GYNECOLOGY

Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer

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OBJECTIVE: The objective of the study was to analyze in a large series of unresectable advanced ovarian cancer (AOC) patients the prognostic role of pathological response to neoadjuvant chemotherapy (NACT).

STUDY DESIGN: We retrospectively evaluated 322 unresectable AOC patients treated with NACT followed by interval debulking surgery (IDS). Pathological response was classified as follows: complete (cPR) in the absence of residual disease, microscopic (microPR) in the presence of microscopic tumor foci (maximum diameter $\leq$3 mm), and macroscopic (macroPR) when macroscopic residual disease was detected.

RESULTS: cPR was observed in 21 (6.5%), microPR in 104 (32.3%), and macroPR in 197 (61.2%) patients. No differences were observed in the distribution of baseline clinicopathological characteristics between the groups. Median progression-free survival was 36 months in cPR, 16 in microPR, and 13 in macroPR ($P = .001$). Median overall survival was 72 months in cPR, 38 in microPR, and 29 in macroPR ($P = .018$). The survival differences between microPR and macroPR patients were not confirmed when the analysis included only cases resected to no gross residual disease at IDS. cPR retained the independent prognostic role in the multivariate analysis. International Federation of Gynecology and Obstetrics stage IV was the only negative independent predictor of cPR ($\chi^2 = 5.362$, $P = .021$).

CONCLUSION: cPR is an uncommon event in AOC patients receiving NACT and is associated with a longer progression-free survival and overall survival compared with women showing no cPR, even in patients receiving IDS with no gross residual disease. The proposed classification of pathological response may serve in the next future as an easily assessable and highly valuable prognostic tool in this clinical setting.

Key words: advanced ovarian cancer, complete pathological response, interval debulking surgery, neoadjuvant chemotherapy, prognosis

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Consolidated evidences from retrospective series demonstrated that residual tumor at first surgery represents the most powerful predictor of clinical outcome in advanced ovarian cancer (AOC).[1-6] Therefore, extensive primary debulking surgery (PDS) is considered the cornerstone in the management of women even with late-stage disease. On the other hand, novel evidences suggest that neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) may provide similar survival benefit, with fewer surgical morbidities.[7,8] In this context, it is urgently needed to develop novel prognostic tools able to identify which patients benefit most from PDS or NACT followed by IDS.

It is well known that the vast majority of women with AOC respond to platinum-based NACT, experiencing a tumor shrinkage, which allows the disease removal, at the time of IDS. However, the magnitude of response to NACT is highly variable, thus identifying specific cohorts of patients, potentially characterized by different clinical outcome.[9,10] In particular, it has been documented that NACT can determine the complete disappearance of all the neoplastic lesions in a small proportion of women with a highly chemosensitive disease.[10] Therefore, it can be hypothesized that this very selected cohort of women may represent the clinical setting that gains the highest benefit from the NACT-based approach. However, very

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few data are currently available about the prognostic role of complete pathologic response (cPR) to NACT. Furthermore, the early identification of these women would be highly valuable, in order to properly tailor the upfront management.

For these reasons, here we investigate the prognostic role of an easily assessable classification of pathologic response to NACT, emphasizing the relevant favorable impact of cPR in terms of overall and progression-free survival. Furthermore, we investigated the potential clinicopathological predictors of cPR.

TABLE 1
Distribution of patients' clinicopathological characteristics and treatment details in the overall population and according to pathological response to NACT

Characteristics	All cases, n (%)	cPR, n (%)	microPR, n (%)	macroPR, n (%)	*P* value[a]
All	322	21 (6.4)	104 (31.5)	197 (59.7)	
Age, y					
≤65	226 (70.2)	16 (76.2)	75 (72.1)	135 (68.5)	
>65	96 (29.8)	5 (23.8)	29 (27.9)	62 (31.5)	.688
FIGO stage					
IIIC	251 (77.7)	18 (85.7)	77 (74.0)	155 (78.7)	
IV	72 (22.3)	3 (14.3)	27 (26.0)	42 (21.3)	.430
Carcinomatosis at diagnosis					
No	37 (11.5)	5 (23.8)	12 (11.5)	20 (10.2)	
Yes	285 (88.5)	16 (76.2)	92 (88.5)	177 (89.8)	.175
Ascites					
No	75 (23.3)	6 (28.6)	25 (24.0)	44 (22.3)	
Yes	247 (76.7)	15 (71.4)	79 (76.0)	153 (77.7)	.794
Tumor histotype					
Serous	264 (82.0)	15 (71.4)	90 (86.5)	159 (80.7)	
Others	58 (18.0)	6 (28.6)	14 (13.5)	38 (19.3)	.196
Tumor grade					
G1	9 (2.7)	1 (4.8)	0 (0.0)	8 (4.1)	
G2-3	313 (97.3)	20 (95.2)	104 (100.0)	189 (95.9)	.108
CA-125, IU/mL[b]					
Median serum levels (range)	548 (9—9.999)	404 (9—9.999)	888 (9—9.999)	516 (4—9.999)	.328
First-line chemotherapy regimen					
Carboplatin alone	51 (15.8)	4 (19.0)	11 (10.6)	36 (18.3)	
Carboplatin/paclitaxel or PLD	271 (84.2)	17 (81.0)	93 (89.4)	161 (81.7)	.202
NACT cycles					
3-4	216 (82.3)	16 (76.2)	78 (75.0)	122 (61.9)	
6	57 (17.7)	5 (23.8)	26 (25.0)	75 (38.1)	.047
Clinical response to NACT					
Complete	41 (15.8)	15 (71.4)	10 (9.6)	26 (13.2)	
Partial/Stable disease	271 (84.2)	6 (28.6)	94 (90.4)	171 (86.8)	.001

cPR, complete pathological response; *FIGO*, International Federation of Gynecology and Obstetrics; *macroPR*, macroscopic pathological response; *microPR*, microscopic pathological response; *NACT*, neoadjuvant chemotherapy; *PLD*, pegylated liposomal doxorubicin.

[a] Calculated by χ^2 test. Patients with progressive disease at clinical revaluation, not receiving surgery after NACT, were excluded from the analysis; [b] Calculated by a Kruskal-Wallis nonparametric test.

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Materials and Methods

Data for the current analysis were retrieved from the electronic database of our Gynecologic Oncology Unit. Patients' demographics, medical, surgical, and follow-up data were prospectively collected and retrospectively analyzed.

Study group

Between January 1995 and December 2010, 322 patients were admitted to the Gynecologic Oncology Unit of the Catholic University of Rome and Campobasso, with a diagnosis of advanced ovarian, tubal, or peritoneal cancer. All these women were judged as having unresectable advanced disease after initial surgical exploration and submitted to NACT followed by IDS.

All patients received 4/6 courses of platinum-based NACT, with the vast majority of women treated with carboplatin/paclitaxel or carboplatin/pegylated-liposomal doxorubicin (PLD) regimens, and only a small proportion of women (15.8%) with single-agent carboplatin. In particular, after 3 cycles of NACT, all patients were submitted to clinical/radiological evaluation of response to treatment, according to the Gynecological Cancer Intergroup and response evaluation criteria in solid tumors criteria.[11]

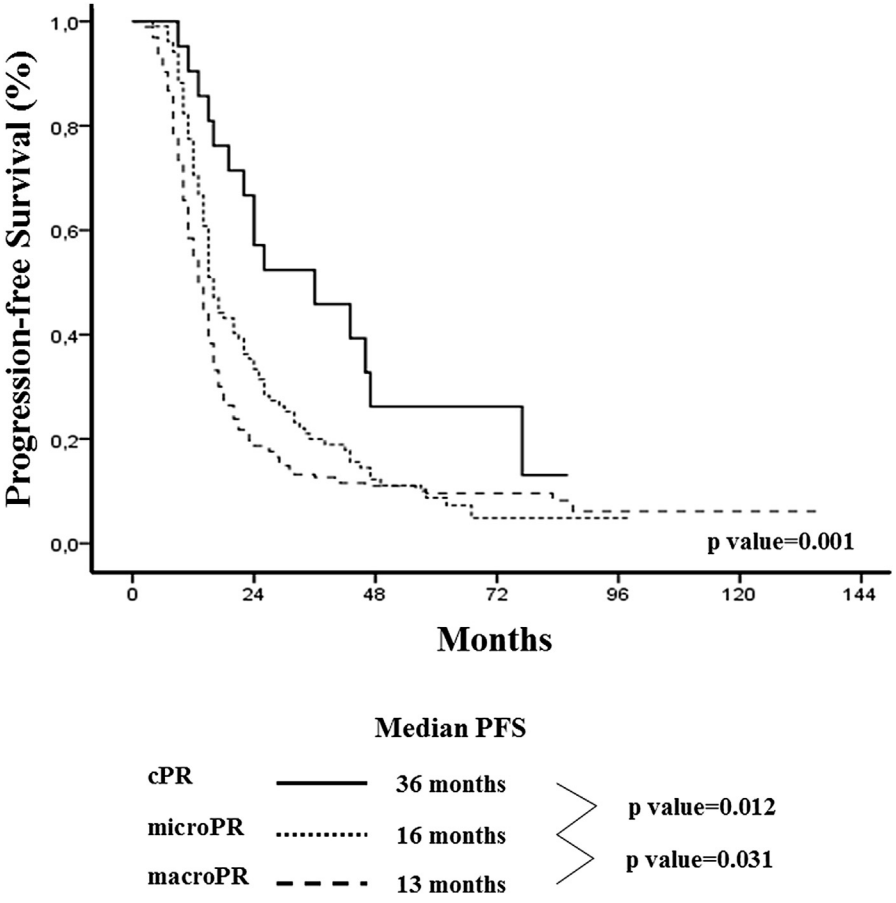
All women experiencing progressive disease were not submitted to IDS, received second-line chemotherapy with nonplatinum agents, and were not included in our analysis. On the other hand, all patients showing complete or partial clinical response to treatment received IDS. Finally, in patients showing stable disease, to achieve a favorable clinical response, fully exploiting the benefit of platinum compounds, 3 further courses of NACT were administered prior to performing IDS.

The extension of tumor disease on surgical samples taken at the time of IDS was carefully evaluated through an extensive sampling of all specimens. Pathological response to NACT was classified as follows: cPR in cases with no residual neoplastic cells in all the surgical specimens, including the adnexa. Cases without macroscopic lesions but with microscopic foci (maximum diameter ≤3 mm) were defined as microscopic response (microPR). The remaining cases with a persistent macroscopic site of disease after NACT were classified as a macroscopic response (macroPR).

All women received, after IDS, 2 additional courses of chemotherapy, with the same regimen used as NACT. After completion of primary treatment, all women were triaged to clinical routine follow-up procedures, with a clinical examination and CA125 dosage every 2/4 months and chest/abdominal/pelvic computed tomography scan every 6 months during the first 2 years and then annually during the following 5 years.

Patients recurring after 6 months from the end of primary chemotherapy were classified as platinum sensitive, and all were treated with platinum-based second-line chemotherapy. On the other hand, all cases with platinum-resistant recurrent disease received salvage chemotherapy with investigational drugs or single agents including pegylated liposomal doxorubicin, topotecan, gemcitabine, or weekly paclitaxel. All women included in the study gave, at the time of diagnosis, written informed consent for the collection and analysis of clinical data for research purposes. The institutional review board approved the prospective collection of data and retrospective analysis for study purposes.

FIGURE 1
PFS in AOC patients receiving NACT



PFS in AOC patients receiving NACT with cPR (cPR group) or microPR/macroPR (microPR and macroPR groups).

AOC, advanced ovarian cancer; *cPR*, complete pathological response; *macroPR*, macroscopic pathological response; *microPR*, microscopic pathological response; *NACT*, neoadjuvant chemotherapy; *PFS*, progression-free survival.

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Statistical analysis

Progression-free survival (PFS) was calculated from the date of diagnosis to the date of first relapse or the date of the last follow-up (second half of 2012 in all women). The duration of overall survival (OS) was defined as the time elapsed between diagnosis and death or date of last follow-up (second half of 2012 in all women). No patient included in the analysis was lost during follow-up. Data are given as median and range. Categorical variables are reported as absolute values and percentages.

Baseline differences between groups were analyzed using the Pearson χ^2 exact test and the Kruskall-Wallis test, as appropriate. Medians and life tables were computed using the product limit estimate by the Kaplan-Meier method,[12] and the log-rank test was used to assess the statistical significance.[13] Cox's regression models were used to analyze the role of clinical-pathological parameters, and pathological response as prognostic factors for PFS and OS.[14] A linear regression model was used to investigate the role of clinical-pathological variables at diagnosis as predictors of cPR. All statistical calculations were performed using the Statistical Package for Social Sciences (version 17.0; SPSS Inc, Chicago, IL).

RESULTS

The clinical-pathological characteristics of the whole series have been summarized in Table 1. cPR to NACT was observed in 21 cases accounting for 6.5% of all women treated with NACT. On the other hand, microPR was documented in 104 women (32.3%), with the remaining 197 patients (61.2%) showing macroscopic residual disease at the time of IDS. International Federation of Gynecology and Obstetrics (FIGO) stage IV was due to the presence of pleural effusion in 37 cases (52.1%) and metastasis in the liver, spleen, or lung in 34 patients (47.9%). No statistically significant differences were observed in terms of age, FIGO stage, tumor grade, carcinomatosis at diagnosis, the presence of ascites, tumor histotype, CA-125 serum levels, or first-line chemotherapy regimen between the cPR, microPR, and macroPR groups (Table 1).

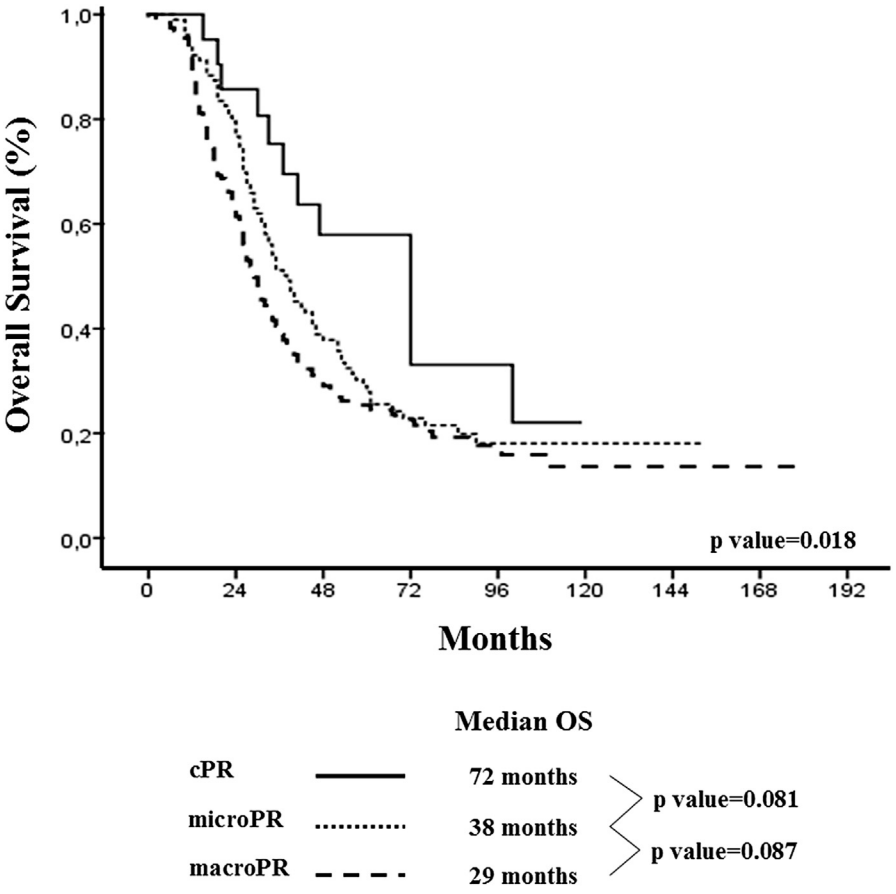
All cases with cPR, and microPR received IDS with no gross residual disease. On the other hand, in the macroPR group, IDS with residual tumor (RT) of 0 was achieved in 111 cases (56.3%), RT of 1 cm or less in 36 cases (18.3%), and RT greater than 1 cm in 50 women (25.4%). As expected, complete clinical response was documented more frequently in the cPR compared with the microPR and macroPR groups (71.4% vs 9.6% vs 13.2%, respectively, $P < .001$).

Survival analysis

The median follow-up of the overall series was 47 (3-181) months, with 35 (7-119) months in the cPR, 36 (5-152) months in the microPR, and 28 (3-181) months in the macroPR group. During the study period, 284 recurrences (88.2%) were observed. In particular, we documented a median PFS of 36 months in the cPR group, which was significantly longer compared with the microPR (median PFS, 16 months) and macroPR groups (median PFS, 13 months) ($P = .001$) (Figure 1). Furthermore, the differences in the term of duration of PFS also reached statistical significance when analyzed between the cPR vs the microPR ($P = .012$) and the microPR vs the macroPR groups ($P = .031$).

Looking at overall survival, death of disease was observed in 239 women (74.2%), and OS duration was approximately 40 months longer in the cPR

FIGURE 2
OS in AOC patients receiving NACT



OS in AOC patients receiving NACT with cPR (cPR group) or microPR/macroPR (microPR and macroPR groups).

AOC, advanced ovarian cancer; *cPR*, complete pathological response; *macroPR*, macroscopic pathological response; *microPR*, microscopic pathological response; *NACT*, neoadjuvant chemotherapy; *OS*, overall survival.

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compared with the no-cPR groups (cPR, 72 months vs microPR, 38 months vs macroPR, 29 months, $P = .018$).

A separate analysis was conducted to compare OS between the cPR and microPR groups, showing only a trend toward a longer OS in the cPR group ($P = .081$). Similarly, the differences in terms of OS between the microPR and macroPR groups did not reach the statistical significance ($P = .087$) (Figure 2).

Finally, a further survival analysis has been conducted including only cases receiving IDS with no gross residual disease (Figure 3). Of note, in this specific cohort of women, no differences were observed in terms of survival outcome between the microPR and macroPR groups (median PFS, 16 vs 16 months, $P = .590$; median OS, 38 vs 38 months, $P = .557$). However, a statistically significant longer PFS and OS were documented in patients showing cPR after NACT compared with cases with no cPR ($P = .038$; Figure 3).

The independent prognostic significance of cPR for PFS and OS was then analyzed using Cox's regression model. Interestingly, at a univariate/multivariate analysis, the prognostic role of pathological response was confirmed, even when adjusted for residual tumor at IDS, with a significant association between cPR and longer duration of PFS and OS (Tables 2 and 3).

Predictors of cPR

To clarify whether specific clinical-pathological factors may predict cPR after NACT, a logistic regression was performed. The presence of FIGO stage IV was the only baseline variable showing a significant inverse correlation with cPR in a univariate analysis ($\chi^2 = 5.362$, $P = .021$) (Table 4). Interestingly, a trend toward a negative predictive role of carcinomatosis for cPR was also observed.

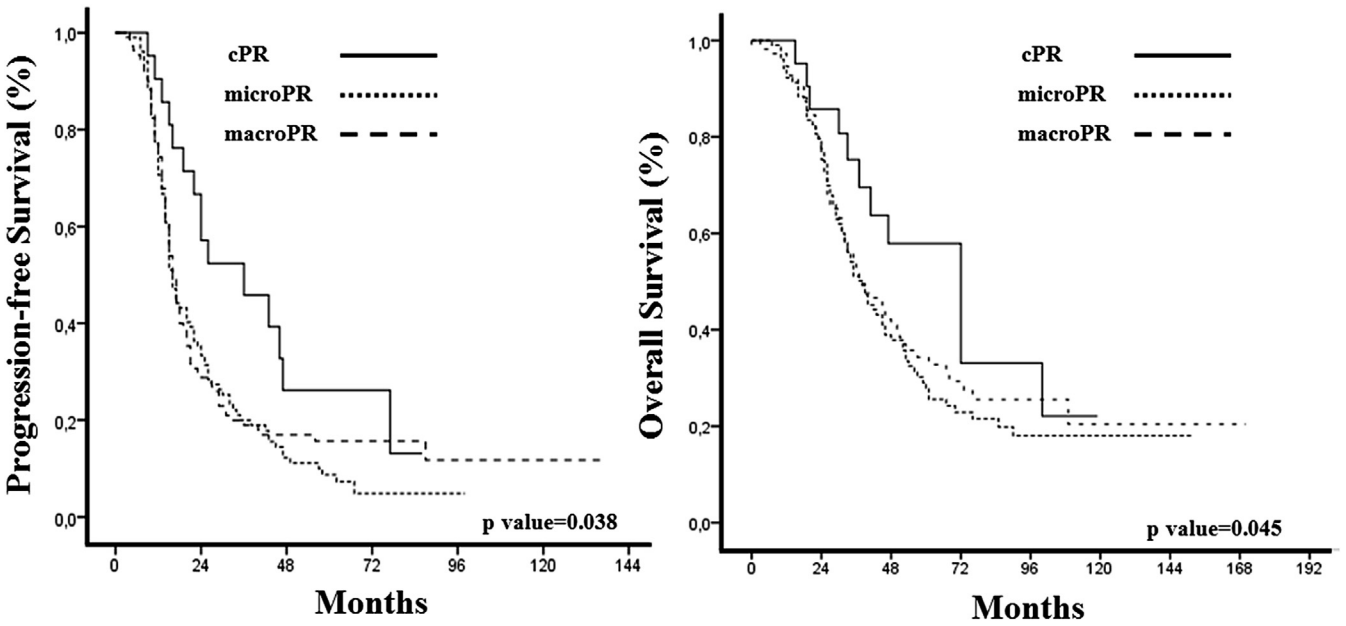
Comment

The prognostic relevance of pathological response to neoadjuvant treatments has been well established in several unresectable human malignancies including breast, cervical, rectal, and lung cancer so that, in these cancers, the complete disappearance of all neoplastic foci is considered one of the main goals to be pursued by preoperative therapeutic approaches.[15-18]

Focusing on AOC, it has been recently reported that the presence of histologically assessed residual disease larger than 1 cm is associated with poorer survival outcome in ovarian cancer patients treated with NACT.[10] Similarly, Le et al[9,19] demonstrated that the residual tumor burden after NACT retains an independent negative prognostic role, particularly when the residual disease is located in the upper abdomen. However, despite these growing evidences, the prognostic role of pathological response in ovarian cancer remains controversial.

In our study the duration of PFS in the cPR group was approximately 35 months, which is superimposable to the survival data reported for women with AOC treated with complete primary debulking surgery.[1-6] The relevance of these findings has not been underestimated because they strongly suggest that patients experiencing cPR represent

FIGURE 3
PFS and OS according to pathological response



PFS and OS according to pathological response in AOC patients treated with NACT followed by IDS with no gross residual disease.

AOC, advanced ovarian cancer; *IDS*, interval debulking surgery; *NACT*, neoadjuvant chemotherapy; *OS*, overall survival; *PFS*, progression-free survival.

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TABLE 2
Univariate and multivariate analysis of clinico-pathological parameters as predictor of progression-free survival in AOC patients receiving NACT

	Univariate analysis		Multivariate analysis	
Variable	χ^2	***P* value**	χ^2	***P* value**
Age, y[a]	3.700	.047[b]	2.864	.091
FIGO stage				
IIIC				
IV	1.423	.233	—	—
Tumor histotype				
Other				
Serous	3.232	.074	—	—
Tumor grade				
G1				
G2-3	0.022	.881	—	—
Carcinomatosis at diagnosis				
No				
Yes	3.756	.054	1.321	.154
Ascites				
No				
Yes	0.363	.547	—	—
CA-125 median levels, IU/mL[a]	4.962	.033[b]	4.851	.028[b]
First-line chemotherapy regimen				
Carboplatin alone				
Carboplatin/paclitaxel or PLD	0.199	.655		—
Residual tumor at IDS				
RT = 0				
RT ≤1 cm				
Explorative laparotomy	42.696	.001[b]	39.716	.001[b]
Pathological response				
cPR				
microPR				
macroPR	13.965	.001[b]	10.832	.001[b]

AOC, advanced ovarian cancer; *FIGO*, International Federation of Gynecology and Obstetrics; *IDS*, interval debulking surgery; *NACT*, neoadjuvant chemotherapy; *PLD*, pegylated liposomal doxorubicin; *RT*, residual tumor.

[a] Considered as continuous variable; [b] Statistical significance differences.

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the clinical setting that gains the highest benefit from NACT.

Relevant survival differences were also documented according to pathological response to NACT. It could be argued that these findings may be mainly related to differences in the extension of disease at diagnosis and/or to the imbalance in terms of complete cytoreduction at the time of IDS in favor of the cPR/microPR groups. However, the similar distribution of baseline characteristics between the groups as well as the results of the multivariate analysis strongly confirms the independent association between cPR and longer survival.

Another relevant finding of our study is the fact that patients with microPR and macroPR showed the same PFS and OS if they undergo resection to no gross residual disease at the time of IDS. However, when an analysis of all patients who were resected to no gross residual disease was performed, women in the cPR group had the best outcome.

It is interesting to note that very slight differences in the extension of disease in removed surgical specimens, as in cPR and microPR cases, can determine quite a relevant impact in terms of survival outcome. As a possible explanation, it has to be considered that cPR, rather than only an estimation of disease extension after NACT, clearly emerges as a marker of extreme sensitivity to platinum-based chemotherapy. In this context, it has to be emphasized that growing evidences have documented a correlation between BRCAness profile, increased sensitivity to platinum-based chemotherapy, and longer survival; therefore, it can be hypothesized that women showing cPR more frequently may retain BRCA1/2 mutations compared with the other groups.[20,21]

In our series, we confirmed the low rate of cPR in AOC patients treated with NACT (approximately 6%),[10] which appears significantly lower compared with data from other malignancies.[15-18] These observations could be explained by the very large diffusion of disease at the time of diagnosis in women with unresectable ovarian cancer. Furthermore, we observed that the vast majority of women achieved cPR or microPR after 4 cycles of NACT, emphasizing that most of the tumor reduction occurs early during induction chemotherapy.

As recently reported, one of the hypothesized biological drawbacks of preoperative NACT is the development of chemoresistant tumor foci.[22,23] Therefore, there is an urgent need to develop effective tests to correctly identify patients who gain the highest benefit from this therapeutic strategy. In our series, FIGO stage IV emerged as the only negative predictor of cPR, thus suggesting that extraperitoneal localizations

TABLE 3
Univariate and multivariate analysis of clinicopathological parameters as predictor of OS in AOC patients receiving NACT

Variable	Univariate analysis χ^2	Univariate analysis *P* value	Multivariate analysis χ^2	Multivariate analysis *P* value
Age, y[a]	3.321	.072	—	—
FIGO stage				
IIIC				
IV	2.888	.089	—	—
Tumor histotype				
Other				
Serous	1.564	.164	—	—
Tumor grade				
G1				
G2-3	1.323	.157		
Carcinomatosis at diagnosis				
No				
Yes	1.804	.179	—	—
Ascites				
No				
Yes	2.848	.092	—	—
CA-125 median levels, IU/mL[a]	0.151	.698	—	—
First-line chemotherapy regimen				
Carboplatin alone				
Carboplatin/paclitaxel or PLD	0.051	.822	—	—
Residual tumor at IDS				
RT = 0				
RT = ≤1 cm				
Explorative laparotomy	29.042	.001[b]	24.591	.001[b]
Pathological response				
cPR				
microPR				
macroPR	7.628	.006[b]	7.209	.007[b]

AOC, advanced ovarian cancer; *FIGO*, International Federation of Gynecology and Obstetrics; *IDS*, interval debulking surgery; *NACT*, neoadjuvant chemotherapy; *OS*, overall survival; *PLD*, pegylated liposomal doxorubicin; *RT*, residual tumor.

[a] Considered as continuous variable; [b] Statistical significance differences.

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TABLE 4
Univariate analysis of clinicopathological parameters as a predictor of cPR in women with AOC receiving NACT

Variable	Univariate analysis χ^2	Univariate analysis *P* value
Age, y[a]	1.110	.293
FIGO stage		
IIIC		
IV	5.362	.021[b]
Tumor histotype		
Other		
Serous	1.694	.126
Tumor grade		
G1		
G2-3	0.597	.440
Carcinomatosis at diagnosis		
No		
Yes	3.366	.067
Ascites		
No		
Yes	0.174	.677
CA-125 median levels, IU/mL[a]	0.034	.855
First-line chemotherapy regimen		
Carboplatin alone		
Carboplatin/paclitaxel or PLD	0.173	.678
NACT cycles		
3-4		
6	1.608	.206

AOC, advanced ovarian cancer; *cPR*, complete pathological response; *FIGO*, International Federation of Gynecology and Obstetrics; *NACT*, neoadjuvant chemotherapy; *PLD*, pegylated liposomal doxorubicin.

[a] Considered as a continuous variable; [b] Statistical significance differences.

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could represent foci of more aggressive chemoresistant disease, less prone to be removed by conventional NACT. Of note, although the presence of carcinomatosis emerged as predictor of poor pathological response to NACT with a borderline significance, it did not retain an independent prognostic role in terms of PFS and OS, thus suggesting that cytoreduction to no gross residual disease at the time of IDS may probably overcome the negative prognostic impact of a wide initial tumor diffusion.

We acknowledge that the retrospective nature of our study represents an unavoidable source of selection bias.

However, the large case series, the magnitude of the survival differences and the results of the multivariate analysis support the reliability of our findings.

In conclusion, our study demonstrates that cPR is an uncommon event in AOC patients receiving NACT and is associated with a longer survival compared with women showing no cPR. The proposed classification of pathological response may serve in the near future as an easily assessable and reliable prognostic tool in this specific clinical setting. Further studies are required to clarify whether location of residual disease in women experiencing micro/macroPR may influence PFS and OS. ■

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