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ORIGINAL REPORT

Relationship Between Time Interval From Primary Surgery to the Start of Taxane- Plus Platinum-Based Chemotherapy and Clinical Outcome of Patients With Advanced Epithelial Ovarian Cancer: Results of a Multicenter Retrospective Italian Study

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A B S T R A C T

Purpose
To assess whether the interval from primary surgery to the start of taxane- plus platinum-based chemotherapy has any impact on the clinical outcome of advanced ovarian cancer patients.

Patients and Methods
The study was conducted on 313 patients who underwent surgery followed by taxane- plus platinum-based chemotherapy. The median follow-up of survivors was 30.7 months (range, 6 to 109 months).

Results
The 25%, 50%, and 75% quantiles of intervals from surgery to the start of chemotherapy were 11, 21, and 31 days, respectively. After the sixth cycle, 102 patients achieved a pathologic complete response at second-look surgery and 98 obtained a clinical complete response but were not submitted to second-look surgery. Taking into consideration the best assessed response, a complete (either clinical or pathologic) response was found in 200 patients. Residual disease (≤ 1 $v > 1$ cm; $P < .0001$) and ascites (absent v present; $P = .003$) were independent predictive factors for achieving a complete response, whereas residual disease ($P = .001$) and stage (IIc to III v IV; $P = .04$) were independent prognostic variables for survival. Conversely, statistical analyses failed to detect significant differences in complete response rates and survival among patients with an interval from surgery to chemotherapy shorter than 11 days, 12 to 21 days, 22 to 31 days, and longer than 31 days.

Conclusion
The interval from surgery to the start of taxane- plus platinum-based chemotherapy seems to have neither a predictive value for response to treatment nor a prognostic relevance for survival of advanced ovarian cancer patients.

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INTRODUCTION

Advanced epithelial ovarian cancer is the most lethal gynecologic cancer. According to the International Federation of Gynecology and Obstetrics (FIGO) Annual Report No. 24, the 5-year survival was 58.5% for stage IIIa, 39.9% for stage IIIb, 28.7% for stage IIIc, and 16.8% for stage IV disease.[1] Residual disease after initial surgery,[2-6] tumor grade,[3-5] and histologic types[2,3,5,7] are the most commonly assessed clinicopathologic variables influencing the response rate to chemotherapy and survival rate. Recently, many efforts have been made to identify biologic parameters, such as DNA

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ploidy,[3,8,9] oncogenes and tumor suppressor genes,[8-15] growth factors and growth factor receptors,[9,16,17] and degree of tumor angiogenesis,[18-21] that have a predictive or prognostic value for advanced epithelial ovarian cancer.

Some experimental investigations on different animal models showed that the removal of the primary tumor accelerated metastatic tumor growth assessed as both gross tumor size and metastatic cell kinetics.[22-26] The increase in tumor growth is probably due to a conversion of noncycling cells in G_0 phase into proliferation.[26] However, limited and conflicting data are currently available about the relationship between the time interval from surgery to the start of chemotherapy and treatment effectiveness in animal tumor models,[27-29] and in human malignancies including epithelial ovarian cancer.[30-35]

The aim of this retrospective investigation was to assess whether the length of the interval from primary surgery to taxane- plus platinum-based chemotherapy has any impact on response to treatment and survival of patients with advanced epithelial ovarian cancer.

PATIENTS AND METHODS

This retrospective study was conducted on 313 patients who underwent primary surgery followed by taxane- plus platinum-based chemotherapy for advanced epithelial ovarian cancer at the Departments of Gynecology and Obstetrics of University of Brescia, Pisa, and Turin, and at the Department of Gynecologic Oncology of the European Institute of Oncology of Milan (Italy) between January 1994 and January 2003.

The tumor stage and histologic diagnosis of each patient were determined according to FIGO criteria and the histologic typing system of the WHO, respectively. Tumors were graded as well (G_1), moderately (G_2), or poorly (G_3) differentiated.

The planned combination chemotherapy consisted of six cycles of paclitaxel plus carboplatin in 258 patients, epirubicin plus paclitaxel plus carboplatin in 18 patients, docetaxel plus carboplatin in 15 patients, ifosfamide plus paclitaxel plus cisplatin in 10 patients, paclitaxel plus cisplatin in seven patients, and epirubicin plus paclitaxel plus cisplatin in five patients.

The evaluation of the clinical course of disease was based on clinical examination, serum CA-125 assay, chest x-ray, abdominal-pelvic ultrasound, and computed tomography scan. Additional investigations were performed when appropriate. After the sixth cycle of chemotherapy, patients with no evidence of disease at clinical, serologic, sonographic, and radiologic examinations were defined as being in clinical complete response. Three to 5 weeks after the end of chemotherapy, a second-look surgery was usually proposed to clinically complete responders, mostly to patients enrolled onto clinical trials. A pathologic complete response at second-look surgery was defined as the disappearance of all macroscopic tumor deposits with negative peritoneal washing and negative multiple random biopsies. All patients with clinically or surgically detectable persistent disease, as well as some pathologically complete responders, received additional chemotherapy.

All patients were observed until they died or until July 2003. The median follow-up of survivors was 30.7 months (range, 6 to 109 months).

The SAS statistical package (release 8.2; SAS Institute, Cary, NC) was used for computations.

Time intervals from primary surgery to the start of chemotherapy were related to tumor stage, residual disease, and presence or absence of ascites using the median test.

Rates of complete response were compared to explicative variables using Pearson's χ^2 test (or two-tailed Fisher's exact test when appropriate). Multiple logistic regression was carried out to investigate the relationship among the probability of achieving a complete response and the explanatory variables.

The cumulative probability of overall survival from the time of initial surgery was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables. The relationship between time interval from primary surgery to the start of chemotherapy and overall survival was also estimated using the nonparametric Spearman rank correlation coefficient (computed on unrecorded values). A multiple regression analysis based on the Cox proportional hazards model was used to test jointly the relative importance of variables as predictors of survival times.

RESULTS

The median age of patients was 56 years (range, 23 to 77 years). According to the FIGO classification, tumor stage was IIc in 24 patients, III in 249 patients, and IV in 40 patients. Histologically, 205 carcinomas were serous, 35 were endometrioid, 29 were undifferentiated, 26 were mixed, 13 were clear-cell, four were mucinous, and one was a malignant Brenner tumor. Tumor grade was G_1 in eight patients, G_2 in 82 patients, and G_3 in 223 patients. After initial surgery, 138 patients had residual disease ≤ 1 cm and 175 patients had a larger residual tumor. Ascites was detected in 217 patients. Time intervals from primary surgery to the start of chemotherapy ranged from 3 to 62 days. The 25%, 50%, and 75% quantiles of intervals from primary surgery to the start of chemotherapy were 11, 21, and 31 days, respectively.

Time intervals from primary surgery to the start of chemotherapy were not related to residual disease (≤ 1 v > 1 cm; median, 20 v 22 days; range, 5 to 62 v 3 to 60 days; P = not significant [ns]) or absence or presence of ascites (median, 22.5 v 20 days; range, 6 to 60 v 3 to 62 days; P = ns). Conversely, time interval was shorter for patients with stage IV disease compared with those with stage IIc to IV disease (median, 14 v 21 days; range, 6 to 47 v 3 to 62 days; P = .0419).

Sixteen patients experienced disease progression early during first-line chemotherapy. After the sixth cycle of chemotherapy, 102 patients achieved a pathologic complete response at second-look surgery, 98 patients obtained a clinical complete response but were not submitted to second-look surgery, and 113 patients had clinically or surgically detectable persistent disease. Therefore, taking

into consideration the best assessed response, a complete (either clinical or pathologic) response was observed in 200 patients.

Residual disease (≤ 1 $v > 1$ cm) and ascites (absent v present) were the only variables related to the chance of achieving a complete response to chemotherapy at both univariate ($P < .0001$ and $P = .0002$, respectively; Table 1) and multivariate analysis ($P < .0001$ and $P = .003$, respectively; Table 2), whereas the interval from primary surgery to chemotherapy had no predictive value.

By log-rank test, overall survival was related to residual disease (≤ 1 cm $v > 1$ cm; $P = .0003$; Fig 1), ascites (absent v present; $P = .0161$; Fig 2), and tumor stage (IIc to III v IV; $P = .0055$; Fig 3), but not to interval from primary surgery to chemotherapy (Fig 4), age (data not shown), histologic type (data not shown), and histologic grade (data not shown).

The nonparametric correlation between time interval from primary surgery to the start of chemotherapy and overall survival did not show any statistical significance (Spearman rank correlation coefficient $r_S = 0.02$; $P = $ ns; Fig 5).

The Cox proportional hazards model showed that residual disease ($P = .001$) and tumor stage ($P = .04$) were the only independent prognostic variables for overall survival (Table 3).

DISCUSSION

Cytoreductive surgery followed by paclitaxel- plus platinum-based chemotherapy represents the standard treatment for patients with advanced epithelial ovarian cancer. Current regimens are able to obtain a clinical complete response rate of approximately 50%, a pathologic complete response rate of 25% to 30%, a median progression-free survival of 15.5 to 22 months, and a median overall survival of 31 to 44 months.[36-44] Randomized studies comparing paclitaxel plus cisplatin versus paclitaxel plus carboplatin showed that the two regimens are equally effective; the carboplatin combination is well tolerated.[37,41,42,44] A recent randomized study revealed no difference in response rates, progression-free survivals, and early survival data between docetaxel plus carboplatin versus paclitaxel plus carboplatin, whereas a significant difference in toxicity profiles emerged between the two regimens, with less neurotoxicity and more myelosuppression for docetaxel plus carboplatin.[45,46] Several ongoing phase III

Table 1. Variables Predictive of Complete Response to Taxane- Plus Platinum-Based Chemotherapy (univariate analysis)				
Variable	Complete Responders*	No. of Patients	%	P
Age, years				
≤ 56	100	158	63.2	NS
> 56	100	155	64.5	
Stage				
II-III	179	273	65.6	NS
IV	21	40	52.5	
Grade				
G_1-G_2	59	90	65.6	NS
G_3	141	223	63.2	
Histologic type				
Serous	133	205	64.8	NS
Nonserous	67	108	62.0	
Residual disease				
≤ 1 cm	109	138	78.9	$< .0001$
> 1 cm	91	175	52.0	
Ascites				
No	76	96	79.1	.0002
Yes	124	217	57.1	
Interval time from primary surgery to the start of chemotherapy, days				
≤ 11	51	86	59.3	
12–21	49	77	63.6	
22–31	48	75	64.0	NS
> 31	52	75	69.3	

Abbreviation: NS, not significant.
*The 200 complete responders included the 102 pathologically complete responders and the 98 clinically complete responders who did not undergo surgical reassessment.

Table 2. Variables Predictive of Complete Response to Taxane- Plus Platinum-Based Chemotherapy (multiple logistic regression)

Variable	Parameter Estimate	SE	Wald χ^2	P	OR	95% CI
Intercept	−1.8987	0.2994	40.2272	< .0001		
Residual disease	1.1342	0.2627	18.6367	< .0001	3.109	1.858 to 5.202
Ascites	0.8771	0.2957	8.7954	.0030	2.404	1.346 to 4.292

Abbreviation: OR, odds ratio.

studies are assessing whether the addition of other drugs to paclitaxel and carboplatin provides a clinical benefit.[43]

Residual disease after initial surgery is the most important prognostic factor for advanced epithelial ovarian cancer.[2-6] For instance, according to the FIGO Annual Report No. 24, the 5-year survival rates in stage IIIc disease were 55%, 42.3%, and 15.2%, respectively, for patients with no macroscopic residuum, macroscopic residuum less than 2 cm, and residuum more than 2 cm.[1] Several other clinicopathologic and biologic variables have been related to the clinical outcome of patients with this malignancy,[2-21] whereas the predictive and prognostic relevance of the interval time from primary surgery to the start of chemotherapy has not yet been clarified.[33,35] There are little data regarding the effectiveness of chemotherapy in relation to timing of such therapy from surgery in animal tumor models[27-29] as well as in human malignancies including epithelial ovarian cancer.[30-35] By assessing how a variation in the time interval between primary tumor removal and cyclophosphamide administration affected residual tumor cell kinetics and animal survival in a murine mammary adenocarcinoma, Fisher et al[27] detected that the shorter the time after operation that therapy is begun, the more com-plete is the abrogation of the kinetic changes in distant tumor foci, the more effective becomes the suppression of residual tumor burden, and the more prolonged is the survival. When cyclophosphamide was given before the operation, it completely prevented the increase in labeling index resulting from tumor removal, and prolonged mice survival to the greatest extent. In a murine osteosarcoma model, the perioperative administration of cytotoxic drugs demonstrated a significant advantage in preventing systemic relapses when compared with postoperative chemotherapy.[28] Conversely, in the study of Berg et al[29] there was no significant difference in survival between dogs with osteosarcoma that began cisplatin and doxorubicin chemotherapy 2 days after amputation and those that started chemotherapy 10 days after surgery.

In a series including 460 stage I and II breast cancer patients who received adjuvant chemotherapy consisting of fluorouracil, doxorubicin, and cyclophosphamide, there was no difference in 4-year disease-free survival for patient subgroups with interval times from surgery to chemotherapy of less than 10 weeks, 10 to 13, 14 to 17, or ≥ 18 weeks (64%, 68%, 60%, and 63%, respectively).[30] Conversely, in the study of Pronzato et al,[32] which enrolled
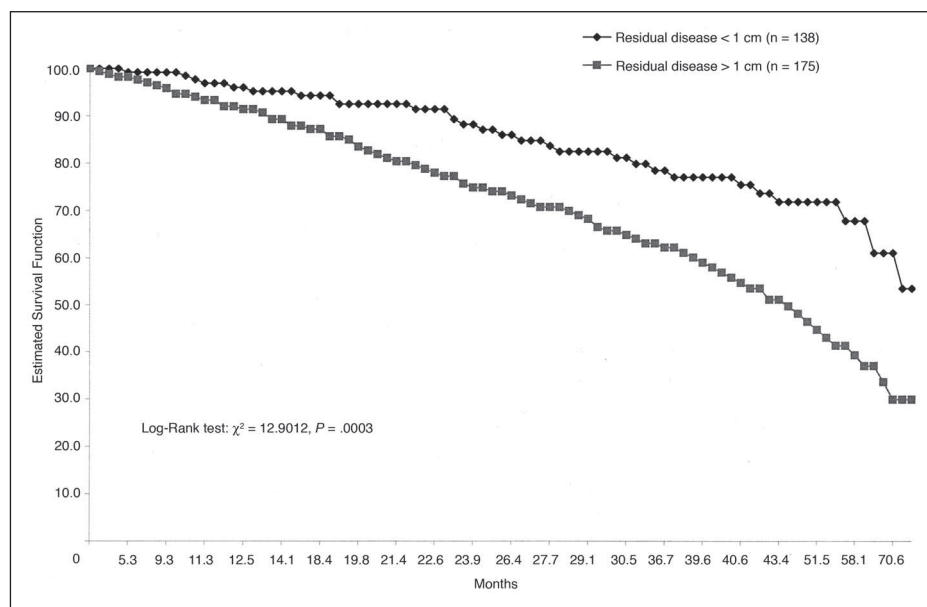

Fig 1. Overall survival in patients with advanced epithelial ovarian cancer by residual disease after primary surgery.
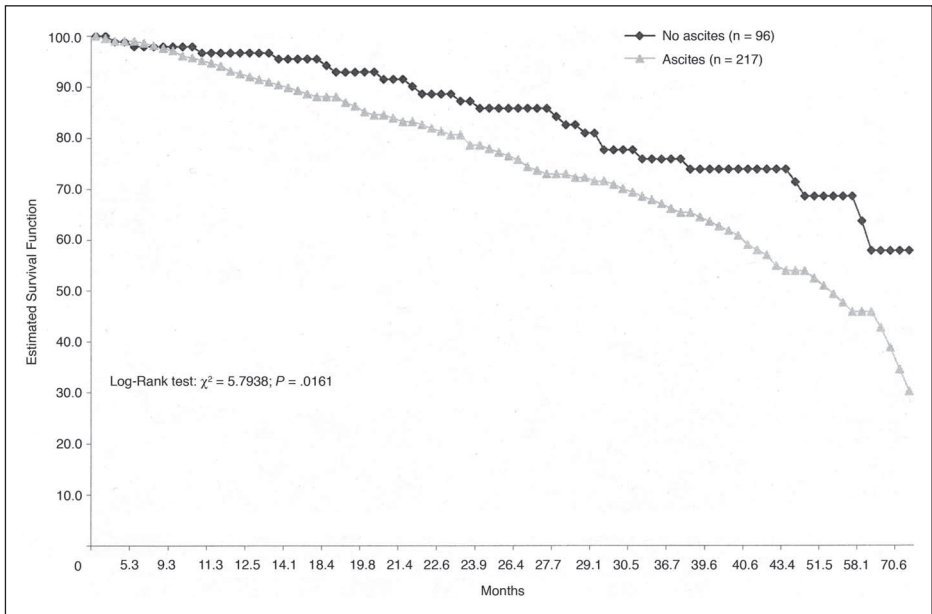
Fig 2. Overall survival in patients with advanced epithelial ovarian cancer by ascites.

229 patients with node-positive primary operable breast cancer who underwent adjuvant chemotherapy consisting of fluorouracil, methotrexate, and cyclophosphamide, survival was significantly improved in patients who began chemotherapy within 35 days from surgery compared with those who started adjuvant treatment later ($P = .01$). Colleoni et al[34] investigated the relationship between early initiation of chemotherapy, estrogen receptor (ER) status, and prognosis in 1,788 premenopausal, node-positive patients treated on different International Breast Cancer Study Group trials. Among patients with ER-negative tumors, 10-year disease-free survival was 60% for patients who

started chemotherapy within 20 days compared with 34% for those who started chemotherapy later ($P = .0003$). Conversely, timing of chemotherapy initiation had no prognostic relevance for patients with ER-positive tumors.

For epithelial ovarian cancer, in the cohort study of Warwick et al[33] including 362 patients with advanced disease treated with surgery followed by platinum-based chemotherapy, those patients with a longer interval appeared to have a worse outcome, but the interval was not an independent prognostic factor at multivariate analysis. The Scottish Gynaecological Cancer Trials Group investigated whether the length of the interval from primary surgery to
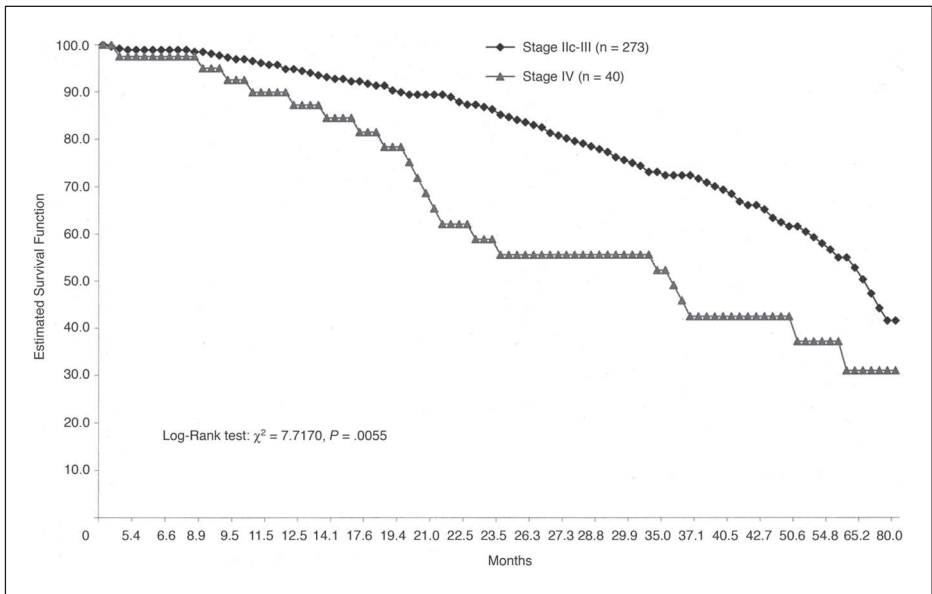

Fig 3. Overall survival in patients with advanced epithelial ovarian cancer by International Federation of Gynecology and Obstetrics stage.
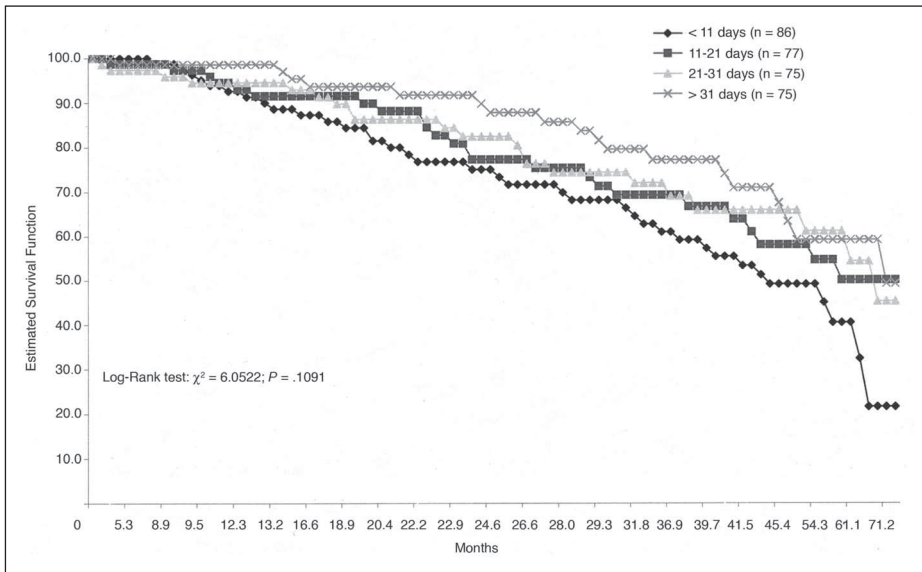
Fig 4. Overall survival in patients with advanced epithelial ovarian cancer by interval time from primary surgery to the start of taxane- plus platinum-based chemotherapy.

chemotherapy has any effect on the progression-free survival of 472 patients enrolled onto four studies who had all received platinum-containing chemotherapy in combination with either a taxane (paclitaxel or docetaxel) or with cyclophosphamide.[35] The median interval from surgery to chemotherapy was 22 days (range, 5 to 113 days). Univariate analysis showed a trend for worse progression-free survival for patients with earlier therapy, but women treated earlier tended to have bulkier residual disease. Therefore, multivariate analysis revealed that the interval from surgery to chemotherapy is not an independent prognostic factor for progression-free survival.

The predictive or prognostic relevance of a variable should be assessed in a group of patients who receive homogenous treatments. In our study, we investigated the clinical relevance of time interval from primary surgery to chemotherapy in a series of 313 patients with advanced epithelial ovarian cancer who had all undergone taxane- plus platinum-based chemotherapy. The 25%, 50%, and 75% quantiles of intervals were 11, 21, and 31 days, respectively. Residual disease after initial surgery and the absence or presence of ascites were independent predictive factors for the chance of achieving a complete response, whereas residual disease and tumor stage were
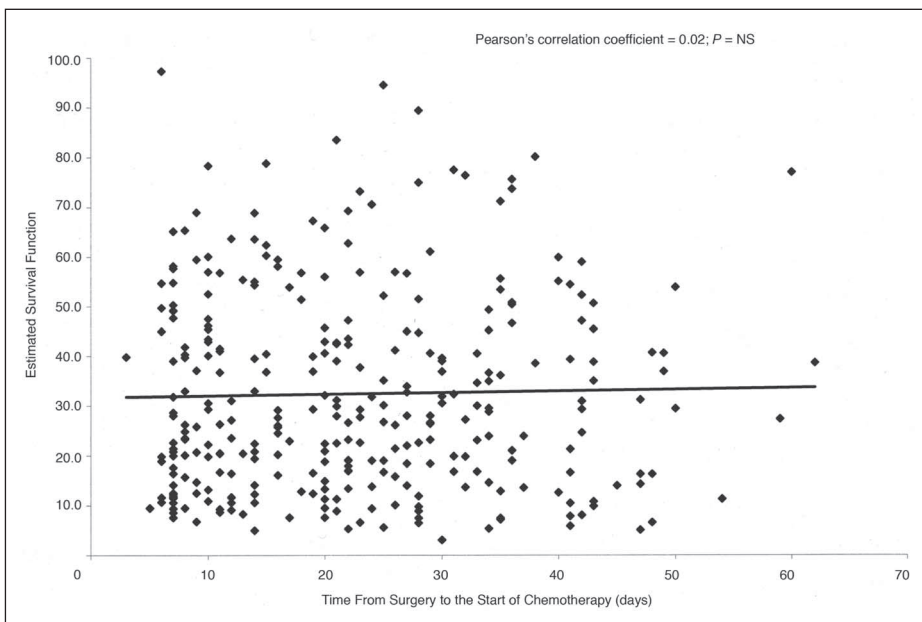

Fig 5. Relationship between interval time from primary surgery to the start of taxane- plus platinum-based chemotherapy and overall survival (nonparametric correlation analysis).

	Parameter Estimate	SE	Wald χ^2	P	HR	95% CI
Table 3. Variables Predictive of Overall Survival (Cox model)						
Variable						
Stage	0.51585	0.25327	4.1486	.0417	1.675	1.020 to 2.752
Residual disease	0.75048	0.23067	10.5849	.0011	2.118	1.348 to 3.329
Abbreviation: HR, hazard ratio.						

independent prognostic variables for overall survival. Conversely, statistical analyses failed to detect significant differences in complete response rates and survival among patients with time interval from surgery to chemotherapy shorter than 11, 12 to 21, 22 to 31, and longer than 31 days.

From a theoretical viewpoint, residual lesions after cytoreductive surgery have a high growth fraction, and therefore the earlier the start of chemotherapy, the greater is the chance that chemotherapy controls residual disease. The currently available chemotherapy regimens obtain satisfactory response rates in patients with advanced epithelial ovarian cancer, but most responders will subsequently experience tumor recurrence and up to more than 80% of patients will need a second-line treatment for chemotherapy-resistant disease.[47,48] Drug resistance is the major obstacle in developing systemic therapies for advanced cancer and might be involved particularly in the secondary treatment failure frequently seen in epithelial ovarian cancer.[49-51] On the basis of somatic mutation theory, it can be hypothesized that resistant mutants arise spontaneously early in the natural history of cancers and that the likelihood of developing genetically resistant clones is closely related to cell number.[52] The onset of permanent resistance accounts for the inverse relationship between cell number and curability by drugs. At the time of clinical detection, advanced epithelial ovarian cancer consists of 10^{12} to 10^{13} tumor cells and therefore often contains a high rate of genetically chemotherapy-resistant clones. This can explain why an early administration of chemotherapy after

surgery seems to give no clinical benefit when compared with a more delayed treatment.

In the clinical practice, the start of chemotherapy can be delayed because of different situations, such as when patients are referred from other institutions some weeks after surgery; when patients are submitted to aggressive cytoreductive surgery with consequent recovery delay; when patients present low hemoglobin levels and need more time to recover after surgery; when patients need to be discharged home earlier after surgery to get adjusted to their cancer diagnosis before starting chemotherapy that can be administered in a outpatient facility; and in difficult cases for the pathologist, for which the morphological interpretation is not unequivocal and more time is required for additional investigations (ie, immunohistochemistry and molecular analysis) to define with certainty the histologic type of the tumor. Only a prospective, specifically planned study can definitely clarify the clinical relevance of interval time between surgery and chemotherapy. However, the currently available data failed to detect that a few weeks of delay in starting chemotherapy influences the clinical outcome of patients with advanced epithelial ovarian cancer.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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