Chapter 2

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. Baptist Trimbos
Ignace Vergote
Giorgio Bolis
Jan B. Vermorken
Constantino Mangioni
Caterina Madronal
Massimo Franchi
Saverio Tateo
Gerardo Zanetta
Giovanna Scarfone
Livia Giurgea
Petra Timmers
Corneel Coens
Sergio Pecorelli
For the EORTC–ACTION collaborators

J Natl Cancer Inst 2003; 95(2): 113–125

ABSTRACT

Background: All randomized trials of adjuvant chemotherapy for early-stage ovarian cancer have lacked the statistical power to show a difference in the effect on survival between adjuvant chemotherapy and no adjuvant chemotherapy.
They have also not taken into account the adequacy of surgical staging. We performed a prospective unblinded, randomized phase III trial to test the efficacy of adjuvant chemotherapy in patients with early-stage ovarian cancer, with emphasis on the extent of surgical staging.

Methods: Between November 1990 and January 2000, 448 patients from 40 centers in nine European countries were randomly assigned to either adjuvant platinum-based chemotherapy (n = 224) or observation (n = 224) following surgery. Endpoints were overall survival and recurrence-free survival, and the analysis was on an intention-to-treat basis. The Kaplan–Meier method was used to perform time-to-event analysis, and the log-rank test was used to compare differences between treatment arms. Statistical tests were two sided.

Results: After a median follow-up of 5.5 years, the difference in overall survival between the two trial arms was not statistically significant (hazard ratio [HR] = 0.69, 95% confidence interval [CI] = 0.44 to 1.08; $P = 0.10$).
Recurrence-free survival, however, was statistically significantly improved in the adjuvant chemotherapy arm (HR = 0.63, 95% CI = 0.43 to 0.92; $P = 0.02$). Approximately one-third of patients (n = 151) had been optimally staged and two-thirds (n = 297) had not. Among patients in the observation arm, optimal staging was associated with a statistically significant improvement in overall and recurrence-free survival (HR = 2.31 [95% CI = 1.08 to 4.96]; $P = 0.03$ and HR = 1.82 [95% CI = 1.02 to 3.24] $P = 0.04$, respectively).
No such association was observed in the chemotherapy arm. In the non-optimally staged patients, adjuvant chemotherapy was associated with statistically significant improvements in overall and recurrence-free survival (HR = 1.75 [95% CI = 1.04 to 2.95]; $P = 0.03$ and HR = 1.78 [95% CI = 1.15 to 2.77]; $P = 0.009$, respectively). In the optimally staged patients, no benefit of adjuvant chemotherapy was seen.

Conclusions: Adjuvant chemotherapy was associated with statistically significantly improved recurrence-free survival in patients with early-stage ovarian cancer. The benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging, i.e., patients with more risk of unappreciated residual disease.

INTRODUCTION

Ovarian cancer is a common gynecologic malignancy. Approximately 30% of patients with ovarian cancer are diagnosed with early-stage disease, which is localized to the gynecologic organs and has not spread to adjacent structures in the pelvis or the upper abdomen. Nevertheless, 10%–50% of patients who receive surgery for treatment of early-stage ovarian cancer have a recurrence, and these recurrences are often resistant to various forms of salvage treatment [1].

This high recurrence rate has led to attempts to use different forms of adjuvant treatment, but solid scientific proof of the clinical effectiveness of adjuvant treatment is lacking. Not only is the clinical significance of adjuvant treatment unclear, but the definition of which patients are at high risk of recurrence—that is, in potential need of adjuvant treatment—has remained obscure.

Few randomized trials have tried to address the uncertainties that have been created by this 'act-before-proof' approach. Young et al. [2] reported a Gynecologic Oncology Group (GOG) study in which patients with stage Ia or Ib and grade I or II ovarian cancer were randomly assigned to either observation or intermittent oral melphalan following surgery. There was no survival difference between the two groups of patients. Although the number of patients in this trial was too small to draw definitive conclusions, the authors advocated not administering any adjuvant treatment following surgery and comprehensive staging in patients with this stage and grade of disease [2].

Recently the results of two randomized European trials that included an observation arm have become available [3,4]. In the Italian study [3], patients with early-stage ovarian cancer were randomly assigned to receive either cisplatin or observation following surgery. Patients in both arms received salvage therapy on recurrence. A statistically significant difference in recurrence- free survival was found in favor of chemotherapy, but no difference in overall survival was demonstrated (overall survival: hazard ratio [HR] = 1.15 [95% confidence interval [CI] = 0.44 to 2.98]; recurrence-free survival: HR = 0.35 [95% CI = 0.14 to 0.89]). The authors suggested that salvage treatment was more effective in the observation arm than in the adjuvant chemotherapy arm and that, although patient numbers were small, these findings support a policy of deferring chemotherapy until the actual time of recurrence [3]. In the Scandinavian study [4], 162 patients with early-stage ovarian carcinoma were randomly assigned to receive carboplatin or observation following surgery. No difference in disease-specific survival or disease-free survival was seen (disease-specific survival: HR = 0.94 [95% CI = 0.37 to 2.36]; disease-free survival: HR = 0.98 [95% CI = 0.52 to 1.83]) [4]. However, both

the Italian and Scandinavian studies lacked the power to draw definitive conclusions and did not take into account the extent of the surgical staging of their study groups. The quality of surgical staging in ovarian cancer relates to the reliability of the diagnosis of early-stage disease because it has been well documented that approximately 24% of non-optimally staged patients with early-stage ovarian cancer actually harbor occult residual disease in the peritoneal cavity (stage III disease) [5–8].

In 1990 the European Organisation for Research and Treatment of Cancer–Gynaecological Cancer Group (EORTC–GCG) initiated a randomized clinical trial comparing platinum-based adjuvant chemotherapy with no further treatment (i.e., observation) following surgery in patients with early-stage ovarian cancer.

The study, called Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION), which ran between November 1990 and January 2000, was designed to have more statistical power than previous trials to detect a survival difference and to emphasize the completeness of surgical staging in the analysis of the endpoints of the study. At the same time, the International Collaborative Ovarian Neoplasm Collaborators initiated a similar trial (ICON1), the results of which are also published [9]. We report on the findings of the ACTION trial.

PATIENTS AND METHODS

Patients and Surgery

Patients with International Federation of Gynecology and Obstetrics (FIGO) stages Ia–Ib, grade II–III; all stages Ic and IIa, and all stages I–IIa with clear cell epithelial cancer of the ovary were eligible for the study [10,11]. Surgical treatment had to consist of total abdominal hysterectomy and bilateral salpingo-oophorectomy, followed by surgical staging. In cases of stage Ia cancer, unilateral salpingo-oophorectomy followed by surgical staging was permitted. This kind of conservative surgery has been shown to be adequate treatment for women with stage Ia disease who wish to preserve fertility [12,13]. Patients with a prior or concomitant second malignancy were excluded, as were patients with a World Health Organization (WHO) performance status of more than 3, previous treatment with chemotherapy or radiation therapy, expected inadequacy of follow-up, and an interval of more than 6 weeks between surgical staging procedure and randomization. The Institutional Review Board of each participating center had to approve the study, and informed consent of each patient was a prerequisite.

Surgical Staging

Surgical staging had to consist of at least careful inspection and palpation of all peritoneal surfaces, with biopsies of any suspect lesions, such as adhesions adjacent to the ovarian tumor.

However, far more comprehensive staging was strongly advised, including omentectomy; peritoneal washings; blind biopsies from the peritoneum in the pelvis (pouch of Douglas, bladder, pelvic sidewalls), the paracolic gutters, and the right hemidiaphragm; and iliac and peri-aortic lymph node sampling. If all of these staging requirements were met, the staging performance was considered to be optimal. Three other, less comprehensive staging categories were defined: modified, minimal, and inadequate (Table 1). Strict guidelines were also given for the microscopic assessment of histologic cell type and for the assessment of tumor differentiation, according to WHO criteria [10].

Table 1. Requirements for surgical staging following bilateral salpingo-oophorectomy and total abdominal hysterectomy*

Surgical staging category	Staging guidelines
Optimal	Inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy; (blind) biopsies of right hemidiaphragm, of right and left paracolic gutter, of pelvic sidewalls, of ovarian fossa, of bladder peritoneum, and of cul-de-sac; sampling of iliac and peri-aortic lymph nodes.
Modified	Everything between optimal and minimal staging.
Minimal	Inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy.
Inadequate	Less than minimal staging but at least careful inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases.

*Patients with stage Ia disease who wished to preserve fertility were permitted to have only a unilateral salpingo-oophorectomy.

Randomization

Patients were centrally randomly assigned to either the adjuvant chemotherapy arm or the observation arm by a computer program, using a minimization procedure, at the EORTC Data Center in Brussels. Randomization was stratified according to institution, FIGO stage, and grade of tumor differentiation.

Adjuvant Chemotherapy

Treatment in the adjuvant chemotherapy arm had to consist of at least four courses

of a platinum-based regimen following surgery; however, six courses of treatment were recommended.

Single-agent platinum chemotherapy was also allowed as well as combination regimens. In the case of cisplatin, the required dose was 75 mg/m^2, and for carboplatin the required dose was 350 mg/m^2. Dose modifications in the case of drug toxicity were given when appropriate. Each center had to define its adjuvant chemotherapy regimen in advance and had to remain with that regimen for the duration of the trial. After surgery, patients in the observation arm were not treated again until recurrence. Tumor recurrence had to be confirmed cytologically or histologically.

Patients in the observation arm who had tumor recurrence were given the same chemotherapy regimen that their particular center was using in the adjuvant chemotherapy arm.

Statistical Analysis

Analysis of results was on an intention-to-treat basis. The primary endpoint was overall survival, and the secondary endpoint was recurrence-free survival. Time-to-event analyses were based on the Kaplan–Meier method [14] and events were compared using the log-rank test. Prognostic factor analysis used the Cox proportional hazards regression model, after necessary assumptions were met, to determine statistically significant covariates, such as FIGO stage, tumor grade, histologic cell type, completeness of surgical staging, age, tumor marker carcino antigen 125 (CA 125) level and performance status. Differences in relative size of treatment effect between subgroups of staging performance were tested using a chi-square (χ^2) test for interaction.

Because of the relatively long life expectancy of patients with early-stage ovarian carcinoma and the small expected improvements in survival, the sample size was set, more or less arbitrarily, to 1000 or more patients. An independent interim data-monitoring committee assessed the data and the progress of the study at fixed intervals. A single independent data-monitoring committee monitored the combined accumulating data from ACTION and the parallel trial (ICON1). Interim analyses were interpreted by using conservative statistical significance tests. If the *P* value for the comparison of survival between treatment arms fell below 0.01, consideration was given to stopping the trial. Because patient accrual took longer than expected, the committee decided to close the study in 2000, before the target number of patients was accrued. Audits by an independent quality control panel were done during the course of the study to verify the quality of the data. A separate publication on the findings of this panel is in preparation, but preliminary analysis has confirmed the reliability of the surgical staging data.

RESULTS

Baseline Characteristics

Between November 1990 and January 2000, a total of 448 patients were accrued to the trial by 40 centers from nine European countries. Analysis is complete through March 26, 2001 (Fig. 1). Table 2 shows the clinical and tumor characteristics of the patients in both trial arms. The majority of patients in the chemotherapy arm received cisplatin combined with cyclophosphamide (102 patients or 47%) or single-agent carboplatin (71 patients or 33%). The various clinical and pathologic risk factors were well balanced between the two arms. Thirteen patients in the observation arm received

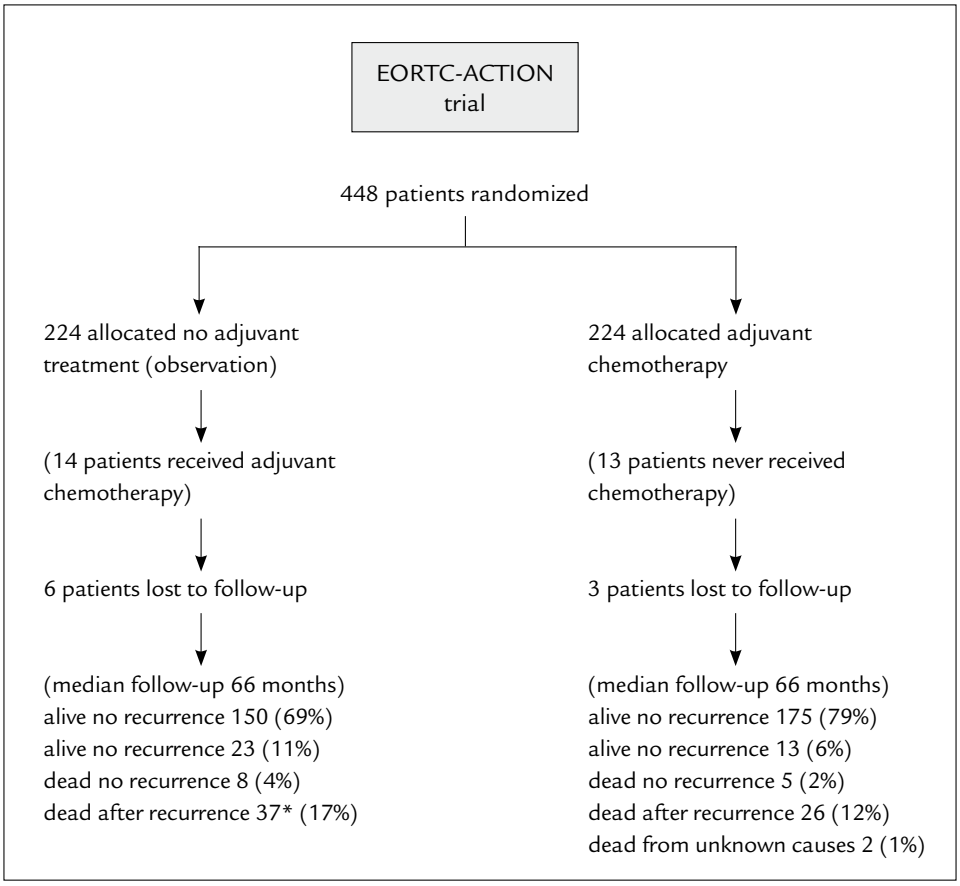


Figure 1. CONSORT diagram of the trial profile of the European Organisation for Research and Treatment of Cancer (EORTC)–Adjuvant ChemoTherapy In Ovarian Neoplasm (ACTION) trial.
*In one patient, no recurrent disease was suspected before the time of death.

Table 2. Clinical and tumor characteristics in patients with early ovarian cancer (stage I–IIa) by treatment arm*

Characteristic	Observation (N =224)	Adjuvant chemotherapy (N =224)
Age, y (median; range)	55 (22–77)	54 (18–84)
Performance status†, n (%)		
0	199 (89)	188 (84)
1	21 (9)	34 (15)
2	3 (1)	2 (1)
Missing 1 (1)	0 (0)	
FIGO stage‡, n (%)		
Ia	76 (33)	79 (35)
Ib	18 (8)	19 (8)
Ic, ovarian surface	28 (13)	22 (10)
Ic, capsule ruptured	52 (23)	64 (29)
Ic, ascites/malignant washing	33 (15)	24 (11)
IIa	15 (7)	16 (7)
Missing	2 (1)	0 (0)
Tumor grade§, n (%)		
Well differentiated	28 (12)	26 (12)
Moderately differentiated	114 (51)	114 (50)
Poorly differentiated	78 (35)	78 (35)
Unknown	2 (1)	6 (3)
Missing	2 (1)	0 (0)
Histologic cell type, n (%)		
Serous	74 (33)	82 (37)
Mucinous	35 (16)	42 (19)
Endometrioid	72 (32)	48 (21)
Clear-cell	26 (12)	37 (17)
Undifferentiated	5 (2)	3 (1)
Other	9 (4)	7 (3)
Missing	3 (1)	5 (2)
CA 125, n (%)		
Normal	55 (24)	73 (33)
Abnormal	116 (52)	0 (40)
Not done	51 (23)	7 (25)
Missing	2 (1)	4 (2)
Surgical staging performance, n (%)		
Optimal	75 (34)	76 (34)
Modified	68 (30)	70 (31)
Minimal	60 (27)	54 (24)
Inadequate	19 (9)	24 (11)
Missing	2 (1)	0 (0)

*Missing = patient information was missing.
†Performance status was in accordance with World Health Organization guidelines [15].
‡FIGO = International Federation of Gynecology and Obstetrics staging system [11].
§Tumor grade was in accordance with World Health Organization grading criteria [10].

chemotherapy, and 14 patients in the adjuvant chemotherapy arm did not. The reasons for these protocol violations were morbidity, disease progression, administrative error, and patient refusal. Follow-up ranged from 3 months to 9 years, with a median follow-up of 5.5 years. Nine patients were lost to follow-up, six in the observation arm and three in the chemotherapy arm.

During the follow-up period 100 recurrences were detected, 60 in the observation arm and 40 in the chemotherapy arm. The incidence of recurrence in the locoregional, extrapelvic, and combined pelvic and extrapelvic sites in the observation and chemotherapy arms was 33%, 47%, and 20% and 35%, 50%, and 15%, respectively (Table 3). Overall, 78 patients died, 45 in the observation arm and 33 in the chemotherapy arm. Sixty-three of the 78 deaths (81%) were due to ovarian cancer; this percentage was similar between the two trial arms. Eight patients in the observation arm died of causes other than ovarian cancer: two of heart failure, three of other malignancies, two of cerebrovascular accident, and one of respiratory failure. Five patients in the chemotherapy arm died of causes other than ovarian cancer: two of heart failure, one of cerebrovascular accident, one of idiopathic thrombocytopenia, and one of pulmonary thromboembolism following a bone fracture. Two patients in the chemotherapy arm died of unknown causes.

Table 3. Site of disease recurrence in patients with early ovarian cancer by treatment arm

Variable	Adjuvant chemotherapy (N = 224)	Observation (N = 224)	Total (N = 448)
No recurrence, n (%)	184 (82)	164 (73)	348 (78)
Recurrence, n (%)	40 (18)	60 (27)	100 (22)
Pelvic	14 (6)	20 (9)	34 (8)
Extrapelvic	20 (9)	28 (13)	48 (11)
Both (pelvic + extrapelvic)	6 (3)	12 (5)	18 (4)

Survival Data

Kaplan–Meier analysis of overall survival yielded 5-year survival figures in the observation and the adjuvant chemotherapy arms of 78% and 85%, respectively, a difference of 7% (95% CI = –1.08% to 15.72%). The difference in overall survival between the two arms was not statistically significant, as depicted in Fig. 2 (HR = 0.69 (95% CI = 0.44 to 1.08); $P = 0.10$). The Kaplan–Meier curves for recurrence-free survival in both arms are shown in Fig. 3. Patients in the adjuvant chemotherapy arm had statistically better recurrence-free survival than patients in the observation arm, with an HR of 0.63 (95% CI = 0.43 to 0.92; $P = 0.02$). These results translate into 5-year survival figures of 68% for patients in the observation arm and 76% for patients in the adjuvant chemotherapy arm, an improvement in recurrence-free survival of 8% (95% CI = –0.88% to 18.04%).

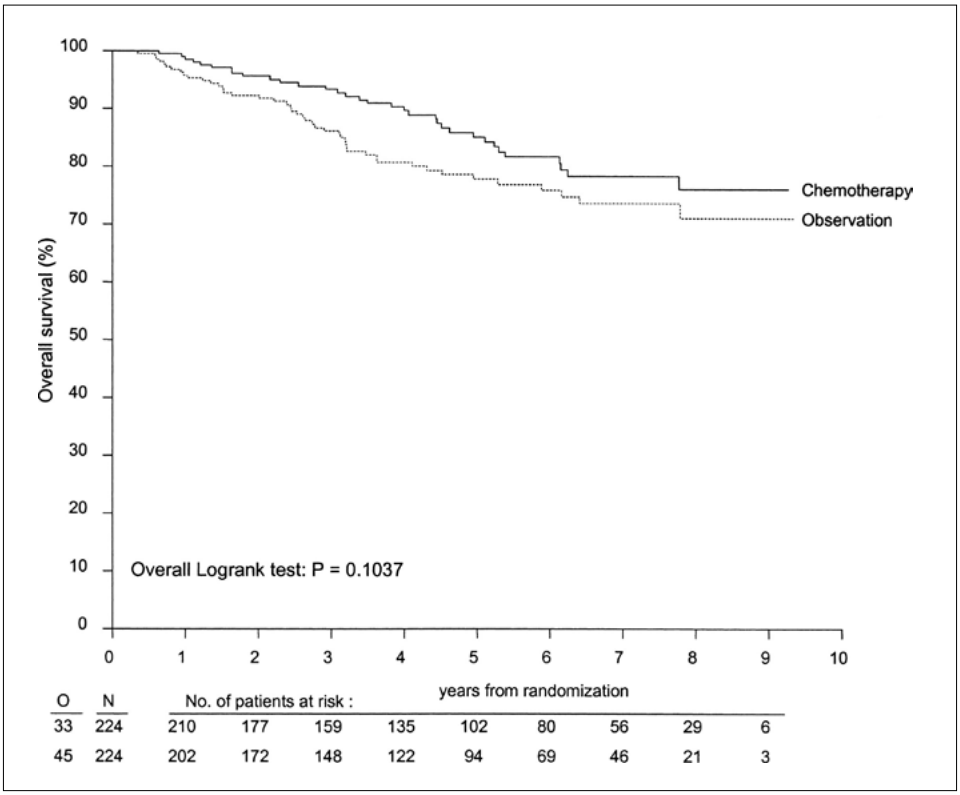


Figure 2. Kaplan–Meier curves for overall survival in patients with early-stage ovarian cancer. Adjuvant chemotherapy patients (n = 224) (**solid line**) were those patients who received immediate adjuvant chemotherapy. Observation patients (n = 224) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated.
The hazard ratio is 1.45 (95% confidence interval [CI] = 0.93 to 2.27, *P* = 0.10 using the log-rank test). These results translate into 5-year overall survival figures of 78% for patients in the observation arm and 85% for patients in the adjuvant chemotherapy arm, a difference of 7% (95% CI = –1.08% to 15.72%). N = number of patients; O = number of observations (events).
Of the 100 patients who had tumor recurrence, 66 died (66%; 62 deaths were due to ovarian cancer). Among the optimally staged patients, six of the 13 (46%) patients who had tumor recurrence in the observation arm died and nine of the 12 (75%) patients who had tumor recurrence in the chemotherapy arm died. Among the non-optimally staged patients, the percentages were different; 33 of the 47 (70%) patients who had tumor recurrence in the observation arm died, and 18 of the 28 (64%) patients who had tumor recurrence in the chemotherapy arm died.

Prognostic Factors and Survival

To determine possible prognostic factors for overall and recurrence-free survival, we performed univariate and multivariable analyses of possible risk factors apart from treatment on the survival data. In Table 4, the univariate and multivariable analyses of possible risk factors apart from treatment are summarized.

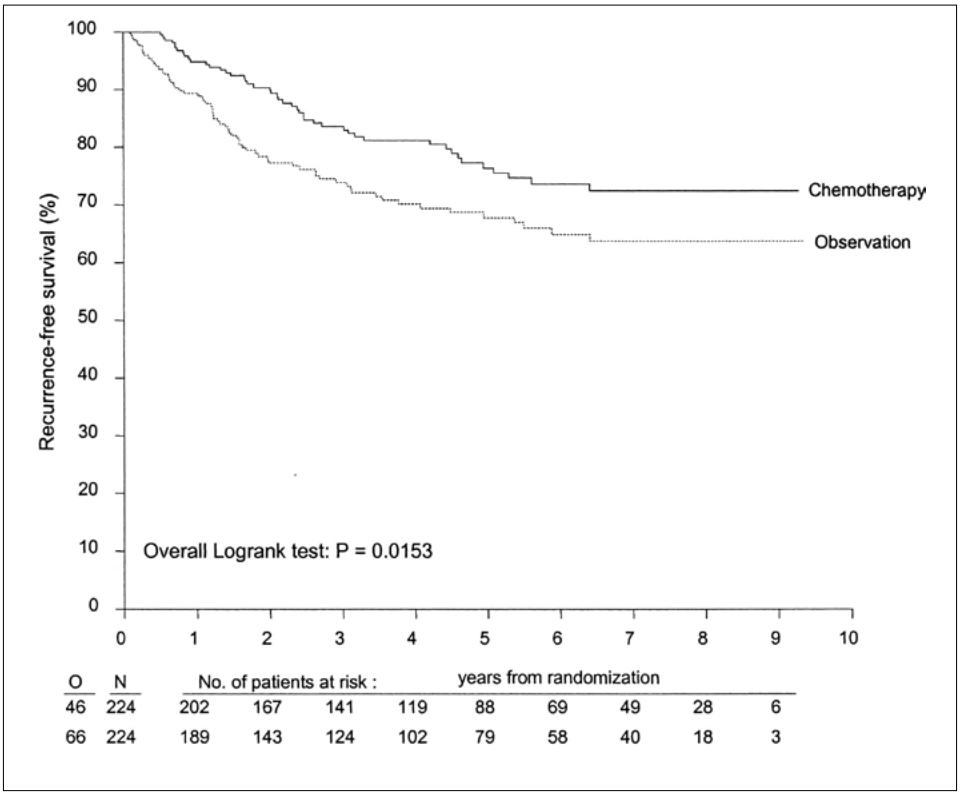


Figure 3. Kaplan–Meier curves for recurrence-free survival in patients with early-stage ovarian cancer.
Adjuvant chemotherapy patients (n = 224) (**solid lin**e) were those patients who received immediate adjuvant chemotherapy.
Observation patients (n = 224) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated. The hazard ratio is 1.59 (95% confidence interval [CI] = 1.09 to 2.31, *P* = 0.02 using the log-rank test) in favor of adjuvant chemotherapy.
These results translate into 5-year recurrence-free survival figures of 68% for patients in the observation arm and 76% for patients in the adjuvant chemotherapy arm, a difference of 8% (95% CI = 0.88% to 18.04%).
N = number of patients; O = number of observations (events).

CA 125 analysis was performed in too few of the patients to be considered in the multivariable analysis. FIGO stage was not a statistically significant prognostic factor. Staging adequacy and tumor grade were statistically significant prognostic factors for overall survival and recurrence-free survival in the univariate and multivariable analysis. Histologic cell type was a statistically significant prognostic factor only for overall survival in the univariate and multivariable analysis.

Table 4. Prognostic factors that were identified in the univariate and multivariable analyses*

	Univariate		Multivariable	
Variable	HR (95% CI)	*P* value†	HR (95% CI)	*P* value‡
Overall survival				
Surgical staging	2.24 (1.29 to 3.90)	0.004	2.05 (1.14 to 3.67)	0.04
Tumor grade	1.64 (1.05 to 2.56)	0.03	1.62 (1.03 to 2.54)	0.03
Histologic cell type	1.79 (1.11 to 2.88)	0.02	1.72 (1.06 to 2.79)	0.02
Recurrence-free survival				
Surgical staging	2.06 (1.25 to 3.39)	0.004	1.96 (1.18 to 3.26)	0.009
Tumor grade	1.85 (1.28 to 2.69)	0.001	1.86 (1.28 to 2.70)	0.001
Histologic cell type	N.S.		N.S.	

*HR = hazard ratio; CI = confidence interval. Surgical staging = inadequate versus minimal, modified, and optimal. Tumor grade was in accordance with World Health Organization grading criteria (10). Histologic cell type = mucinous/endometrioid versus serous, clear-cell, undifferentiated, and other (rare) histology. N.S. = not statistically significant.
†*P* value was determined using the Cox proportional hazards regression model.
‡*P* value was determined using the Cox proportional hazards regression model.

Because staging adequacy was a statistically significant prognostic factor, we investigated survival by different categories of staging (Table 1). Four categories were defined, and the survival curves are shown in Fig. 4. However, for further survival analyses, these categories were dichotomized into just two categories: optimal and non-optimal. This particular dichotomization was done a priori and for reasons of clarity. From a clinical point of view, optimal staging would be easy to define; that is, all staging steps had to be performed. The other staging categories— modified, minimal, and inadequate (regardless of what and how many staging steps were omitted) were regarded as non-optimal.

Of the 448 patients, 151 were optimally staged (observation arm, 75; chemotherapy arm, 76) and 295 were non-optimally staged (observation arm, 147; chemotherapy arm, 148) and in two patients, the staging status was unknown (Table 2). The various baseline characteristics were well balanced among the different staging categories (data not shown). In the observation arm, patients who underwent non-optimal surgical staging had statistically significantly worse overall survival (Fig. 5, A) (HR = 2.31, 95% CI = 1.08 to 4.96; $P = 0.03$) and recurrence-free survival (Fig. 5, C) (HR = 1.82, 95% CI = 1.02 to 3.24; $P = 0.04$) than the optimally staged patients. However, no difference in overall or recurrence-free survival was evident in the patients in the adjuvant chemotherapy arm (Fig. 5, B and D).

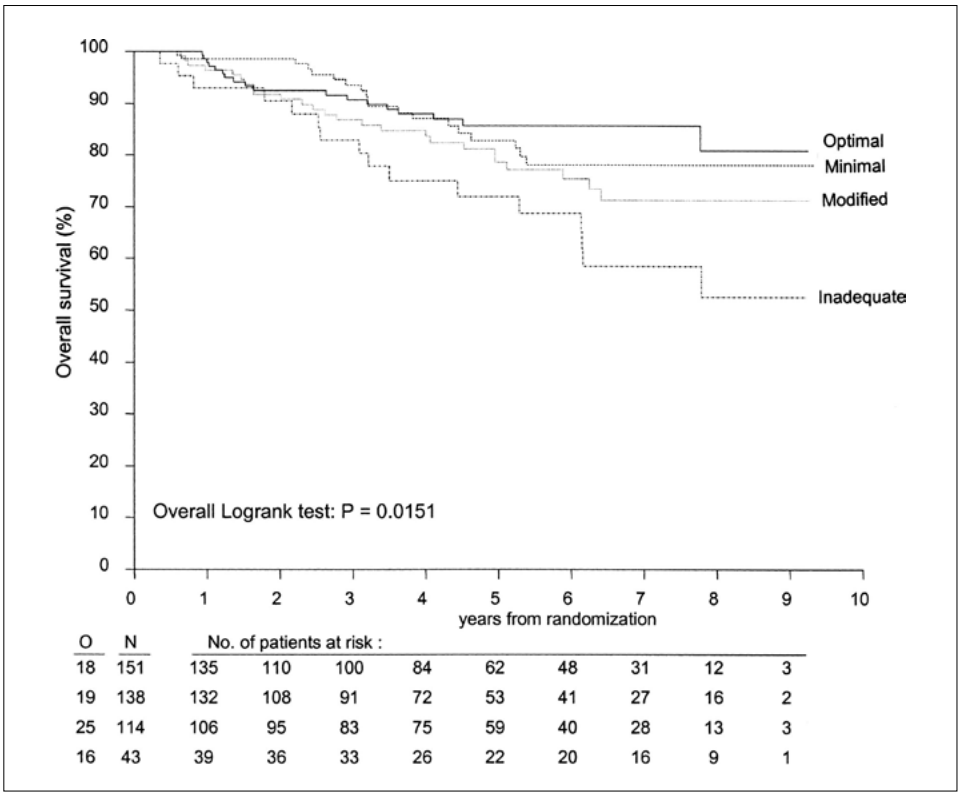


Figure 4. Kaplan–Meier curves for overall survival in patients with early-stage ovarian carcinoma by staging type. Optimal staging (n = 151) (**solid line**), modified staging (n = 138) (**solid dotted line**), minimal staging (n = 114) (**fine dotted line**), and inadequate staging (n = 43) (**solid/fine dotted line**) are in accordance with the staging guidelines presented in Table 1. The hazard ratio is 2.17 (95% confidence interval [CI] = 1.25 to 3.76; *P* = 0.02 using the log-rank test) in favor of optimal staging. N = number of patients; O = number of observations (events).

Extending this subgroup analysis further by looking at the optimal and non-optimal staging groups separately, no difference in overall survival between the observation arm and the chemotherapy arm was found in the optimally staged patients (Fig. 6, A), whereas a statistically significant difference in overall survival between the two arms was demonstrated in the non-optimally staged patients (Fig. 6, B) (HR = 1.75, 95% CI = 1.04 to 2.95; *P* = 0.03). A similar phenomenon was seen for recurrence-free survival (optimally staged patients: HR =1.14, 95% CI = 0.54 to 2.39; *P* = 0.7 [Fig. 6, C]; non-optimally staged patients: HR = 1.78, 95% CI = 1.15 to 2.77; *P* = 0.009 [Fig. 6, D]). However, interactions between treatment effect and the staging subgroups did not reach statistical significance (HR = 2.18, 95% CI . 0.74 to 6.38; *P* = 0.15; Fig. 7).

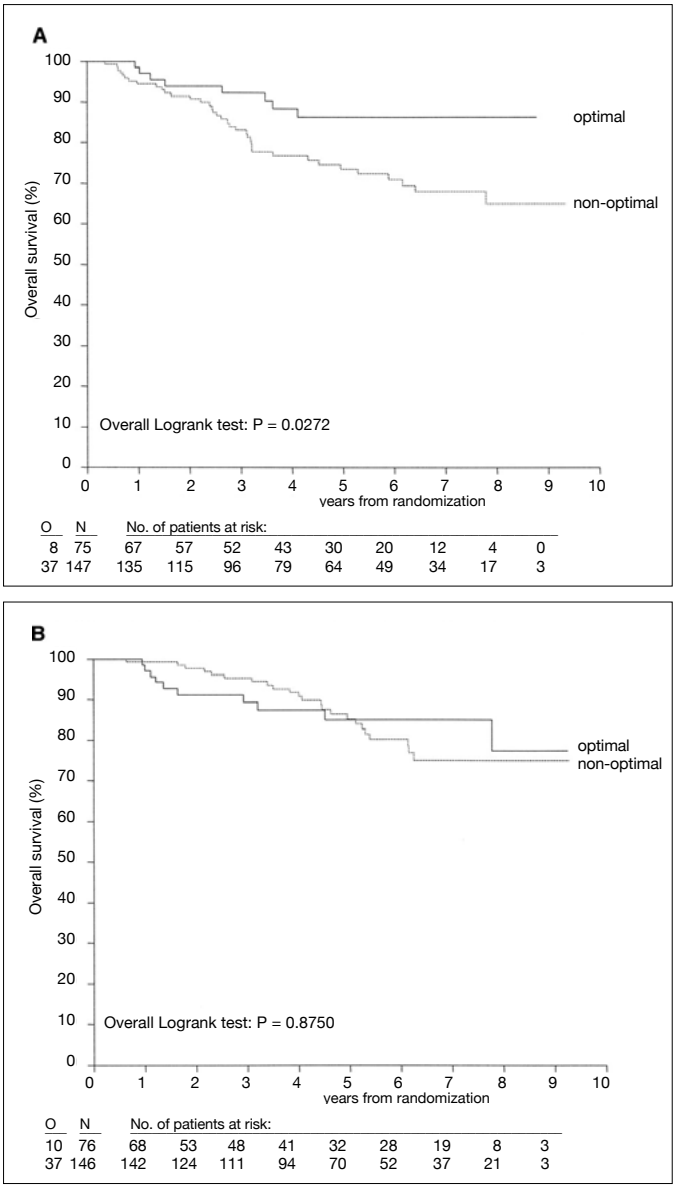
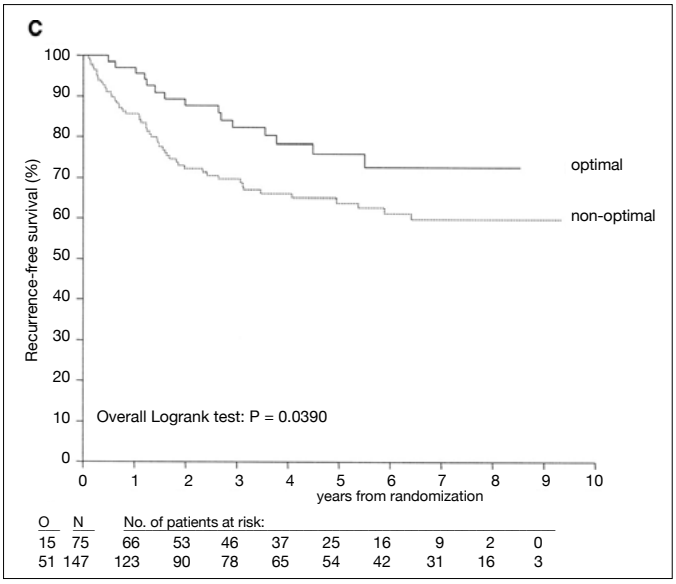
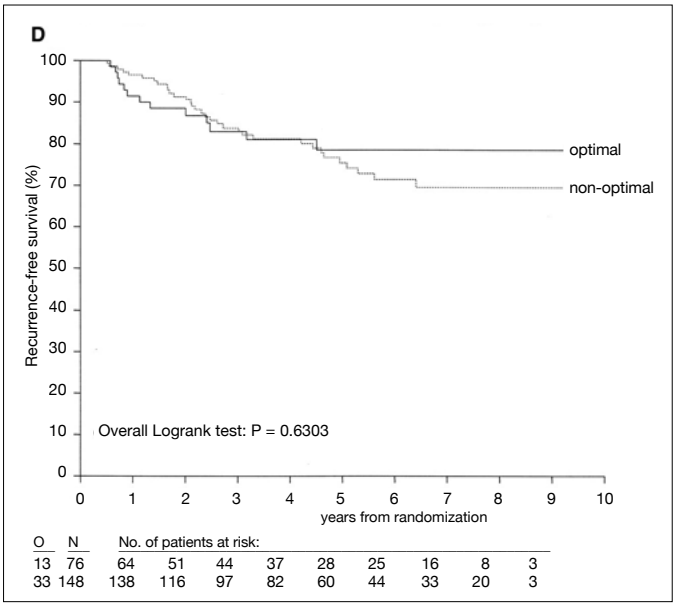


Figure 5. Kaplan–Meier curves for overall and recurrence-free survival in patients with early-stage ovarian cancer by staging type.
Optimal staging (n = 75 in the observation arm and n = 76 in the chemotherapy arm) (**solid line**) and non-optimal staging (modified, minimal, inadequate staging categories combined) (n = 147 in the observation arm and n = 148 in the chemotherapy arm) (**dotted line**) are in accordance with the staging guidelines presented in Table 1. N = number of patients; O = number of observations (events).
A) Overall survival in the observation arm. The hazard ratio [HR] = 2.31 (95% confidence interval [CI] = 1.06 to 4.96, *P* = 0.03 using the log-rank test) in favor of optimal staging. B) Overall survival in the adjuvant chemotherapy arm. HR = 1.06 (95% CI = 0.51 to 2.23, *P* = 0.9 using the log-rank test).





C) Recurrence-free survival in the observation arm. HR = 1.82 (95% CI =1.02 to 3.24, *P* = 0.04 using the log-rank test) in favor of optimal staging. D) Recurrence-free survival in the adjuvant chemotherapy arm. HR 1.17 (95% CI = 0.0.62 to 2.22, *P* = 0.6 using the log-rank test).

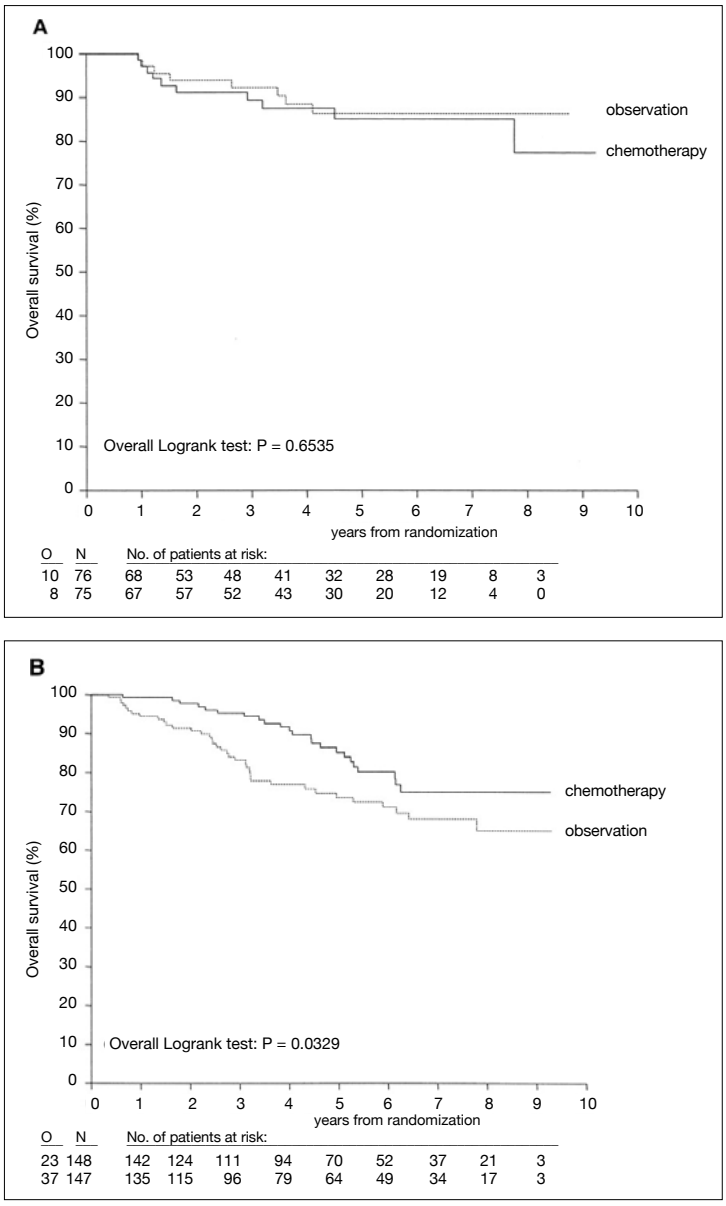
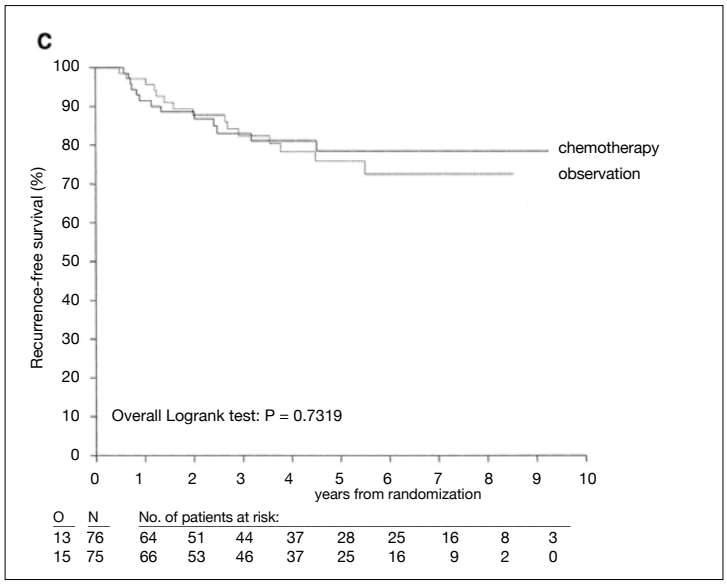
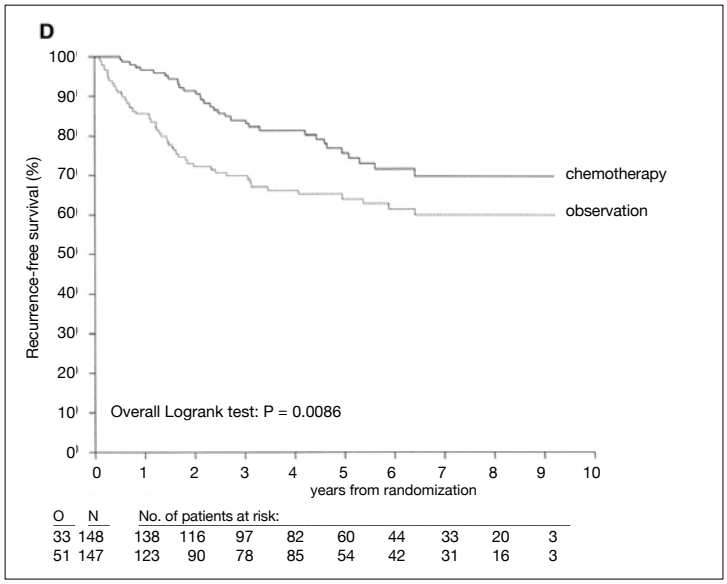


Figure 6. Kaplan–Meier curves for overall and recurrence-free survival in patients with early-stage ovarian cancer by treatment arm.

Chemotherapy patients (**solid line**) were those patients who received immediate adjuvant chemotherapy (n = 76 in optimally staged arm, and n = 148 in non-optimally staged arm). Observation patients (**dotted line**) were those patients who were observed until chemotherapy was indicated (n = 75 in optimally staged arm, and n = 147 in non-optimally staged arm). N = number of patients; O = number of observations (events). A) Overall survival in the optimally staged patients. The hazard ratio (HR) = 0.81 (95% confidence interval [CI] = 0.32 to 2.05, *P* = 0.7 using the log-rank test). B) Overall survival in the non-optimally staged patients. HR = 1.75 (95% CI = 1.04 to 2.95, *P* = 0.03 using the log-rank test) in favor of adjuvant chemotherapy.





C) Recurrence-free survival in the optimally staged patients. HR = 1.14 (95% CI = 0.54 to 2.93, *P* = 0.7 using the log-rank test). D) Recurrence-free survival in the non-optimally staged patients. HR = 1.78 (95% CI = 1.51 to 2.77, *P* = 0.009 using the log-rank test) in favor of adjuvant chemotherapy.

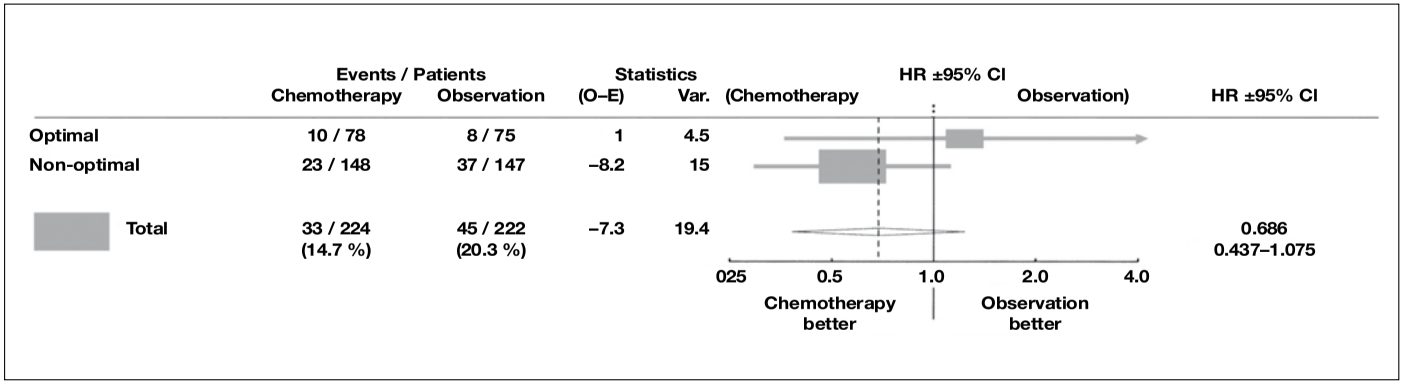


Figure 7. Forest plots of the interaction between the surgical staging groups optimal and non-optimal staging versus treatment effect (adjuvant chemotherapy better versus observation better) for overall survival.

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 95% confidence interval (CI). The **arrow** at the end of the horizontal line indicates that the 95% CI is larger than the scale of the figure. The **diamond** indicates the HR (middle of the diamond) and the 95% CI (extremes of the diamond) for the combined data. Linear trends and heterogeneity of the HRs to detect differences in relative size of treatment effect were assessed by a chi-square (χ^2) test for interaction. χ^2 test for heterogeneity = 2.01, degrees of freedom = 1; P = 0.15. The HR for overall survival in optimally staged and non-optimally staged patients is 2.18 (95% CI = 0.74 to 6.38; P = 0 .15). O-E = number of events observed minus number of events expected under the null hypothesis. Variance = variance of 1/logarithm of the HR. The HR for overall survival in the chemotherapy arm and the observation arm is 0.686 (95% CI = 0.437 to 1.075)

DISCUSSION

The present study provides evidence that adjuvant chemotherapy delays disease recurrence in patients with early-stage ovarian cancer, of whom two-thirds (n =297) had undergone non-optimal surgical staging. For overall survival, however, no statistically significant differences were observed.

In addition to the well known risk factors for overall and recurrence-free survival, such as tumor grade and histologic cell type [16], the completeness of surgical staging was found to be an independent prognostic factor. The impact of surgical staging on prognosis is not surprising, because the extent of staging influences the likelihood of residual disease. Optimal surgical staging minimizes the likelihood of residual stage III disease, and incomplete surgical staging increases the possibility of hidden occult cancer in the peritoneal cavity. The finding that completeness of surgical staging is an independent prognostic factor is not completely new. For example, in 1992 the Department of Obstetrics and Gynecology at Yale University compared expert and comprehensive surgery (i.e., complete surgical staging) in early-stage ovarian cancer with incomplete surgical staging and tumor removal [17]. Although the number of patients in that study was small, a statistically significant survival advantage was demonstrated in favor of the completely staged group. More recently, Italian investigators have also identified the extent of surgical staging with early-stage ovarian carcinoma as an independent prognostic factor in their multivariable analysis [18].

In the current study, patients in the observation arm who were optimally staged had statistically significantly better overall and recurrence-free survival than patients who were non-optimally staged (Fig. 5, A and C). However, the poor prognosis of the non-optimally staged patients could be corrected by administering adjuvant chemotherapy (Fig. 5, B and D). This finding suggests that adjuvant chemotherapy in early-stage ovarian cancer may work predominantly by affecting small-volume or microscopic tumor implants or metastases that remain unnoticed at the time of surgical staging. This hypothesis is supported by the finding that chemotherapy improved both overall and recurrence-free survival in the non-optimally staged patients (i.e., those patients who may have had residual disease) and not in the optimally staged patients (i.e., those patients who had only a minimal chance of residual disease) (Fig. 6, B and D). The finding that adjuvant chemotherapy is effective in non-optimally staged patients might also explain the results of the ICON1 trial [9] and the combined ICON1/ACTION analysis [19], in which the majority of patients were most probably not optimally staged. Although FIGO stage is generally a well known risk factor for survival of patients with ovarian cancer, it was not found to be a prognostic factor in this study. For example,

stage Ic disease was not associated with a higher risk of recurrence or death compared with moderately and poorly differentiated stages Ia and Ib disease (data not shown). In addition, in a recent meta-analysis of more than 1500 cases of early-stage ovarian cancer, Vergote et al. [16] found that stage Ic disease had a prognosis similar to that of stage Ib disease. Thus, these findings might be an important consideration when redefining high-risk early-stage ovarian cancer.

Salvage treatment of patients with recurrent disease showed a difference in salvage rate (i.e., the percentage of patients successfully treated for tumor recurrence) between the optimally staged and the non-optimally staged patients. In the non-optimally staged patients, the salvage rate in the observation and the adjuvant chemotherapy arms was similar (70% and 64%, respectively). In the optimally staged patients, salvage treatment with adjuvant chemotherapy was more successful in the observation arm than in the adjuvant chemotherapy arm (75% and 46%, respectively). The number of patients involved in this analysis was small, but it is of interest that the same difference in the effectiveness of chemotherapy salvage treatment was found in the Italian Gruppo Interregionale Collaborative Oncology Group (GICOG) study, in which patients also underwent complete surgical staging [3]. If this difference in the effectiveness of salvage treatment were to be observed in larger studies, it would give additional support to a policy of postponing chemotherapy until the time of actual tumor recurrence, providing that optimal surgical staging had been performed.

Like other analyses of this kind, this study has several potential limitations. First, the ACTION trial was not specifically designed to compare different surgical staging procedures, and patients were not prospectively stratified according to the various surgical staging categories. Retrospective stratification, however, showed a well-balanced distribution of the four staging categories between the two treatment arms (data not shown) and no differences in the distribution of other risk factors, such as tumor grade and histologic cell type, between optimally and non-optimally staged patients. Second, the numbers of patients become increasingly smaller when performing subgroup analyses.

Although this study is the largest randomized trial in early-stage ovarian cancer in terms of the number of assessable patients, it still suffers from a limited sample size. Therefore, the interpretation of results should be made with sufficient care, because, although interactions of this kind are generally hard to detect, a lack of statistically significant differences between two groups does not necessarily imply equivalence. Statistical tests to analyze the potential interaction between the chemotherapy effect and the staging adequacy showed only trends and no proof ($P = 0.15$). In Fig. 7, a

graphic representation of this analysis can be seen. The hazard ratios of optimal and non-optimal staging regarding overall survival seem to be different, but statistical proof at a $P = 0.05$ level was prevented by the large 95% confidence interval in the optimally staged patients. The main determinant of the width of the 95% confidence interval is the number of events, and events were infrequent following complete surgical staging. It is, therefore, exactly the factor that has to be proven that is hampering the statistical ability to do so.

This effect, the opposite of a self-fulfilling prophecy, sheds doubt on the possibility that stronger statistical proof will ever be feasible in terms of necessary numbers of patients. Although we have stressed the clinical significance of complete surgical staging of early-stage ovarian cancer, some concern may be raised about its feasibility in clinical practice.

In the ACTION trial, even though strict guidelines for optimal surgical staging were set, only one-third of the patients were optimally staged according to the guidelines in Table 1. The reasons for this low number of patients actually receiving staging according to trial protocols are well known. Early-stage ovarian cancer often presents with symptoms mimicking a benign ovarian cyst. This clinical condition is then dealt with by surgeons with either a lack of knowledge of ovarian cancer spread or a lack of surgical experience (e.g., in lymph node sampling) [20,21]. The findings of this study underscore the clinical significance of surgical staging and will hopefully influence the current practice of referral and centralization to oncology centers of suspected early-stage ovarian cancer patients.

In conclusion, this trial studied patients who were completely and comprehensively (i.e., optimally) staged in only one-third of cases. Taking all patients into account, adjuvant chemotherapy statistically significantly improved recurrence-free survival, but no improvement was seen in overall survival. Tumor grade, histologic cell type, and completeness of surgical staging were independent prognostic factors. In the subgroup analysis of different staging adequacy, indications were found that adjuvant chemotherapy is not effective in optimally staged patients. Thus, we suggest that adjuvant chemotherapy in early-stage ovarian cancer is predominantly effective in patients with occult residual disease and that its effectiveness is dependent on the likelihood of remaining ovarian cancer spread. The adequacy of surgical staging is indicative of the likelihood of unappreciated residual cancer, and the observed benefit of adjuvant chemotherapy - primarily in non-optimally staged patients - may be indicative of a benefit of adjuvant chemotherapy only in patients with appreciable residual disease. In the next EORTC trial we will attempt to confirm the findings that adjuvant

chemotherapy in early-stage ovarian cancer, is not effective after optimal surgical staging. We are considering a trial protocol to randomly assign non-optimally staged patients into either restaging (i.e., to make the patient optimally staged) followed by observation or direct adjuvant chemotherapy without restaging. Because the two trial arms may be equivalent in terms of survival, quality-of-life issues will be an important endpoint of this study.

APPENDIX

EORTC—ACTION TRIAL COLLABORATORS AND AFFILIATIONS*:

Centro di Referimento Oncologico, Aviano, Italy: S. Tumolo; Velindre Hospital, Whitchurch, U. K.: M. Adams; Ziekenhuis de Heel, Zaandam, The Netherlands: A. v Bochove; Erasmus Medisch Centrum, Rotterdam, The Netherlands: M. E. L. v. d. Burg; Hospital Clinico Universitario de Valencia, Spain: A. Cervantes; Centre Henri Becquerce, Rouen, France: B. Chevalier; Istituto Europeo di Oncologia, Milan, Italy: N. Colombo; Kaiser Franz Josef Spital, Vienna, Austria: C. Dittrich; Eemland Ziekenhuis, Amersfoort, The Netherlands: J. Duk; Medical University of Gdansk, Poland: J. Emerich; Universita di Brescia, Italy: C. Favalli; Policlinico A. Gemelli-Universita del Sacro Cuore, Rome, Italy: S. Greggi; Centre Leon Berard, Lyon, France: J. P. Guastalla; Hospital General de Asturias, Oviedo, Spain: A. J. Lacave; Rigshospitalet, Copenhagen, Denmark: B. Lund; Universita di Padova, Italy: T. Maggino; Instituto Scientifico H. S. Raffaele, Milan, Italy: G. Mangili; Azienda Ospedaliera di Parma, Italy: M. Melpignano; Centre Antoine Lacassagne, Nice, France: M. Namer; Instituto Regina Elena, Rome, Italy: M. Nardi; Instituto Portugues de Oncologia-centro de Coimbra, Portugal: C. F. de Oliviera; Instituto di Science Biomediche San Paolo, Milan, Italy: U. Radaelli; Ospedale Civile, Voghera, Italy: C. Scarabelli; University Medical Centre Nijmegen, The Netherlands: Ch. Schijf; Ospedale Generale di Zona san Carlo di Nancy, Rome, Italy: Scotto di Palumbo; Atrium Medisch Centrum, Heerlen, The Netherlands: J. E. G. M. Stoot; Stichting Streekziekenhuis Midden-Twente, Hengelo, The Netherlands: R. v.d. Sijde; Academisch Medisch Centrum, Amsterdam, The Netherlands: C. Veenhof; Academisch Ziekenhuis Groningen, The Netherlands: A. v. d. Zee; Clinica Universita Torino, Turin, Italy: A. Ferrero; Academic Medical Center, Amsterdam, The Netherlands: A. H. Zwinderman. Medical supervisor: I. Teodorovic, EORTC Data Center, Brussels, Belgium. Statistical supervisor: R. Sylvester, EORTC Data Center, Brussels.

* at the time the trial was ongoing

REFERENCES

1. Young RC, Knapp FC, Fuks Z, Disaia PJ. Cancer of the ovary. In: De Vita V, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 6th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2001. p. 1083–1117.
2. Young RC, Walton LA, Ellenberg SS, 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: 1021–1027.
3. Bolis G, Colombo N, Pecorelli S, 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: 887–893.
4. Tropé C, Kærn J, Hogberg T, 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: 281–288.
5. Young RC, Decker DG, Wharton JT, et al. Staging laparotomy in early ovarian cancer. JAMA 1983; 250(22): 3072–3076.
6. Helewa ME, Krepart GV, Lotocki R. Staging laparotomy in early epithelial ovarian carcinoma. Am J Obstet Gynecol 1986; 154: 282–286.
7. Soper JT, Johnson P, Johnson V, Berchuck A, Clarke-Pearson DL. Comprehensive restaging laparotomy in women with apparent early ovarian carcinoma. Obstet Gynecol 1992; 80: 949–953.
8. Schueler JA, Trimbos JB, Hermans J, Fleuren GJ. The yield of surgical staging in presumed early stage ovarian cancer; benefits or doubts? Int J Gynecol Cancer 1998; 8: 95–102.
9. Colombo N, Guthrie D, Chiari S, et al. 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(2): 125–132.
10. Serov SF, Scully RE, Sobin LH. Histological Typing of Ovarian Tumours. In International Histological Classification of Tumours, no 9. Geneva, World Health Organization; 1973: 17-54.
11. Staging announcement. FIGO Cancer Committee. Gynecol Oncol 1986; 50: 383–385.
12. Zanetta G, Chiari S, Rota S, et al. Conservative surgery for stage I ovarian carcinoma in women of childbearing age. Br J Obstet Gynaecol 1997; 104: 1030–1035.
13. Morice P, Wicart-Poque F, Rey, et al. Results of conservative treatment in epithelial ovarian carcinoma. Cancer 2001; 92: 2412–2418.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–481.
15. Wester JP, de Valk HW, Nieuwenhuis HK, et al. Risk factors for bleeding during treatment of acute venous thromboembolism. Thromb Haemost 1996; 76: 682–688.
16. Vergote I, De Brabander J, Fyles A, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001; 357: 176–182.
17. Mayer AR, Chambers SK, Graves E, et al. Ovarian cancer staging: does it require a gynecologic oncologist? Gynecol Oncol 1992; 47: 223–227.
18. Zanetta G, Rota S, Chiari S, et al. The accuracy of staging: an important prognostic determinator in stage I ovarian carcinoma. A multivariate analysis. Ann Oncol 1998; 9(10): 1097–1101.
19. Trimbos JB, Parmar M, Vergote I, et al. 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. J Natl Cancer Inst 2003; 95(2): 105–112.
20. Mc Gowan L, Lesher LP, Norris HJ, Barnett M. Misstaging of ovarian cancer. Obstet Gynecol 1985; 65: 568–572.
21. Trimbos JB, Schueler JA, Lent M van, Hermans J, Fleuren GJ. Reasons for incomplete surgical staging in early ovarian carcinoma. Gynecol Oncol 1990; 37:374–377.