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Long-term Prognosis Following Macroscopic Complete Response at Second-look Laparotomy in Advanced Ovarian Cancer Patients Treated with Platinum-based Chemotherapy

S. Chiara, R. Lionetto, E. Campora, C. Oliva, L. Merlini, P. Bruzzi, R. Rosso and P.F. Conte for the Gruppo Oncologico Nord Ovest

Survival (S) and progression-free survival (PFS) were evaluated in 129 advanced ovarian cancer patients, who achieved a macroscopic complete response (112 pathological complete response and 17 microscopic disease) at second-look after platinum-based combination chemotherapy with or without doxorubicin (DX). The impact on S and PFS of age, performance status (PS), stage, histology, grade (G), residual disease after first surgery (RD), chemotherapy regimen, disease status at second-look and consolidation therapy were evaluated by univariate and multivariate analysis. In the 118 months observation period, median S and PFS were 81 and 34 months, respectively. Stage, G, RD, PS and disease status at second-look had significant impact on both S and PFS in univariate analysis, whereas consolidation therapy did not influence outcome. Cox's regression analysis showed that G, RD and PS had an independent impact on PFS. Test for interaction demonstrated no statistically significant relationship between RD, chemotherapy regimen and outcome. In conclusion, advanced ovarian cancer patients with macroscopically complete remission at second-look have a substantial risk of relapse after aggressive treatment. The risk of recurrence was estimated to be maximal in the first 3 years after restaging, and was correlated with poor PS, RD >2 cm after first surgery and undifferentiated tumour.

Key words: prognostic factors, ovarian cancer, second-look, complete response, cisplatin-based chemotherapy
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INTRODUCTION

DATA FROM the literature of long-term survival in advanced ovarian carcinoma are scanty, and therefore identification of patient categories that might be curable with chemotherapy is still difficult. In earlier reports, the main prognostic factors predicting improved survival in advanced stages included good performance status, residual mass of less than 2 cm prior to therapy, and well-differentiated histology [1–3]. Recently, combination chemotherapy including cisplatin was demonstrated to enhance survival by approximately 10% compared with alkylating agents, and multivariate analyses confirmed that the use of cisplatin and the residual tumour were the only factors of prognostic relevance for survival [4, 5].

The achievement of a complete response is an important step for definitive cure in cancer treatment. In ovarian cancer, the only method to accurately assess response is a second-look laparotomy. Although many authors have suggested that findings at second-look correlate with clinical outcome, the long-term prognostic significance of a pathologically negative second-look has been unclear, since approximately one-third of patients without evidence of disease at restaging develop recurrence within 2 years. Furthermore, several authors have reported similar survival between pathologically complete response patients and those with microscopic remnants. An explanation for the extended survival of patients with microscopically positive second-look laparotomies is still lacking [6–10].

In an attempt to define the predictive factors associated with survival duration after second-look, we undertook a retrospective review in a large group of patients with advanced ovarian cancer who achieved a macroscopic complete response at second-look surgery (complete response and microscopic disease) after platinum-based first line chemotherapy and for whom long-term follow-up was available.

PATIENTS AND METHODS

From June 1981 to December 1990, 477 patients with histologically documented advanced ovarian carcinoma were entered into consecutive clinical trials carried out by the Gruppo Oncologico Nord Ovest (GONO) [11–14]. Stage of disease and grade of tumour differentiation were established according to FIGO classification. After initial laparotomy, patients received cyto-

Correspondence to S. Chiara.
S. Chiara, R. Lionetto, E. Campora, C. Oliva, L. Merlini, P. Bruzzi and R. Rosso are at the Medical Oncology Department and Clinical Epidemiology and Trials Department, National Institute for Cancer Research, Vle Benedetto XV, 10, 16132 Genova, Italy; P.F. Conte is at the S. Chiara Hospital, Pisa, Italy.
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toxic therapy comprising cisplatin 50–100 mg/m^2 or carboplatin 200 mg/m^2 and cyclophosphamide 600 mg/m^2, with or without doxorubicin 45 mg/m^2 day 1 every 4 weeks for 6 courses. Clinical and long-term follow-up data of these patients had been collected prospectively in a computerised data base.

252 patients with non clinical, radiographic or serologic evidence of residual disease after completion of the planned 6 months of the aforementioned combined chemotherapy underwent second-look laparotomy. The surgical technique used for second-look surgery has been previously detailed [12]. Macroscopic complete remission was demonstrated in 129 patients of which 112 had a documented pathological complete response and 17 had microscopic residual disease. Patients with macroscopic residual disease in whom disease was completely resected during second-look surgery were not included in the present analyses. Patients' characteristics are summarised in Table 1.

59 of 112 patients with a pathological complete response at second-look, and all 17 patients with microscopic residual disease (MD) received additional treatment. Therapy consisted of either whole abdominopelvic irradiation (13 patients) or 3 further courses of the same chemotherapy employed to induce the response (63 patients). Radiotherapies were administered according to moving strip or open field techniques, as described elsewhere [15, 16].

Survival and progression-free survival (PFS) measured as the time from second-look until death from any cause, and until disease relapse, respectively, were analysed. Curves computed with the Kaplan–Meier method were compared for statistical significance by use of the log rank test. Cox proportional hazard model for censored survival data [17] was used to assess the prognostic role of the following parameters: patient age, performance status, stage of disease at diagnosis, histology, tumour grade, residual disease at initial laparotomy, anthracycline-containing first line chemotherapy and further treatment after second-look. For exploratory purposes, a 10% significance level

Table 1. Patients' characteristics and survival from second-look (univariate analysis)

Variable	Number of patients	Observed/expected	Median survival (mos)	χ^2	df	*P*
Age						
≤55 years	70	1	58	0.000	1	0.99
>55 years	59	1	86			
ECOG PS						
0	107	0.90	86	4.69	1	0.03
1–2	22	1.94	42			
Stage						
II	23	1.17	58	13.85	2	0.001
III	93	0.78	*			
IV	13	2.96	26			
Histology						
serous	78	1.07	71	4.88	2	0.08
muc+endom	32	0.63	104			
undiff+others	19	1.63	38			
Grading						
G1	17	0.21	*	8.74	2	0.01
G2	44	1.07	56			
G3	50	1.36	42			
undetermined	18					
RD at initial surgery						
≤2	80	0.81	86	4.53	1	0.03
>2	49	1.47	42			
CT						
without DX	36	1.10	58	0.28	1	0.59
with DX	93	0.94	86			
Disease status at second-look						
pCR	112	0.88	86	6.82	1	0.009
MD	17	2.14	27			
Further therapy						
no	53	1.08	56	0.31	1	0.58
yes	76	0.92	109			

* Median S not reached; PS, performance status; RD, residual disease; muc; mucinous; endom, endometroid; undiff, undifferentiated; CT, chemotherapy; DX, doxorubicin; pCR, pathological complete response; MD, microscopic residual disease; mos, months; χ^2, chi-square test; df, degrees of freedom.

Table 2. Progression-free survival from second-look. Univariate analysis

Variable	Number of patients	Observed/expected	Median survival (mos)	χ^2	df	*P*
Age						
≤55 years	70	1.06	32	0.24	1	0.62
>55 years	59	0.93	61			
ECOG PS						
0	107	0.84	61	11.83	1	0.0006
1–2	22	2.17	15			
Stage						
II	23	0.82	34	17.37	2	0.0002
III	93	1.06	61			
IV	13	2.95	13			
Histology						
serous	73	1.17	27	7.81	2	0.02
muc+endom	32	0.50	*			
undiff+others	19	1.48	25			
Grading						
G1	17	0.18	*	10.02	2	0.0067
G2	44	1.11	32			
G3	50	1.32	23			
undetermined	18					
RD at initial surgery						
≤2	80	0.79	63	6.46	1	0.011
>2	49	1.47	22			
CT						
without DX	36	1.13	34	0.45	1	0.5
with DX	93	0.94	32			
Disease status at second-look						
pCR	112	0.91	49	4.09	1	0.04
MD	17	1.72	19			
Further therapy						
no	53	1.10	32	0.477	1	0.49
yes	76	0.92	34			

* Median PFS not reached; PS, performance status; RD, residual disease; muc, mucinous; endom, endometroid; undiff, undifferentiated; CT, chemotherapy; DX, doxorubicin; pCR, pathological complete response; MD, microscopic residual disease; mos, months; χ^2, chi-square test; df, degrees of freedom.

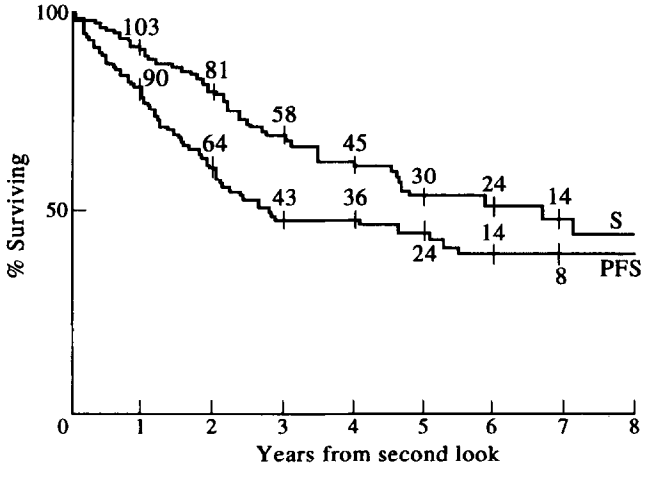

Figure 1. Survival (S) and progression-free survival (PFS) (129 patients).

was used for retaining variables in the model. The hazard function for survival and progression-free survival, to characterise the risk of death and of relapse throughout the whole period of follow-up, was computed by means of the product-limit estimate [18].

RESULTS

During the 118 month observation period, overall 5 and 8-year survival rates of the whole patient populations of GONO trials were 29 and 23%, respectively, and 5 and 10-year PFS rates were 22 and 17%, respectively. Of the 129 patients with macroscopic complete response at second-look, 49 patients (38%) died and disease progression occurred in 63 (49%) cases. Survival and progression-free survival for all 129 patients are shown in Figure 1: 5 and 8-year survival rate were 54 and 44.5% and 5 and 8-year progression-free survival rates were 45 and 39%, respectively. Median survival and median progression-free

survival for this same group of patients were 81 and 34 months, respectively.

Univariate analysis showed that ECOG performance status, FIGO stage, tumour grade, residual disease at initial surgery and disease status at second-look had a significant impact on both survival (Table 1) and disease-free survival (Table 2), whereas histology had a significant impact on disease-free survival but not on survival. Complete clinical data were available for 110 of the 129 macroscopically disease-free patients, and for 95 of the 112 pathological complete response patients, since the tumour grade and the amount of residual disease after initial surgery were unknown in 18 and in 1 patient, respectively. Data from these 110 patients were considered for Cox regression analysis and results are reported in Table 3. Tumour grade and residual disease after initial laparotomy had a significant and independent impact on both survival and progression-free survival. Although the difference was not significant ($P = 0.11$ and $P = 0.07$, respectively), survival and progression-free survival of patients receiving a doxorubicin-containing chemotherapy regimen was improved compared with patients treated with cisplatin and cyclophosphamide. The possible interaction between the amount of residual disease after initial surgery and chemotherapy was estimated on survival and progression-free survival by Cox regression analysis (Table 4). In the patients submitted to doxorubicin-containing chemotherapy, no statistically significant relationship was evident by the test for interaction, even if the relative risk for survival and progression-free survival was reduced in both groups, with the greatest benefit observed for patients with residual disease > 2 cm.

Results of Cox regression analysis in the group of 95 pathological complete response patients are reported in Table 5. Tumour grade and residual disease after initial surgery were significant and independent parameters for relapse-free survival, whereas survival was influenced only by tumour grade.

The hazard function for survival and progression-free survival was calculated and is shown in Figures 2 and 3, respectively. The chi-square test for trend was statistically significant for progression-free survival ($P = 0.0027$), but not for survival ($P = 0.88$). Therefore, the risk of relapse was maximal in the first 3 years of follow-up and then progressively decreased whereas no trend was apparent for the risk of dying.

DISCUSSION

The achievement of a pathological complete response to chemotherapy at second-look laparotomy in advanced ovarian cancer patients appears to correlate with improved survival. However, from data in the literature, the long-term prognostic significance of a negative second-look is still unclear since a high percentage of patients with no visible tumour at laparotomy develop recurrence within a few years, and patients with microscopic disease have the same survival experience of complete response patients [6–10].

It therefore seems reasonable to attempt identification of patients macroscopically free of disease at second-look surgery whose prognostic variables are related to better long-term outcome. Prior studies have generally included patients treated both with platinum-based and with non-platinum chemotherapy regimens, and follow-up has often been relatively short [6, 19–21].

In the present study, we have reported 5 and 8-year survival rates of 54 and 44.5%, respectively, and 5 and 8-year progression free survival rates of 45 and 39%, respectively, in a large group of macroscopic complete response patients treated with platinum-based chemotherapy, with or without doxorubicin. Similar results were observed by Neijt and Podraz in the few long-term analyses of advanced ovarian cancer patients [4, 20].

The prognostic significance of findings at second-look was confirmed in this review, with better survival and progression-free survival of the macroscopic complete response patients compared to the whole patient population entered into GONO

Table 3. Relative risk, 95% confidence interval and P values estimated by Cox's multiple regression analysis for survival and progression-free survival (110 patients)

Variable	Survival			Progression-free survival		
	Relative risk	95% CI	*P*	Relative risk	95% CI	*P*
Grading						
G1	1			1		
G2	5.2	1.2–23.3		5.5	1.3–23.3	
G3	6.9	1.5–30.9	0.0075	6.4	1.5–27.1	0.011
RD at initial surgery						
≤2 cm	1			1		0.012
>2 cm	2.0	1.1–3.9	0.03	2.1	1.2–3.7	
Chemotherapy						
without DX	1			1		
with DX	0.59	0.31–1.12	0.11	0.56	0.30–1.05	0.07
PS						
0				1		
1–2	sixth excluded		0.19	2.2	1.1–4.3	0.03
Age	first excluded		0.91	second excluded		
Disease status at second-look	second excluded		0.47	first excluded		
Further therapy	third excluded		0.38	third excluded		
Stage	fourth excluded		0.33	fourth excluded		
Histology	fifth excluded		0.21	fifth excluded		

RD, residual disease; DX, doxorubicin; PS, performance status.

Table 4. Relative risk estimated by Cox's multiple regression analysis of the interaction between chemotherapy and residual disease for survival and progression-free survival

		Survival Chemotherapy		Progression-free survival Chemotherapy	
		without DX	with DX	without DX	with DX
Residual disease	≤2 cm	1	0.7	1	0.6
	>2 cm	2.9	1.2	2.4	1.2
LLR test for interaction:					
effect of treatment			$P = 0.11$		$P = 0.07$
effect of RD			$P = 0.03$		$P = 0.01$
interaction between treatment and RD			$P = 0.43$		$P = 0.79$

LLR, log likelihood ratio; DX, doxorubicin.

Table 5. Relative risk, 95% confidence interval and P values estimated by Cox's multiple regression analysis for survival and progression-free survival (95 pCR patients)

Variable	Survival Relative risk	95% CI	*P*	Progression-free survival Relative risk	95% CI	*P*
Grading						
G1	1			1		
G2	4.8	1.1–21.8		4.9	1.1–21.0	
G3	5.8	1.2–27.2	0.02	5.0	1.1–21.9	0.048
Histology						
serous	1			1		
muc+endom	1.1	0.5–2.6		1.4	0.7–3.1	
undiff+others	2.8	1.0–7.5	0.07	2.7	0.7–7.3	0.10
Age	first excluded		0.84	first excluded		0.99
Stage	second excluded		0.62	third excluded		0.55
Chemotherapy	third excluded		0.49	second excluded		0.47
RD at initial surgery						
≤2 cm	fourth excluded		0.37	1		
>2 cm				2.0	1.1–3.7	0.02
PS	fifth excluded		0.16	fifth excluded		0.21
Further therapy	sixth excluded		0.21	fourth excluded		0.20

pCR, pathological complete response; muc, mucinous; endom, endometroid; undiff, undifferentiated; RD, residual disease; PS, performance status.

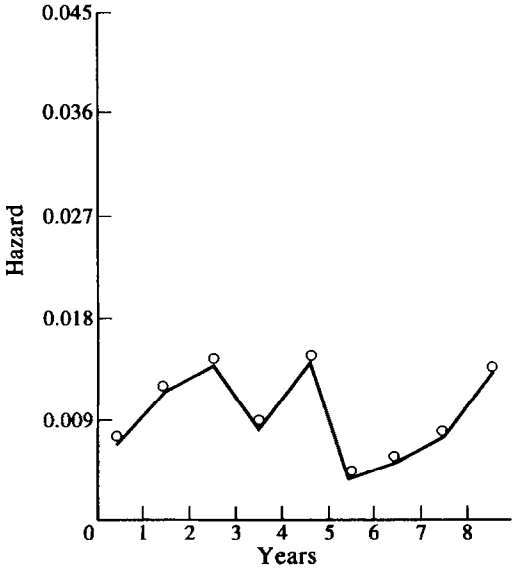

Figure 2. Hazard function for survival.

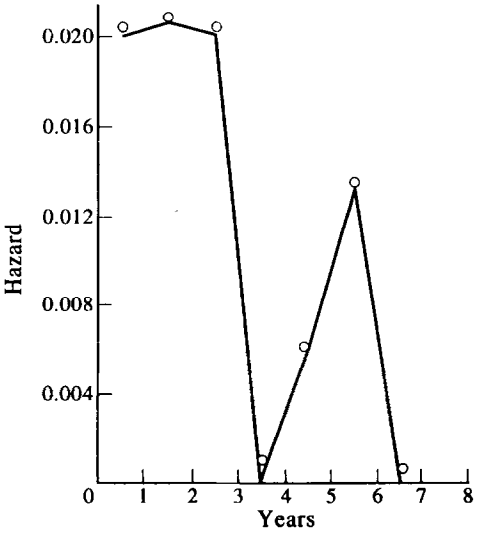

Figure 3. Hazard function for progression-free survival.

trials. In particular, the good long-term outlook for patients in pathological complete response compared to patients with microscopic disease at second-look was evident. However, the importance of disease status at second-look in relation to other prognostic variables was of no prognostic significance since it was removed as a second variable from the model in Cox analyses.

The present Cox regression analysis demonstrated that histological grade, residual disease after first surgery and performance status had independent impact on relapse-free survival. These parameters, with the exception of PS, confirmed their prognostic importance in the group of pathological complete response patients. Data from the literature show that the same factors had prognostic significance in predicting survival, progression-free survival and response to therapy in the whole population of advanced ovarian cancer patients. Our results demonstrate that these pretreatment variables retain their prognostic value in the group of patients macroscopically free of disease at second-look. Whether these clinical and biological features present at diagnosis are modified by the subsequent therapy is questionable. In fact, the addition of doxorubicin to chemotherapy regimens did not statistically influence the outcome of patient population in univariate and Cox regression analyses. Since the Ovarian Cancer Meta-Analyses Project demonstrated a statistically significant 7% survival advantage for the PAC (platinum, doxorubicin and cyclophosphamide) arm in 1194 advanced ovarian cancer patients [22], the role of this first line chemotherapy regimen in the group of surgically complete responders should be further investigated.

Of our patients, 59% received consolidation therapy after second-look surgery. Additional treatment did not influence survival and relapse-free survival of this subset of patients. Since only a minority of patients entered a randomised clinical trial [15], definitive conclusions on the role of consolidation treatment cannot be drawn.

In conclusion, advanced ovarian cancer patients with macroscopically complete remission at second-look have a substantial risk of relapse after aggressive treatment; the risk of recurrence was estimated to be maximal in the first 3 years after second-look surgery.

Patients with a poor performance status, residual disease >2 cm after first surgery and undifferentiated tumour at diagnosis appear to have a poorer prognosis compared with patients with a performance status of 0, residual disease <2 cm and G1 tumour. These results require verification in another patient population. Should survival be demonstrated significantly different between risk categories, then treatment could be tailored according to prognosis. High risk patients are actually the best candidates to evaluate new treatment approaches, such as paclitaxel-containing chemotherapy regimens. Preliminary results of paclitaxel and cisplatin first line chemotherapy are very encouraging, demonstrating a 32% reduction in recurrence risk compared with that with standard treatment in suboptimally debulked advanced ovarian cancer patients.

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