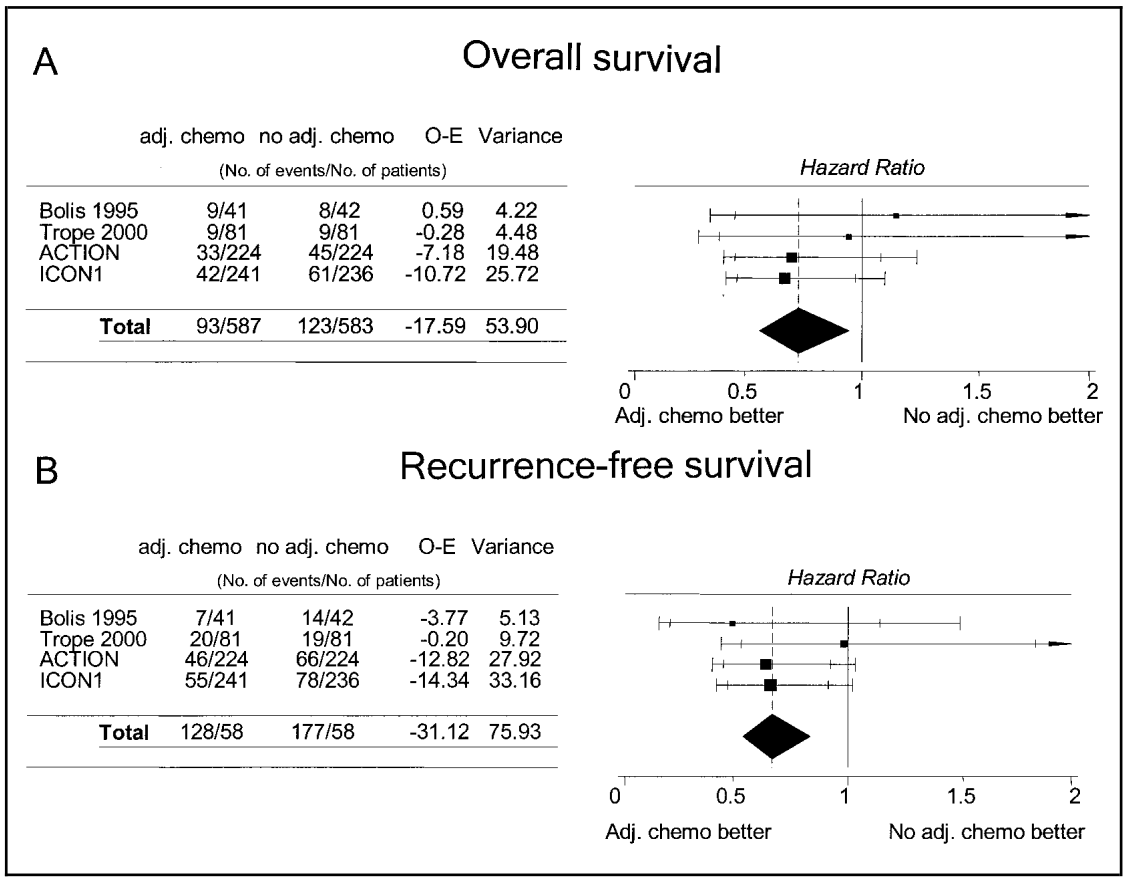

Fig. 4. Forest plots of a meta-analysis of four randomized trials *(2,5–7)* comparing no adjuvant chemotherapy with adjuvant chemotherapy in early-stage ovarian cancer for overall survival (**A**) and recurrence free survival (**B**). The position of each **square** indicates the hazard ratio, and the area of the square is proportional to the variance of the estimated effect. The length of the horizontal line through the square indicates the 99% confidence interval (CI), and the inner tick marks indicate the 95% CI. The **arrow** at the end of the horizontal line indicates that the 99% CI is larger than the scale of the figure. The **diamond** indicates the hazard ratio (middle of the diamond) and the 95% CI (extremes of the diamond) for the combined data from the four randomized trials. Linear trends and heterogeneity of the hazard ratios were assessed by a chi-square test for trend (χ^2) and a χ^2 for heterogeneity (Het χ^2), respectively. Degrees of freedom for each χ^2 test are given in parentheses. The hazard ratio for overall survival is 0.722 (95% CI = 0.552 to 0.942), $\chi^2_{(1)} = 5.740$, $P = .017$; Het $\chi^2_{(1)} = 1.474$, $P = .688$, and for recurrence-free survival is 0.664 (95% CI = 0.530 to 0.831), $\chi^2_{(1)} = 12.756$, $P<.001$, Het $\chi^2_{(1)} = 2.101$, $P = .552$, both in favor of adjuvant chemotherapy. O–E = number of events observed minus number of events expected under the null hypothesis. Variance = variance of 1/logarithm of the hazard ratio.

Luesley, H. M. Earl, C. J. Poole; George Eliot Hospital, Nuneaton: V. G. Kenyon; Guy's Hospital, London: P. G. Harper; Hammersmith Hospital, London: H. Thomas; Jersey General Hospital, St. Helier: S. Hima; Kent & Canterbury Hospital, Canterbury: R. S. Coltart; Leeds General Infirmary, Leeds: K. R. Peel; Manor Hospital, Walsall: A. D. Chetiyawardana; Middlesex Hospital, London: J. A. Ledermann, R. L. Souhami; Mount Vernon Hospital, London: D. C. Fermont, G. Rustin; North Staffordshire Royal Infirmary, Stoke on Trent: C. W. E. Redman, J. E. Scoble; Northern General Hospital, Sheffield: M. E. L. Paterson; Poole General Hospital, Poole: R. J. Osborne; Queen Elizabeth Hospital, Birmingham: A. D. Chetiyawardana, I. N. Fernando, J. J. Mould, C. J. Poole; Royal Devon & Exeter Hospital, Exeter: A. Hong; Royal South Hants Hospital, Southampton: V. Hall, C. J. Williams, T. J. Iveson; Royal Sussex County Hospital, Brighton: D. S. Murrell, G. Newman; Royal United Hospital, Bath: E. Gilby; Solihull Hospital, Solihull: C. J. F. Rowbotham, D. W. Sturdee; South Cleveland Hospital, Middlesborough: D. J. Cruickshank; Southampton General Hospital, Southampton: C. J. Williams; Southend General Hospital, Southend: A. Lamont, C. W. L. Trask; St. George's Hospital, Lincoln: E. C. Murray; Stobhill Hospital, Glasgow: J. A. Davis; Stoke City General Hospital, Stoke on Trent: A. W. Clubb; Tameside General Hospital, Ashton-under-Lyne: J. K. Roberts; Walsgrave Hospital, Coventry: C. J. R. Irwin, D. A. Jones, A. D. Stockdale; Western General Hospital, Edinburgh: J. F. Smyth; Weston Park Hospital, Sheffield: R. E. Coleman, M. J. Whipp; Whittington Hospital, London: J. A. Ledermann. Italy: Casa di Cura Malzoni, Avellino: C. Malzoni; Ospedale degli Infermi, Biella: V. Vavalà; Ospedale Caduti Bollatesi, Bollate, Milan: E. Piatto; Policlinico S. Orsola-Malpighi, Bologna: A. Martoni; Ospedale SS. Trinità, Borgomanero, Novara: P. G. Fornara; Unità Sanitaria Locale Brindisi/1, Brindisi: M. C. Chetrì; Ospedale Civile Sirai, Carbonia, Cagliari: G. Chessa; Ospedale Ramazzini, Carpi, Modena: F. Artioli; Ospedale S. Bambino, Catania: S. Cavallaro Nigro; Ospedale Generale Valduce, Como: C. Belloni; Ospedale Civile, Conegliano, Veneto, Treviso: E. Candiotto; Ospedale di Circolo, Desio, Milan: G. Orfanotti; Azienda Ospedaliera Università di Ferrara, Ferrara: A. Bianchi; Ospedale S. Cuore di Gesù, Gallipoli, Lecce: G. Mele; Ospedale Civile, Genova Sampierdarena: G. Marrè, Brunenghi; Ospedale Civile Misericordia, Grosseto: R. Algeri; Ospedale Generale S. Salvatore, L'Aquila: M. Moscarini; Ospedale Civile Renzetti, Lanciano, Chieti: G. Belfiore; Ospedale S. Maria Goretti, Latina: M. D'Aprile; Ospedale Alessandro Manzoni, Lecco: N. Natale; Ospedale Maggiore, Lodi, Milan: M. Luerti; Ospedale Mandic/Unità Socio Sanitaria Locale 14, Merate, Como: A. Vecchione; Clinica Mangiagalli-Università degli studi di Milano, Milan: R. Maggi; Istituto Europeo di Oncologia, Milan: L. Bocciolone; Ospedale San Gerardo dei Tintori, Monza, Milan: C. Bonazzi, A. A. Lissoni, S. M. Rota; Azienda Ospedaliera San Luigi, Orbassano, Torino: L. Dogliotti; Ospedale Buccheri La Ferla Fatebenefratelli, Palermo: G. Vegna; Ospedale V. Cervello, Palermo: D. Gueli Alletti; Policlinico S. Pietro, Ponte S. Pietro, Bergamo: A. Epis; Ospedale Generale S. Camillo, Rieti: V. Scotto di Palumbo; Università

La Sapienza, Rome: L. Marzetti; Ospedale Civile, Rovereto, Trento: G. Gorga; Ospedale S. Leonardo, Salerno: S. Cariello; Ospedale Civile Agnelli, Savigliano, Cuneo: L. Galletto; Ospedale Civile, Sesto San Giovanni, Milan: A. Raina; Ospedale Unità Sanitaria Locale Roma 26, Tivoli, Rome: F. Corrado; Ospedale S. Anna-Div A, Torino: E. Guercio; Ospedale S. Anna-Div B, Torino: R. Jura; Ospedale S. Giovanni Azienda Sanitaria, Torino: C. Bumma; Università Dipartimento Discipline Ginecologiche-Ostetriche, Torino: M. Massobrio; Ospedale Civile Consortile, Treviglio, Bergamo: R. Grassi; Ospedale di Circolo, Varese: M. Grampa; Azienda Ospedaliera, Verona: G. Cetto; Ospedale Civile S. Bortolo, Vicenza; V. Fosser. Republic of Ireland: South Infirmary-Victoria Hospital, Cork: A. Curtain. Brazil: Fêmina S.A., Porto Alegre: E. Palmeiro. Switzerland: Kantonsspital, Basel: A. Dieterle; Inselspital Onkologie, Bern: T. Hardegger; Centre Hospitalier Universitaire Vaudois, Lausanne: J. F. Delaloye; Ospedale Civico, Lugano: M. Rabaglio, C. Sessa; Ospedale Beata Vergine, Mendrisio: A. Goldhirsch, M. P. Saletti; Ospedale San Giovanni, Bellinzona: M. Wörtelboer; Frauenfeld, St. Gallen: C. Furrer; Hôpital Cantonal Universitaire, Geneva: A. Hügli, H. Bonnefoi; Kantonsspital, St. Gallen: B. Thürlimann. Data Management: ICON office Mario Negri Institute, Italy: Monica Flann, Alessandro Buda, Irene Floriani, Angelo Tinazzi. Medical Research Council (MRC) Clinical Trials Unit, U.K.: Nicholas Chadwick, Josie Sandercock, Ben Tham, Sarah Wheeler. Statistical analysis: ICON office in Italy: Angelo Tinazzi, Valter Torri. MRC in the U.K.: Wendi Qian, Mahesh Parmar.

EORTC–ACTION Trial Collaborators and Affiliations

Institut d'Oncologica Corachan, Barcelona, Spain: C. Madronal; Centro di Referimento Oncologico, Italy: S. Tumolo; Velindre Hospital, U.K.: M. Adams; Ziekenhuis de Heel, The Netherlands: A. v. Bochove; Daniel den Hoedkliniek, The Netherlands: M. E. L. van der Burg; Hospital Clinico Universitario de Valencia, Spain: A. Cervantes; Centre Henri Becquerce, France: B. Chevalier; Instituto Europeo di Oncologia, Italy: N. Colombo; Kaiser Franz Josef Spital, Austria: C. Dittrich; Eemland Ziekenhuis, The Netherlands: J. Duk; Medical University of Gdansk, Poland: J. Emerich; Universita di Brescia, Italy: C. Favalli; Clinica Universita Torino, Italy: A. Ferrero; Ospedale di Circulo e Fondazione Macchi, Varese, Italy: M. Franchi; Policlinico A. Gemelli-Università del Sacro Cuore, Italy: S. Greggi; Centre Leon Berard, France: J. P. Guastalla; Hospital General de Asturias, Spain: A. J. Lacave; Rigshospitalet, Denmark: B. Lund; Università di Padova, Italy: T. Maggino; Istituto Scientifico H. S. Raffaele, Italy: G. Mangili; Azienda Ospedaliera di Parma, Italy: M. Melpignano; Centre Antoine Lacassagne, France: M. Namer; Instituto Regina Elena, Italy: M. Nardi; Instituto Portugues de Oncologia–Centro de Coimbra, Portugal: C. F. de Oliviera; Instituto di Science Biomediche San Paolo, Italy: U. Radaelli; Ospedale Civile, Italy: C. Scarabelli; Instituto Mangiagalli, Milan, Italy: G. Scarfone; University Medical Centre Nijmegen, The Netherlands: Ch. Schijf; Ospedale Generale di Zona san Carlo di Nancy, Italy: Scotto di Palumbo; Atrium Medisch Centrum, The Netherlands: J. E. G. M. Stoot; Stichting Streekziekenhuis Midden-Twente, The Netherlands: R. van der Sijde; Policlinico San Matteo, Pavia, Italy: S. Tateo; Leiden University Medical Center, The Netherlands: P. Timmers; Academisch Medisch Centrum, The Netherlands: C. Veenhof; Ospedale San Gerardo, Monza, Italy: G. Zanetta; Academisch Ziekenhuis Groningen, The Netherlands: A. van der Zee; Academic Medical Center, Amsterdam, The Netherlands: A. H. Zwinderman. Medical Supervisor: Ivana Teodorovic, EORTC Data Center, Brussels, Belgium. Data Management: Livia Giurgea, EORTC Data Center, Brussels. Statistical Supervision: Corneel Coens, Richard Sylvester, EORTC Data Center, Brussels. Data Monitoring Committee: J. Pater (chair), M. Buyse, G. Omura.

REFERENCES

(1) Richardson GS, Scully RE, Nikrui N, Nelson JH. Common epithelial cancer of the ovaries (first of two parts). N Engl J Med 1985;312:415–24.

(2) Bolis G, Colombo N, Pecorelli S, Torri V, Marsoni S, Bonazzi C, et al. Adjuvant treatment for early epithelial ovarian cancer: results of two randomised clinical trials comparing cisplatin to no further treatment or chromic phosphate (32P). G.I.C.O.G.: Gruppo Interregionale Collaborativo in Ginecologia Oncologica. Ann Oncol 1995;6:887–93.

(3) NIH consensus conference. Ovarian cancer. Screening, treatment and follow-up. JAMA 1995;273:491–7.

(4) 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.

(5) Trope C, Kaern J, Hogberg T, Abeler V, Hagen B, Kristensen G, et al. Randomized study on adjuvant chemotherapy in stage I high-risk ovarian cancer with evaluation of DNA-ploidy as prognostic instrument. Ann Oncol 2000;11:281–8.

(6) International Collaborative Ovarian Neoplasm Trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. J Natl Cancer Inst 2003;95:125–32.

(7) Trimbos JB, Vergote I, Bolis G, Vermorken JB, Mangioni C, Madronal C, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy In Ovarian Neoplasm trial. J Natl Cancer Inst 2003;95:113–25.

(8) Serov SF, Scully RE, Sobin LE. International histological classification of tumors, no 9: histological typing of ovarian tumours. Geneva (Switzerland): World Health Organization; 1973. p. 9.

(9) Staging announcement. FIGO Cancer Committee. Gynecol Oncol 1986;50: 383–5.

(10) Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

(11) Altman DG. Practical statistics for medical research. London (U.K.): Chapman & Hall; 1991.

(12) Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309:1286–91.

(13) Breslow N, Day N. Statistical methods in cancer research. Lyon (France): International Agency for Research on Cancer; 1980.

(14) Hreshchyshyn MM, Park RC, Blessing JA, Norris HJ, Levy D, Lagasse LD, et al. The role of adjuvant therapy in stage I ovarian cancer. Am J Obstet Gynecol 1980;138:139–45.

(15) Krafft W, Morack G, Flach W, Behling H, Schirmer A, Bruckmann D, et al. [The therapy of the early ovarian cancer (T1/T2 M0 N0) (author's transl)]. Arch Geschwulstforsch 1980;50:664–71.

(16) Sigurdsson K, Johnsson JE, Trope C. Carcinoma of the ovary, stages I and II. A prospective randomized study of the effects of postoperative chemotherapy and radiotherapy. Ann Chir Gynaecol 1982;71:321–9.

(17) Colombo N, Chiari S, Maggioni A, Bocciolone L, Torri V, Mangioni C. Controversial issues in the management of early stage epithelial ovarian cancer: conservative surgery and role of adjuvant therapy. Gynecol Oncol 1994;55:S47–51.

(18) Piver MS, Barlow JJ, Shashikant BL. Incidence of subclinical metastases in stage I and II ovarian carcinoma. Obstet Gynecol 1978;52:100–4.

(19) Piver MS. Optimal surgical therapy in stage I and II ovarian malignancies. Int J Radiat Oncol Biol Phys 1982;8:247–9.

(20) Young RC, Decker DG, Wharton JT, Piver MS, Sindelar WF, Edwards BK. Staging laparotomy in early ovarian cancer. JAMA 1983;250:3072–6.
(21) Helewa ME, Krepart GV, Lotocki R. Staging laparotomy in early epithelial ovarian carcinoma. Am J Obstet Gynecol 1986;154:282–6.
(22) McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1–6.
(23) Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000;92:699–708.
(24) Muggia FM, Braly PS, Brady MF, Sutton G, Niemann TH, Lentz SI, et al. Phase II randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2000;18:106–15.
(25) Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 2002; 360:505–15.

NOTES

Supported in Italy by Fondazione Nerina e Mario Mattioli, in the U.K. by the U.K. Medical Research Council, and in Switzerland by the Swiss Group for Clinical Cancer Research.

Manuscript received April 17, 2002; revised November 7, 2002; accepted November 14, 2002.