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BRIEF COMMUNICATION

Surgical Staging and Treatment of Early Ovarian Cancer: Long-term Analysis From a Randomized Trial

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A long-term follow-up analysis of the randomized clinical trial Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) from the European Organization for Research and Treatment of Cancer was undertaken to determine whether the original results with a median follow-up of 5.5 years could be verified after longer follow-up with more events. In the ACTION trial, 448 patients with early ovarian cancer were randomly assigned, after surgery, to adjuvant chemotherapy or to observation (no further treatment). The original analysis found that adjuvant chemotherapy improved recurrence-free survival but not overall survival and found in a subgroup analysis that completeness of surgical staging was an independent prognostic factor, with better recurrence-free and overall survival among those with complete (optimal) surgical staging. After a median follow-up of 10.1 years, we analyzed the more mature data from the ACTION trial and found support for most of the main conclusions of the original analysis, except that overall survival after optimal surgical staging was improved, even among patients who received adjuvant chemotherapy (hazard ratio of death = 1.89, 95% confidence interval = 0.99 to 3.60; overall two-sided log-rank test $P = .05$). More cancer-specific deaths were observed among nonoptimally staged patients (40 [27%] of the 147 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm) than among optimally staged patients (seven [9%] of the 75 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm) (two-sided χ^2 test for heterogeneity, $P = .06$). Thus, completeness of surgical staging in patients with early ovarian cancer was found to be statistically significantly associated with better outcomes, and the benefit from adjuvant chemotherapy appeared to be restricted to patients with nonoptimal surgical staging.

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Results of the European randomized clinical trial called Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) conducted by the European Organization for Research and Treatment of Cancer (EORTC) in patients with early epithelial ovarian cancer were published in 2003 (1), and its conclusions have been discussed previously (2–6). This trial included 448 patients who in the 2003 report (1) had a median follow-up of 5.5 years (range = 3 months to 9 years), a total of 100 recurrences registered, and 78 deaths from ovarian cancer. Adjuvant chemotherapy that was administered after surgical treatment statistically significantly improved recurrence-free survival but not overall survival (1). Subgroup analysis on the effect of surgical staging indicated that the benefit of adjuvant chemotherapy appeared to be limited to patients who underwent nonoptimal staging and so had a higher risk of undetected residual disease. In a subgroup analysis of patients with optimal surgical staging, adjuvant chemotherapy was not associated with overall or recurrence-free survival.

In this study, we analyzed the mature data with a median follow-up of 10.1 years (95% confidence interval [CI] = 9.2 to 11.3 years) to test specifically whether the findings of the initial analysis would be robust over time. We repeated the initial analysis after a longer follow-up with more events and used cancer-specific survival to avoid the bias of intercurrent deaths (ie, deaths from a cause other than ovarian cancer) because this risk increases with the duration of follow-up.

Patients with epithelial ovarian cancer at stages Ia–Ib and grades 2–3 and all stages Ic and IIa and patients with clear cell cancer of the ovary (as defined by the International Federation of Gynecology and Obstetrics [FIGO]) at all stages I–IIa were eligble for the study. After surgery, patients were randomly assigned to adjuvant chemotherapy or to observation. The surgical staging procedure was divided into two groups: optimal and nonoptimal staging. Optimal staging included removal of the affected ovary; removal of the uterus and contralateral ovary (if a patient with a stage IA tumor wanted to remain fertile, the uterus and contralateral ovary could be left in situ); careful inspection and palpation of all peritoneal surfaces and biopsy sampling of any suspicious areas, such as adhesions adjacent to the primary tumor; peritoneal washing for cytology analysis; infracolic omentectomy; blind peritoneal biopsy sampling of the right hemidiaphragm, the right and left paracolic gutters, the pouch of Douglas, the bladder peritoneum and the pelvic side walls; and removal of para-aortic and pelvic lymph nodes. The group of patients with nonoptimal staging was further divided into the categories modified, minimal, and inadequate staging (1). The ACTION trial was conducted between November 1, 1990, and January 23, 2000, in 40 centers from nine European countries (EORTC Gynaecological Cancer Group, trial registry number = 55 904). The Institutional Review Board of each participating center had to approve the study, and informed consent of each patient was a prerequisite.

Cancer-specific survival was measured from the date of randomization to the date of death from ovarian cancer. Patients who were still alive or who had died of other causes were censored at their last known date alive. Recurrence-free survival was measured from the date of randomization

to the first documented date of recurrence or death from any cause, whichever occurred first. Both survival measures were estimated by the Kaplan–Meier method and compared by Cox proportional hazards regression (according to the intention-to-treat principle, after necessary assumptions were met) to determine statistically significant covariates, such as FIGO stage, tumor grade, histological cell type, completeness of surgical staging, age, level of tumor marker CA125, and performance status. Differences in relative size of treatment effect between subgroups of staging performance were tested by use of the χ^2 test for interaction.

To analyze the mature data, follow-up was extended to May 23, 2008, increasing the median follow-up from 5.5 years in the original analysis to 10.1 years (95% CI = 9.2 to 11.3 years). The follow-up duration was equal between the two treatment arms.

The number of events for the original analysis and this updated analysis are presented in Table 1. In a multivariable analysis that was adjusted for treatment, only the extent of surgical staging and tumor grade were statistically significantly associated with cancer-specific survival (hazard ratio [HR] of death = 1.89, 95% CI = 1.23 to 2.91, for patients with nonoptimal staging compared with those with optimal staging; P = .004; HR of death = 1.78, 95% CI = 1.24 to 2.56, for patients with poorly differentiated tumors compared with those with well and moderate tumors; P = .002). In this analysis, well and moderately differentiated tumors were combined because differences between them were minimal.

Cancer-specific and recurrence-free survival for both the observation and the chemotherapy arms are given in Figure 1, A and B. After a 10-year follow-up, cancer-specific survival was similar between the two arms, but recurrence-free survival was statistically significantly higher in the chemotherapy arm (70%) than in the observation arm (62%) (difference = 8%, 95% CI = −1.6% to 17.6%; HR for death = 0.64, 95% CI = 0.46 to 0.89, P = .007).

In both this analysis and the original analysis, patients were also separated into optimally and nonoptimally staged groups. Among the optimally staged group, no differences were observed in 10-year cancer-specific survival and recurrence-free survival between the adjuvant chemotherapy and the observational arms (Figure 1, C and D).

In contrast, among the nonoptimally staged group, statistically significantly better 10-year cancer-specific survival was found among those in the adjuvant chemotherapy arm (80%) than among those in the observation arm (69%) (difference = 11%, 95% CI = 0% to 22%; HR for death = 0.58, 95% CI = 0.35 to 0.95, P = .029) (Figure 1, E). In addition, among the nonoptimally staged group, statistically significantly better 10-year recurrence-free survival was found among those in the chemotherapy arm (65%) than among those in the observation arm (56%) (difference = 9%, 95% CI = −2.8% to 20.8%; HR for death = 0.60, 95% CI = 0.41 to 0.87, P = .007) (Figure 1, F).

Among patients in the observation arm after a median follow-up of 10.1 years, optimally staged patients had statistically significantly better rates for cancer-specific survival and recurrence-free survival than nonoptimally staged patients (Table 2). Among patients in the chemotherapy arm after a median follow-up of 10.1 years, the rates for cancer-specific survival and recurrence-free survival were similar in optimally staged patients and nonoptimally staged patients (Table 2).

CONTEXT AND CAVEATS

Prior knowledge

In the randomized clinical trial Adjuvant Chemotherapy in Ovarian Neoplasm, 448 patients with early ovarian cancer were randomly assigned, after surgery, to adjuvant chemotherapy or to observation. After a median follow-up of 5.5 years, adjuvant chemotherapy was associated with improved recurrence-free survival but not overall survival. In a subgroup analysis, better recurrence-free and overall survival were observed among those with nonoptimal surgical staging than those with optimal staging.

Study design

Long-term analysis of data from this trial after a median of 10.1 years of follow-up.

Contribution

The long-term analysis supported most conclusions from the original analysis, except that overall survival after optimal surgical staging was improved, even among patients who received adjuvant chemotherapy. More cancer-specific deaths were observed among nonoptimally staged patients than among optimally staged patients.

Implications

Completeness of surgical staging among patients with early ovarian cancer was statistically significantly associated with better outcomes, and the benefit from adjuvant chemotherapy was restricted to patients with nonoptimal surgical staging.

Limitations

The trial was not designed to compare different surgical staging procedures. Patients could not be prospectively stratified by surgical staging category. The study had a limited sample size. Quality of life was not studied.

From the Editors

Table 1. Comparison of recurrences and deaths among the 448 patients (224 in the observation arm and 224 in the adjuvant chemotherapy arm) from the original analysis (2003) and from the updated analysis of the mature data: the Adjuvant Chemotherapy in Ovarian Neoplasm Trial*

	Original analysis (1)		Analysis of mature data	
Events (deaths or recurrences)	**Adjuvant chemotherapy arm**	**Observation arm**	**Adjuvant chemotherapy arm**	**Observation arm**
Recurrences, No. (%)	40 (17.8)	60 (26.8)	61 (27.2)	87 (38.8)
Deaths, No. (% of total deaths)				
Total	33 (14.7)	45 (20.1)	52 (23.2)	67 (29.9)
From ovarian cancer	26 (78.8)	37 (82.2)	36 (69.2)	47 (70.1)
From other causes	5 (15.2)	8 (17.8)	12 (23.1)	19 (28.4)
From unknown causes	2 (6.0)	—	4 (7.7)	1 (1.5)

* Adjuvant chemotherapy had to consist of at least four courses of a platinum-based regimen after surgery but six courses were recommended.

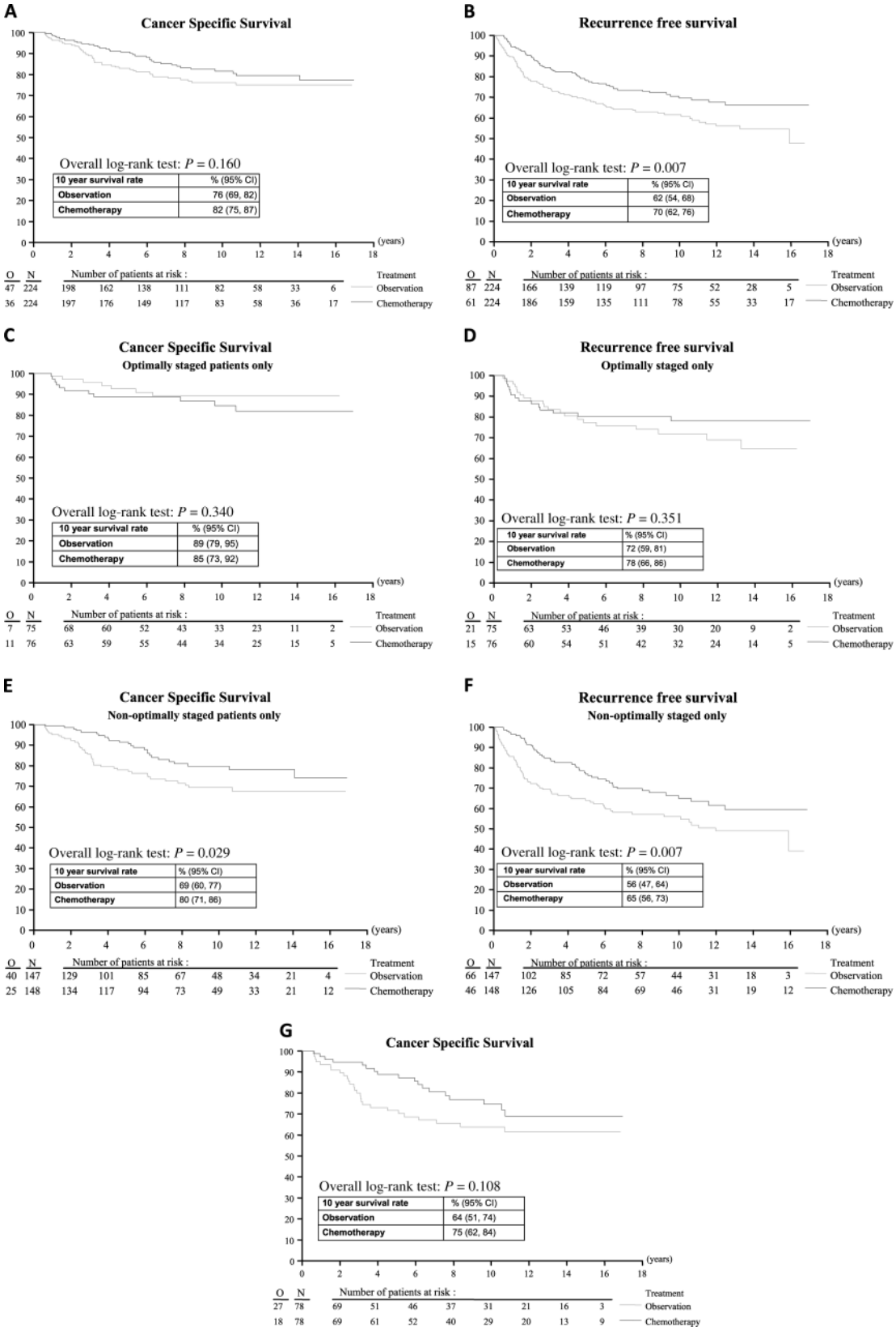

Figure 1. Kaplan–Meier curves for cancer-specific and recurrence-free survival among patients with early-stage ovarian carcinoma by staging type and treatment arm (observation and adjuvant chemotherapy). All comparisons were between the observational arm and the adjuvant chemotherapy arm. The survival percentage is shown on the *y*-axis, and time is shown on the *x*-axis. **A**) Cancer-specific survival in all 448 patients (hazard ratio [HR] of death = 0.73, 95% confidence interval [CI] = 0.48 to 1.13, *P* = .16). **B**) Recurrence-free survival in all 448 patients (HR of death = 0.64, 95% CI = 0.46 to 0.89, *P* = .007, in favor of adjuvant chemotherapy). **C**) Cancer-specific survival in optimally staged patients

(continued)

Table 2. The 10-year cancer-specific survival and recurrence-free survival rates by the extent of surgical staging: the Adjuvant Chemotherapy in Ovarian Neoplasm Trial*

Survival type and arm	% survival (95% CI)		HR (95% CI)	P†
	With optimal staging	With nonoptimal staging		
Cancer-specific survival				
Observation	89 (79 to 95)	69 (60 to 77)	3.28 (1.47 to 7.33)	.002
Chemotherapy	85 (73 to 92)	80 (71 to 86)	1.27 (0.62 to 2.58)	.52
Recurrence-free survival				
Observation	72 (59 to 81)	56 (47 to 64)	1.91 (1.17 to 3.11)	.009
Chemotherapy	78 (66 to 86)	65 (56 to 73)	1.64 (0.91 to 2.93)	.09

* CI = confidence interval; HR = hazard ratio of death or recurrence.

† The statistical test was the two-sided log-rank test.

Because the differentiation grade of early ovarian cancer is a strong prognostic factor for survival, the optimally staged 156 patients in the ACTION trial with a poorly differentiated (grade 3) tumor (78 in the observation arm and 78 in the adjuvant chemotherapy arm) were analyzed separately. After a median follow-up of 10.1 years, we found no differences between the observation and the chemotherapy arms in stage, age, performance status, histological cell type, or cancer-specific survival (Figure 1, G, and Table 3). This finding did not change when the optimally staged patients with a grade 3 tumor were analyzed separately. However, when nonoptimally staged patients with a grade 3 tumor were analyzed, cancer-specific survival was better in the adjuvant chemotherapy arm than in the observation arm (HR of death = 0.40, 95% CI = 0.19 to 0.81, $P = .009$) (Table 3).

The long-term results of the ACTION trial strongly substantiate the results of the original analysis (1), with only one exception. After 10.1 years of follow-up, the multivariable analysis found no association between cancer-specific survival and histological cell type. Both staging adequacy and differentiation grade remained highly statistically significant prognostic factors. A well or moderately differentiated tumor, compared with a poorly differentiated tumor, was associated with increased cancer-specific survival (HR of death = 1.78, 95% CI = 1.24 to 2.56).

For the analysis of data with a median follow-up of 10.1 years, we deliberately choose to report cancer-specific survival instead of overall survival because results for overall survival were the same as in the original analysis, except that in the chemotherapy arm, statistically significantly better overall survival was found in the group with optimal surgical staging than in the group with nonoptimal staging. Thus, the mature data support a beneficial effect of optimal surgical staging for patients with early ovarian cancer, even among those receiving adjuvant chemotherapy (HR of death = 1.89, 95% CI = 0.99 to 3.60; overall two-sided log-rank test $P = .05$).

For the entire cohort studied in the ACTION trial after a median follow-up of 10.1 years, cancer-specific survival was not associated with adjuvant chemotherapy. However, adjuvant chemotherapy was associated with statistically significantly improved recurrence-free survival (HR of death = 0.64, 95% CI = 0.46 to 0.89). Among optimally staged patients, recurrence-free survival was similar for both the observation arm (72%) and the adjuvant chemotherapy arm (73%), as was cancer-specific survival (89% and 86%, respectively). Thus, the conclusions of the original report of the ACTION trial appear to be robust and consistent during 10.1 years of follow-up. Among the group with poorly differentiated tumors, it is of interest that survival between optimally and nonoptimally staged patients followed the same pattern. Among all patients with a grade 3 tumor, the recurrence-free survival and cancer-specific survival were lower than those of the entire cohort; this observation is consistent with the dismal prognosis of poorly differentiated tumors (7). However, findings from the analysis with a median follow-up of 10.1 years indicate that administration of adjuvant chemotherapy after optimal surgical staging in this group is not associated with improved survival, perhaps because poorly differentiated early ovarian carcinomas have a tendency to metastasize earlier than those that are well differentiated (8). Optimal surgical staging might detect this early spread so that patients with occult stage III disease can be identified and separated from the group of really early ovarian carcinomas.

Survival analyses (Figure 1, C–F) indicated that the completeness of staging (optimal vs nonoptimal) in the ACTION trial defined two subgroups in which adjuvant chemotherapy has different effects: no benefit in the optimally staged group and a statistically significant benefit in the nonoptimally staged group. The heterogeneity in cancer-specific survival was also observed between the treatment effects and the staging groups, as shown in forest plots (Figure 2) and with a χ^2 test for interaction (cancer-specific deaths among the nonoptimally staged patients = 40 [27%] of the 147 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm; and among optimally staged patients, cancer-specific deaths = seven [9%] of the 75 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm; two-sided χ^2 test for heterogeneity, $P = .06$).

This study has several limitations. The ACTION trial was not specifically designed to compare different surgical staging procedures, and patients could not be prospectively stratified according to the various surgical staging categories. Retrospective stratification, however, showed a well-balanced distribution of the various staging

Figure 1 (continued).

(HR of death = 1.58, 95% CI = 0.61 to 4.08, $P = .34$). **D**) Recurrence-free survival in optimally staged patients (HR of death = 0.73, 95% CI = 0.38 to 1.42, $P = .35$). **E**) Cancer-specific survival in nonoptimally staged patients (HR of death = 0.58, 95% CI = 0.35 to 0.95, $P = .029$, in favor of adjuvant chemotherapy). **F**) Recurrence-free survival in nonoptimally staged patients (HR of death = 0.60, 95% CI = 0.41 to 0.87, $P = .007$, in favor of adjuvant chemotherapy). **G**) Cancer-specific survival in patients with a poorly differentiated (grade 3) early-stage ovarian carcinoma (HR or death = 0.62, 95% CI = 0.34 to 1.12, $P = .108$). The two-sided log-rank test was used to determine P values. All statistical tests were two-sided. N = number of patients; O = number of events observed.

Table 3. Recurrence-free survival (RFS) and cancer-specific survival (CSS) after 10 years of follow-up among the 156 patients with poorly differentiated (grade 3) tumors: the Adjuvant Chemotherapy in Ovarian Neoplasm Trial*

Survival type and group	% survival (95% CI)		HR (95% CI)	*P*†
	Observation arm	Chemotherapy arm		
Optimal staging				
RFS	64 (40 to 80)	49 (27 to 68)	1.25 (0.53 to 2.95)	.61
CSS	85 (60 to 95)	69 (43 to 85)	2.58 (0.66 to 9.99)	.15
Nonoptimal staging				
RFS	52 (38 to 65)	55 (39 to 69)	0.58 (0.33 to 1.02)	.05
CSS	56 (41 to 68)	77 (61 to 87)	0.40 (0.19 to 0.81)	.009

* CI = confidence interval; HR = hazard ratio.

† The statistical test was the two-sided log-rank test.

categories between the two treatment arms (data not shown), and no differences in the distribution of other risk factors, such as tumor grade and histological cell type between optimally and nonoptimally staged patients. Furthermore, the study suffered from a limited sample size. At the time of the study design, no realistic power calculation could be made, so the sample size was arbitrarily set to 1000 or more patients. Because of the slow accrual of patients, this number was not met, despite the fact that this is the largest randomized trial in this disease with an observation arm and comparing the extent of surgical staging. Finally, the ACTION trial did not study quality of life. At the time that the study was planned, quality-of-life analyses were not yet considered an important element of clinical trials.

The design of our study permits no clear-cut guidelines for the treatment of all categories of patients with early ovarian carcinoma. It seems clear, however, that nonoptimally staged patients should be restaged or be given adjuvant chemotherapy if restaging is not feasible. Although some people will argue that a *P* value for heterogeneity of .06 in a subgroup analysis is still insufficient evidence to withhold adjuvant chemotherapy from all patients with early ovarian cancer who received optimal surgical staging, others will take the view that, in the largest randomized trial on this issue after a median follow-up of 10.1 years, the consistent lack of an association between cancer-specific or recurrence-free survival and adjuvant chemotherapy among optimally staged patients is convincing evidence to restrict administration of chemotherapy even for patients with grade 3 tumors (6). The latter point of view is supported by the observation that 20% of long-term survivors of ovarian cancer will develop a secondary primary tumor as a result of their treatment with platinum-based chemotherapy (9). In addition, a randomized study design that included deliberately assigning half of the patients to improper surgery would be unethical because of the proven beneficial prognostic effect of adequate surgery.

In conclusion, the long-term analysis of the ACTION trial data 1) substantiated the original findings of the ACTION trial that the completeness of surgical staging in early ovarian cancer is an independent prognostic factor for recurrence-free and overall survival, even when adjuvant chemotherapy is given after surgery and 2) substantiated the original conclusion of the ACTION trial that " . . . the benefit of adjuvant chemotherapy appears to be limited to patients with non-optimal staging, i.e., patients with more risk of unappreciated residual disease" (1).

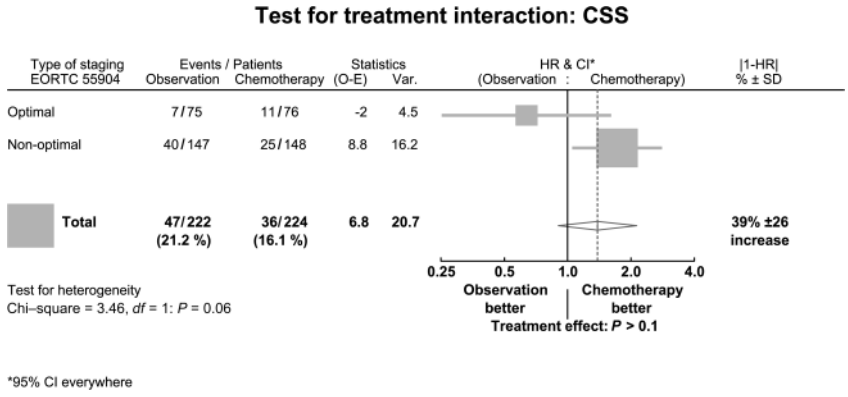

Figure 2. Forest plots of the interaction between the two staging categories (optimal and nonoptimal) vs treatment effect (adjuvant chemotherapy better vs observation better) for cancer-specific survival. **Solid squares** = hazard ratios (HRs) for cancer-specific survival (with the area of the square being proportional to the variance of the estimated effect); **length of the horizontal line through the square** = 95% confidence interval (CI); **open diamond** = HR (middle of the diamond); **horizontal points of the diamond** = 95% CI for the combined data. CSS = cancer-specific survival; EORTC = European Organization of Research and Treatment of Cancer; O − E = number of events observed minus number of events expected under the null hypothesis; SD = standard deviation; Var. = variance of 1 divided by the logarithm of the HR. Linear trends and heterogeneity of the HRs to detect differences in relative size of treatment effect were assessed by a χ^2 test for interaction. All statistical tests were two-sided.

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Notes

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