Survival impact of histological response to neoadjuvant chemotherapy according to number of cycles in patients with advanced ovarian cancer

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ABSTRACT

Objective We sought to evaluate the impact of chemotherapy response score according to the number of cycles of neoadjuvant chemotherapy, on disease-free survival and overall survival, in patients with advanced epithelial ovarian cancer ineligible for primary debulking surgery.

Methods This multicenter retrospective study included patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV epithelial ovarian cancer who underwent 3–4 or 6 cycles of a platinum and taxane-based neoadjuvant chemotherapy, followed by complete cytoreduction surgery (CC-0) or cytoreduction to minimal residual disease (CC-1), between January 2008 and December 2015, in four institutions. Disease-free survival and overall survival were assessed according to the histological response to chemotherapy defined by the validated chemotherapy response score.

Results A total of 365 patients were included: 219 (60.0%) received 3–4 cycles of neoadjuvant chemotherapy, and 146 (40.0%) had 6 cycles of neoadjuvant chemotherapy before cytoreductive surgery. There were no significant differences in early relapses, disease-free survival, and overall survival according to the number of neoadjuvant chemotherapy cycles. However, regardless of the number cycles of neoadjuvant chemotherapy, persistent extensive histological disease (chemotherapy response score 1–2) was significantly associated with a higher peritoneal cancer index, minimal residual disease (CC-1), and early relapses. Median disease-free survival in patients with complete or near-complete response (score 3) was 28.3 months (95% CI 21.6 to 36.8), whereas it was 16.3 months in patients with chemotherapy response score 1–2 (95% CI 14.7 to 18.0, p<0.001).

Conclusion In our cohort, the number of neoadjuvant chemotherapy cycles was not associated with disease-free survival or overall survival. Chemotherapy response score 3 improved oncological outcome regardless of the number of neoadjuvant chemotherapy cycles.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chemotherapy response score assessed on interval debulking specimen reflects chemosensitivity and is associated with survival in advanced high grade serous carcinoma. The impact of histological response on survival according to the number of neoadjuvant chemotherapy cycles remains unknown.

WHAT THIS STUDY ADDS

⇒ Chemotherapy response score is associated with survival, regardless of the number of cycles of neoadjuvant chemotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Chemotherapy response score may be used as a surrogate for chemosensitivity and as a useful endpoint for clinical trials, irrespective of the number of cycles of neoadjuvant chemotherapy.

INTRODUCTION

Primary debulking surgery to achieve complete cytoreduction of all macroscopic visible disease, followed by platinum and taxane-based chemotherapy and appropriate maintenance therapy, are the standard treatment for advanced epithelial ovarian cancer.[1 2] Neoadjuvant chemotherapy followed by interval debulking surgery is an alternative for patients with specific medical conditions precluding them from surgery, or in case of unresectable disease.[3–5] Neoadjuvant chemotherapy allows higher rates of complete cytoreduction, less extensive surgical procedures, fewer postoperative complications, and assessment of chemosensitivity.[6 7] However, the optimal duration of neoadjuvant chemotherapy is not yet established. Usually, three cycles of neoadjuvant chemotherapy is the standard of care according the EORTC 55971 and CHORUS trials.[3 8] Reports evaluating the role of interval debulking surgery after more than four cycles of neoadjuvant chemotherapy are controversial. While some have shown that survival is similar to that of patients undergoing interval debulking surgery after three cycles of neoadjuvant chemotherapy,[9–12] others have reported poorer prognosis of delayed

surgery.[13–16] To date, there has been no randomized controlled trial to determine the best timing for interval debulking surgery.

Neoadjuvant chemotherapy allows *in vivo* tumor chemosensitivity assessment according to histopathologic response. Complete histopathological response, defined as the absence of surgical residual disease, is achieved in fewer than 10% of patients receiving neoadjuvant chemotherapy, and is associated with significantly longer survival.[17 18] Thus, a chemotherapy response score has been developed to describe the response to neoadjuvant chemotherapy in high-grade serous carcinomas. This score is obtained on interval debulking specimens, it has been associated with platinum-sensitivity, and has shown a prognostic role.[19–22] However, most previous studies have limitations such as small sample size, heterogeneity between participants, the number of neoadjuvant chemotherapy cycles, and regimens used.[23–25] To date, the impact of histological response on survival according to the number of neoadjuvant chemotherapy cycles remains unknown.

This study evaluated survival outcome according to the type of histopathological response (measured by the chemotherapy response score) and the number of neoadjuvant chemotherapy cycles received in advanced ovarian cancer patients.

METHODS

Patients and Study Design

Using a computer-generated search of our institutional patient database, we retrospectively identified all patients who underwent neoadjuvant chemotherapy with three to four or six cycles, followed by complete cytoreduction surgery (CC-0) or cytoreduction to minimal residual disease (CC-1), for International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV epithelial ovarian cancer, between January 2008 and December 2015, in four institutions meeting the requirements of the European Society of Gynecological Oncology quality indicators from France and Spain. National and Institutional Review Board approvals were obtained (SLN/MFI/AR193997 and HULP code PI-3432). A flow chart of eligible and included patients is available in Online supplemental figure 1.

Surgical and Chemotherapy Treatment Regimens

At diagnosis, all patients underwent imaging including thoraco-abdomino-pelvic computed tomography (CT). In patients with a suspicion of extra-abdominal disease, positron emission tomography/CT was performed. Patients with deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving large parts of the small bowel and stomach, and infiltration of the duodenum or pancreas, were considered unresectable and were selected for primary chemotherapy. Neoadjuvant chemotherapy was also indicated in patients unfit for extensive resection due to medical co-morbidities or poor performance status, or when too extensive surgery was needed to achieve complete cytoreduction. Neoadjuvant chemotherapy was platinum- and taxane-based chemotherapy, according to our institutional recommendations (carboplatin with area under the curve (AUC) 5–6 and paclitaxel 175 mg/m^2, once every 3 weeks).

Response to neoadjuvant chemotherapy and resectability to neoadjuvant chemotherapy was assessed on imaging after three to four neoadjuvant chemotherapy cycles and according to cancer antigen (CA) 125 dosage. Patients with stable disease on CT scan or at exploratory laparoscopic assessment underwent three additional cycles. If peritoneal carcinomatosis was stable compared with initial assessment, interval debulking surgery was delayed to six cycles. Criteria for non-resectable disease were the same as those at diagnosis. All surgical procedures were performed by experienced oncological surgeons. The extent and distribution of the disease were evaluated with the peritoneal cancer index. Surgery aimed to obtain a complete cytoreduction, using the Completeness of Cytoreduction score (CC-0: no residual tumor; CC-1: residual disease <2.5 mm in diameter; CC-2: residual nodules between 2.5 mm and 2.5 cm; and CC-3: residual nodules >2.5 cm or a confluence of unresectable disease).[26] We used the Aletti Score to quantify surgical complexity.[27]

Pathology examination was performed by an expert gynecologic oncology pathologist in each participating institution. However, omental chemotherapy response score was assessed retrospectively for this study by two experts, using the pathology reports. Chemotherapy response score 3 was defined as good response and chemotherapy response score 1–2 as no significant response (Online supplemental table 1).

When feasible, adjuvant chemotherapy was delivered within 1 or 2 months after cytoreductive surgery with carboplatin and paclitaxel until a total of at least six cycles had been completed. In the event of high tumor burden, minimal residual disease (CC-1) or poor response to neoadjuvant chemotherapy, antiangiogenic maintenance treatment with bevacizumab was added after discussion by the tumor board. When surgery was performed after six cycles of neoadjuvant chemotherapy, two to three additional cycles of chemotherapy were added to the antiangiogenic maintenance treatment with bevacizumab. No maintenance treatment with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors was administered during the study period.

Patients with unresectable disease, with residual disease ≥2.5 mm (CC-2), and those with non-epithelial subtype histology or borderline tumors were excluded from the study. Patients' demographic data, performance status, CA125 dosage, neoadjuvant chemotherapy treatment details, peritoneal cancer index scores recorded during cytoreductive surgery, surgical procedures, histologic data, and follow-up data were recorded. Follow-up was conducted according to each center's protocol. Globally, it included clinical examination, CA125, with or without a thoraco-abdomino-pelvic CT scan every 4 to 6 months for 5 years. Afterwards, the follow-up visits were scheduled annually.

Statistical Analysis

Data were summarized by median and range for quantitative variables and by frequency and percentage for qualitative variables. Comparisons between groups were performed using the Mann-Whitney test for quantitative variables and the χ^2 or Fisher's exact test for qualitative variables. Disease-free survival was defined as the time from the diagnosis to relapse or death from any cause. Patients who were alive and disease-free were censored at last follow-up news. Overall survival was defined as the time from the diagnosis to death from any cause. Patients who were alive were censored at last follow-up. Survival data were summarized using the Kaplan-Meier method. Univariable and multivariable analyses were performed using the Log rank test and the Cox model. Hazard ratios (HR) were estimated with their 95% confidence intervals

Table 1 Baseline characteristics of overall population (n=365) and according to chemotherapy response score (CRS)

	Overall (n=365)	CRS 1–2 (n=277)	CRS 3 (n=88)	P value
Age (years), n (%)				0.770
≤60	161 (44.1)	121 (43.7)	40 (45.5)	
>60	204 (55.9)	156 (56.3)	48 (54.5)	
Median (range)	62 (21–88)	63 (21–88)	62 (38–83)	0.953
BMI (kg/m^2), median (range) Missing	24.1 (15.6–52.0) 13 (-)	24.1 (15.6–52.0) 8 (-)	24.3 (16.4–44.6) 5 (-)	0.795
WHO performance status, n (%)				0.163
0	211 (59.4)	159 (59.3)	52 (59.8)	
1	125 (35.2)	98 (36.6)	27 (31.0)	
≥2	19 (5.4)	11 (4.1)	8 (9.2)	
Missing	10 (-)	9 (-)	1 (-)	
Preoperative CA125 (UI/mL), median (range) Missing	885.0 (5–86000) 27 (-)	868.5 (11–42110) 21 (-)	896.5 (5–86000) 6 (-)	0.750
FIGO stage, n (%)				0.314
IIIC	282 (77.3)	219 (79.1)	63 (71.6)	
IV	83 (22.7)	58 (20.9)	25 (28.4)	
Histological subtype, n (%)				0.578
Serous carcinoma	341 (94.2)	258 (93.8)	83 (95.4)	
High-grade	275 (93.9)	211 (92.5)	64 (98.5)	
Low-grade	18 (6.1)	17 (7.5)	1 (1.5)	
Grade N/A	48 (-)	30 (-)	18 (-)	
Endometrioid carcinoma	10 (2.8)	7 (2.5)	3 (3.4)	
Carcinosarcoma	6 (1.7)	6 (2.2)	0 (0.0)	
Clear cell carcinoma	2 (0.6)	2 (0.7)	0 (0.0)	
Mucinous carcinoma	1 (0.3)	1 (0.4)	0 (0.0)	
Others	2 (0.6)	1 (0.4)	1 (1.1)	
Missing	3 (-)	2 (-)	1 (-)	
Ascites (liter), median (range) Missing	1 (0–10) 51 (-)	1 (0–10) 36 (-)	1 (0–7.5) 15 (-)	0.045

BMI, body mass index; CA125, cancer antigen 125; CRS, chemotherapy response score; FIGO, International Federation of Gynecology and Obstetrics; N/A, not available; WHO, World Health Organization.

(95% CI). Significant variables in the univariable analysis and variables judged clinically relevant were selected for the multivariable analysis. All statistical tests were two-sided and p values <0.05 were considered statistically significant. Statistical analyses were conducted using STATA v16 software.

RESULTS

A total of 365 patients were included in the study. Demographic and clinical baseline characteristics are summarized in Table 1. Among the 365 patients, 219 (60.0%) received three to four cycles of neoadjuvant chemotherapy followed by early interval debulking surgery, and 146 (40.0%) had six cycles of neoadjuvant chemotherapy before delayed debulking surgery. Median peritoneal cancer index (assessed in 363/365 patients) at the time of debulking surgery was 9 (range 0–39). Complete cytoreduction was achieved in 318 patients (87.1%) and cytoreduction to minimal residual disease was performed in 47 (12.9%) patients. Surgical procedures and post-operative data according to chemotherapy response score are presented in Table 2. In total, 105/146 (71.9%) patients who received six cycles of neoadjuvant chemotherapy were also treated with adjuvant chemotherapy, with a median three cycles of adjuvant chemotherapy (range 1–6).

With a median follow-up of 69.0 months (95% CI 62.6 to 74.5), 300 patients relapsed (82.2%). In the total population, 79 patients (22.5%) were considered to be platinum resistant (patients who experienced a relapse within 6 months after the last cycle of carboplatin). Median disease-free survival was 18.1 months (95% CI 16.5 to 19.8) and median overall survival was 49.4 months (95% CI 46.2 to 54.5) in the total population.

In univariable analysis, high peritoneal cancer index and Aletti scores, chemotherapy response score 1–2, and residual disease were significantly associated with worse disease-free survival. Peritoneal cancer index, Aletti scores, and chemotherapy response

Table 2 Surgical and post-operative data for overall population (n=365) and according to chemotherapy response score (CRS)

	Overall (n=365)	CRS 1–2 (n=277)	CRS 3 (n=88)	P value
PCI, n (%)				
≤10	205 (56.5)	132 (47.8)	73 (83.9)	<0.001
>10	158 (43.5)	144 (52.2)	14 (16.1)	
Median (range)	9 (0–39)	11 (0–39)	4 (0–19)	
Missing	2 (-)	1 (-)	1 (-)	
NACT, n (%)				
3–4 cycles	219 (60.0)	174 (62.8)	45 (51.1)	0.051
6 cycles	146 (40.0)	103 (37.2)	43 (48.9)	
CC-score				
CC-0	318 (87.1)	231 (83.4)	87 (98.9)	<0.001
CC-1	47 (12.9)	46 (16.6)	1 (1.1)	
Aletti score, n (%)				
<8	213 (58.4)	139 (50.2)	74 (84.1)	<0.001
≥8	152 (41.6)	138 (49.8)	14 (15.9)	
Post-operative complications*, grade III/IV, n (%)				
No	294 (80.5)	218 (78.7)	76 (86.4)	0.114
Yes	71 (19.5)	59 (21.3)	12 (13.6)	
Bevacizumab maintenance, n (%)				
No	290 (79.5)	213 (76.9)	77 (87.5)	0.032
Yes	75 (20.5)	64 (23.1)	11 (12.5)	
Platinum resistance†, n (%)				
*No	272 (77.5)	194 (73.5)	78 (89.7)	0.002
Yes	79 (22.5)	70 (26.5)	9 (10.3)	
Missing	14 (-)	13 (-)	1 (-)	

*Platinum resistance defined as early relapse within 6 months after last cycle of carboplatin.
†Clavien-Dindo classification.
CC, complete cytoreduction; CRS, chemotherapy response score; NACT, neoadjuvant chemotherapy; PCI, peritoneal cancer index.

score 1–2 were also significantly associated with worse overall survival (Online supplemental table 1). In the overall cohort, 277 patients (75.9%) had a chemotherapy response score 1–2 after neoadjuvant chemotherapy, and 88 patients (24.1%) had a complete or extensive response to neoadjuvant chemotherapy (score 3). Median disease-free survival in patients with chemotherapy response score 3 was 28.3 months (95% CI 21.6 to 36.8), whereas it was 16.3 months in patients with score 1–2 (95% CI 14.7 to 18.0, p<0.001). Median overall survival in chemotherapy response score 3 patients was 104.9 months (95% CI 63.5 to not reached) and 45.8 months (95% CI 40.0 to 49.2) in chemotherapy response score 1–2 patients (p<0.001) (Figure 1).

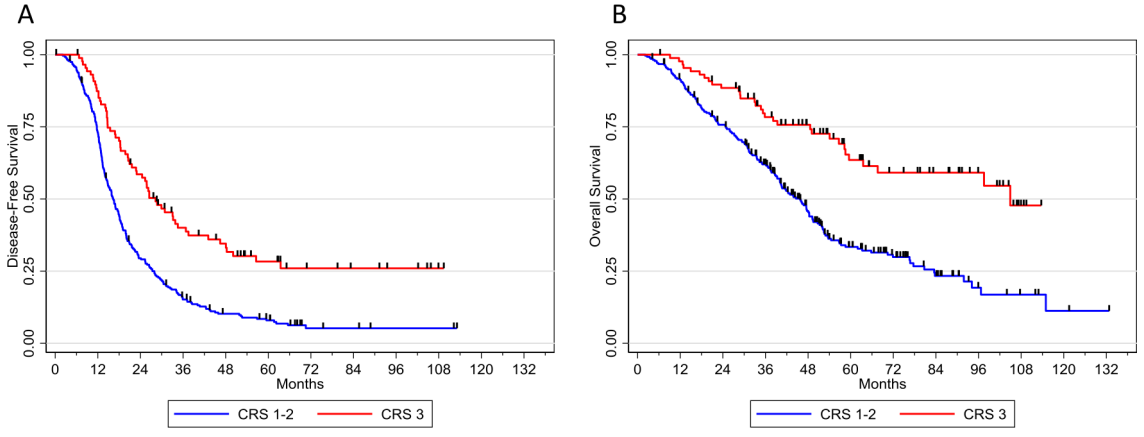

Figure 1 Disease-free survival (A) and overall survival (B) according to histological response to neoadjuvant chemotherapy assessed by chemotherapy response score (CRS).

Table 3 Multivariable disease-free survival and overall survival analysis of total population (n=365)

	Disease-free survival			Overall survival		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
≤60	1.00	Ref	0.852	1.00	Ref	0.489
>60	0.98	(0.78 to 1.23)		1.10	(0.84 to 1.45)	
FIGO stage						
IIIC	1.00	Ref	0.100	1.00	Ref	0.413
IV	1.25	(0.96 to 1.64)		1.15	(0.82 to 1.62)	
Cycles of NACT						
3–4	1.00	Ref	0.498	1.00	Ref	0.145
6	1.09	(0.85 to 1.38)		1.24	(0.93 to 1.65)	
PCI						
≤10	1.00	Ref	0.098	1.00	Ref	0.542
>10	1.25	(0.96 to 1.64)		1.10	(0.80 to 1.51)	
Aletti score						
<8	1.00	Ref	0.209	1.00	Ref	0.248
≥8	1.18	(0.91 to 1.54)		1.20	(0.88 to 1.64)	
CC-score						
CC-0	1.00	Ref	0.362	1.00	Ref	0.726
CC-1	1.16	(0.84 to 1.61)		1.07	(0.73 to 1.58)	
CRS						
CRS 1–2	1.00	Ref	<0.001	1.00	Ref	<0.001
CRS 3	0.53	(0.39 to 0.71)		0.42	(0.28 to 0.63)	

CC, complete cytoreduction; CRS, chemotherapy response score; FIGO, International Federation of Gynecology and Obstetrics; NACT, neoadjuvant chemotherapy; PCI, peritoneal cancer index; Ref, reference.

In multivariable analysis, chemotherapy response score 3 was the only factor independently associated with better disease-free survival (HR 0.53, 95% CI 0.39 to 0.71, p<0.001) and overall survival (HR 0.42, 95% CI 0.28 to 0.63, p<0.001) (Table 3). Among the 219 patients treated with three to four cycles of neoadjuvant chemotherapy, 20.5% (45 patients) achieved chemotherapy response score 3. A total of 146 patients received six cycles of neoadjuvant chemotherapy before delayed debulking surgery, and 43 patients (29.5%) achieved chemotherapy response score 3 (p=0.051). Response score 1 or 2 was significantly associated with a higher peritoneal cancer index, more extensive surgery, minimal residual disease, higher post-operative complications, and use of bevacizumab maintenance therapy. It was also associated with a higher early relapse rate within the 6 months (Table 2).

Regardless of the number of neoadjuvant chemotherapy cycles, score 1 or 2 was significantly associated with worse disease-free survival and overall survival (Figure 2, Online supplemental table 3). Median disease-free survival was 16.5 months (95% CI 13.9 to 18.4) and 15.9 months (95% CI 14.0 to 18.8) for patients with chemotherapy response score 1–2 and who received three to four

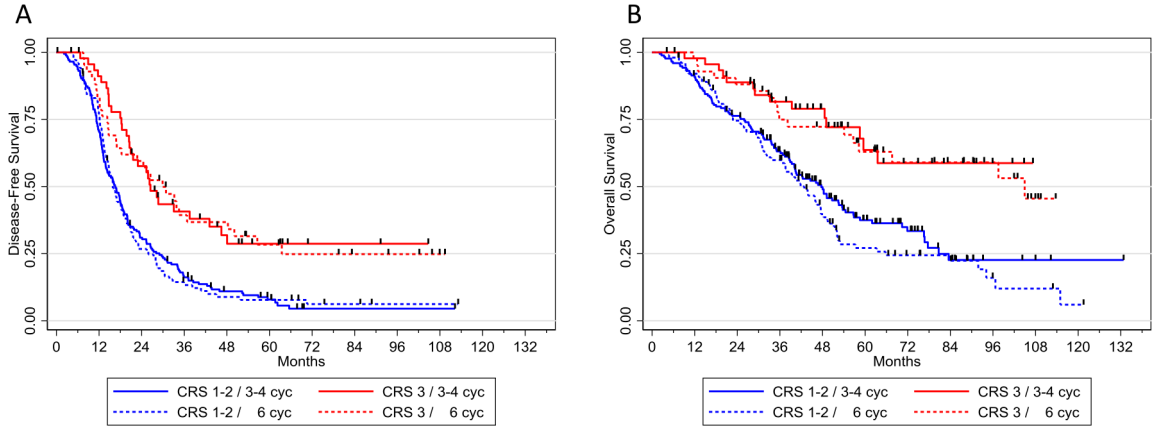

Figure 2 Disease-free survival (A) and overall survival (B) according to number of cycles and histological response assessed by chemotherapy response score (CRS) to neoadjuvant chemotherapy.

neoadjuvant chemotherapy cycles and six neoadjuvant chemotherapy cycles, respectively. Median disease-free survival was 26.5 months (95% CI 20.6 to 43.1) and 29.9 months (95% CI 17.0 to 48.3) for patients with score 3 and who received three to four neoadjuvant chemotherapy cycles and six neoadjuvant chemotherapy cycles, respectively. Disease-free survival rates were 29.5% and 58.6% (HR 0.47, 95% CI 0.36 to 0.63, p<0.001) in chemotherapy response score 1–2 and score 3 groups, respectively. Similarly, 24 months overall survival rates were 75.7% and 88.5% (HR 0.39, 95% CI 0.26 to 0.57, p<0.001) in chemotherapy response score 1–2 and chemotherapy response score 3 groups, respectively. Moreover, there were no significant differences in early relapses, disease-free survival or overall survival according to the number of neoadjuvant chemotherapy cycles in the subset of patients with chemotherapy response score 1–2 and chemotherapy response score 3 (Figure 2, online supplemental table 3, 4).

DISCUSSION

Summary of Main Results

The main finding of our study was that histopathological response, measured by the chemotherapy response score, has a survival impact irrespective of the number of neoadjuvant chemotherapy cycles. There was no significant difference in the rate of early relapses, disease-free and overall survival rates according to the number of neoadjuvant chemotherapy cycles. Regardless of the surgical timing, persistent extensive histological disease was significantly associated with a higher peritoneal cancer index, more extensive surgery, minimal residual disease, early relapses, and disease-free and overall survival rates. Indeed, patients with near complete or complete pathological response had approximately a 50% increase in disease-free survival compared with patients with omental tumor residue. These results validate the prognostic role of histopathologic response assessed by the chemotherapy response score after neoadjuvant chemotherapy, and support other findings.[21 22]

Furthermore, the 9% increase in pathologic response after six cycles did not translate into an increase in overall survival.

Results in the Context of Published Literature

Our results regarding the number of neoadjuvant chemotherapy cycles are in keeping with a retrospective study which showed that six cycles of neoadjuvant chemotherapy were safe, had equivalent survival rates to three cycles, and did not increase perioperative complications.[9] Similarly, Akladios et al reported that the number cycles of neoadjuvant chemotherapy did not seem to affect overall survival in patients with advanced ovarian cancer.[10] Phillips et al reported survival in patients undergoing ≤4 cycles and ≥5 cycles of neoadjuvant chemotherapy, showing that patients treated with >5 cycles achieved a lower rate of complete cytoreduction, with a higher rate of suboptimal cytoreduction, which was associated with a worse survival.[11] Yoneoka et al also compared patients undergoing interval debulking surgery after three cycles of neoadjuvant chemotherapy with those who had six cycles before delayed surgery without postoperative chemotherapy, showing equivalent survival in both groups.[12]

In contrast, other studies found that the number of preoperative chemotherapy cycles was negatively correlated with survival, suggesting that surgery should be performed as early as possible.[28] They hypothesized the progressive emergence of chemoresistant disease with the increasing number of neoadjuvant chemotherapy cycles. Colombo et al and Xu et al reported poorer prognosis in patients undergoing late surgery after more than four neoadjuvant chemotherapy cycles, even in the event of complete cytoreduction.[13 14] Moreover, in a recent study, Nitecki et al showed that residual disease, defined by an incomplete resection (but not by histopathological score), after neoadjuvant chemotherapy was associated with worse survival outcomes, regardless of the number of neoadjuvant chemotherapy cycles.[29] Thus, there appears to be a complex relationship between the number of neoadjuvant chemotherapy cycles, the completeness of resection, and survival outcomes. Our study only included patients with complete or near complete (CC-0 or CC-1) resection, with no significant difference in resection rates according to the number of cycles of neoadjuvant chemotherapy. However, the decision regarding the number of cycles of neoadjuvant chemotherapy was impacted by the clinical, biological, and imaging response to neoadjuvant chemotherapy and may have introduced a selection bias between both groups (3–4 vs >6 cycles). Achieving an optimal resection of all macroscopic disease should always be the ultimate goal in advanced ovarian cancer treatment, regardless of the number of neoadjuvant chemotherapy cycles. We decided to exclude patients with ≥2.5 mm (CC-2) residue to avoid the negative survival impact of tumor residue, which could influence the prognostic effect of other variables. We wanted a homogeneous cohort, but not including ≥2.5 mm (CC-2) residue may have led to a selection bias. We do not know if patients with delayed interval debulking surgery would have had more CC-2 residue. Indeed, our selection criteria probably affected the results of the study, as patients with a poor response to neoadjuvant chemotherapy and CC-2 resection were excluded.

The ongoing CHRONO (NCT03579394) prospective multi-institutional randomized study aims to define the best timing for cytoreductive surgery by comparing disease-free survival when surgery is performed after three or six courses of neoadjuvant chemotherapy, in patients initially unsuitable for primary surgery.

Concerning the chemotherapy response score, our results are in keeping with a recent study by Liontos et al assessing lymphocytic infiltration and the chemotherapy response score as prognostic markers in ovarian cancer patients treated with neoadjuvant chemotherapy followed by delayed surgery.[30] They showed the predictive value of the chemotherapy response score in epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and interval debulking surgery, but also demonstrated the prognostic significance of lymphocytic infiltration. The chemotherapy response score assessed at the omentum predicted progression-free survival when adjusted for age, stage, debulking status, and bevacizumab maintenance.

Our study confirms that the chemosensitivity of advanced epithelial ovarian carcinoma may be assessed by the chemotherapy response score. These results are in line with a meta-analysis conducted by Cohen et al including almost 900 patients. They reported that the chemotherapy response score was significantly associated with progression-free and overall survival and that patients with *BRCA1/2* mutations were more likely to achieve chemotherapy response score 3. They suggested that this score is a very useful biomarker and could be incorporated as a new

endpoint in clinical trials.[31] Similarly and recently, You et al also described that CA125 longitudinal kinetics strongly reflects chemosensitivity to first-line treatment and may be used as highly predictive and prognostic information for progression-free and overall survival.[32 33] No association between CA125 kinetics and chemotherapy response score was evaluated in our study.

Strengths and Weaknesses

This study included a large homogeneous cohort with 365 patients with long-term follow-up. To our knowledge, it is the first to demonstrate the prognostic value of histopathologic response irrespective of the number of neoadjuvant chemotherapy cycles. Histopathological responses were assessed using the validated and objective chemotherapy response score.[19 20] The main limitation is its retrospective design with the intrinsic risk of selection bias. Pathology reports were also reviewed retrospectively. Moreover, the chemotherapy response score was developed to reproducibly describe the response to neoadjuvant chemotherapy only in high-grade serous carcinomas, and our cohort had 24.7% of patients with a different subtype. Its value remains to be confirmed in other histological types. Indeed, given the relative chemoresistance of low-grade, clear-cell and mucinous ovarian cancer, our results may have been influenced by our selected population. Moreover, BRCA status was not collected and may also influence pathologic response and survival outcomes.

Implications for Practice and Future Research

This work may contribute to the current literature by showing that the histopathological response is associated with survival outcome, irrespective of the number of neoadjuvant chemotherapy cycles. This 'retrospective' information obtained after surgery adds additional prognostic information to adapt/intensify the treatment strategy and follow-up. Moreover, our findings confirm the strong prognostic relationship between the chemotherapy response score and survival, and that the chemotherapy response score may be used as a surrogate for chemosensitivity and as a useful endpoint for clinical trials.

CONCLUSION

Our study demonstrates the prognostic value of the validated chemotherapy response score in epithelial ovarian cancer patients treated with neoadjuvant chemotherapy. It also shows that histopathological response is significantly associated with disease-free and overall survival, irrespective of the number of neoadjuvant chemotherapy cycles.

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Supplementary Table 1. Chemotherapy response score according to *Böhm et al. JCO 2015.*

CRS 1	No or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci. Cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration.
CRS 2	Appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated fibro-inflammatory changes with multifocal residual tumor, which is easily identifiable.
CRS 3	Complete or near-complete response with no residual tumor OR minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm maximum size. Mainly regression-associated fibro-inflammatory changes or, in rare cases, no or very little residual tumor in complete absence of any inflammatory response. It is advisable to record whether there is no residual tumor or whether there is microscopic residual tumor present.

NOTE. Regression-associated fibroinflammatory changes consist of fibrosis associated with macrophages, including foam cells, mixed inflammatory cells, and psammoma bodies, as opposed to tumor-related inflammation or desmoplasia.

Supplementary Table 2. Univariable DFS and OS analysis for overall population (n=365)

	Disease-free survival			Overall survival		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age (years)						
≤ 60	1.00	Ref	0.784	1.00		0.386
>60	0.97	[0.77-1.21]		1.13	[0.86-1.48]	
Cycles of NACT						
3-4	1.00	Ref.	0.653	1.00	Ref.	0.562
6	0.95	[0.76-1.19]		1.08	[0.82-1.43]	
FIGO stage						
IIIC	1.00	Ref.	0.415	1.00	Ref.	0.826
IV	1.12	[0.86-1.45]		0.96	[0.69-1.34]	
Histological type						
Serous	1.00	Ref.	0.697	1.00	Ref.	
Other	0.91	[0.57-1.47]		0.91	[0.51-1.63]	0.750
PCI						
≤ 10	1.00	Ref.	**< 0.001**	1.00	Ref.	**0.012**
> 10	1.55	[1.24-1.94]		1.42	[1.08-1.86]	
Aletti score						
< 8	1.00	Ref.	**< 0.001**	1.00	Ref.	**0.005**
≥ 8	1.50	[1.20-1.88]		1.48	[1.12-1.94]	
CC-score						
CC-0	1.00	Ref.	**0.033**	1.00	Ref.	0.145
CC-1	1.41	[1.03-1.95]		1.32	[0.91-1.93]	
CRS						
CRS 1-2	1.00	Ref.	**<0.001**	1.00	Ref.	**< 0.001**
CRS 3	0.47	[0.36-0.63]		0.39	[0.26-0.57]	

HR: hazard ratio

95% CI: 95% confidence interval

NACT: neoadjuvant chemotherapy

FIGO: International Federation of Gynecology and Obstetrics

PCI: peritoneal cancer index

CC-score: completeness cytoreduction score

CRS: chemotherapy response score

Supplementary Table 3. Disease-free survival and overall survival according to number of cycles and histological response to NACT.

	CRS 1-2	**CRS 3**	**p-value**
Disease-free survival *(median, months, 95%CI)*			
• *3-4 NACT*	16.5 (13.9-18.4)	26.5 (20.6-43.1)	**<0.001**
• *6 NACT*	15.9 (14.0-18.8)	29.9 (17.0-48.3)	**<0.001**
Overall survival *(median, months, 95%CI)*			
• *3-4 NACT*	47.7 (40.0-53.7)	NR (58.5-NR)	**0.001**
• *6 NACT*	42.9 (33.5-47.5)	104.9 (56.7-NR)	**<0.001**

NACT: neoadjuvant chemotherapy

Supplementary Table 4. Platinum resistance, DFS and OS according to timing of surgery in a. CRS 1-2; b. CRS3.

a. CRS 1-2

	3-4 cycles N = 174	**6 cycles N = 103**	**p-value**
Relapse < 6 months, n (%)	45 (26.8)	25 (26.0)	**0.895**
Missing	*6 (-)*	*7 (-)*	
Disease free survival *(median, 95%CI months)*	16.5 (13.9-18.4)	15.9 (14.0-18.8)	**0.929**
Overall survival *(median, 95%CI months)*	47.7 (40.0-53.7)	42.9 (33.5-47.5)	**0.212**

b. CRS 3

	3-4 cycles N = 45	**6 cycles N = 43**	**p-value**
Relapse < 6 months, n (%) *Missing*	3 (6.7) *0 (-)*	6 (14.3) *1 (-)*	**0.304**
Disease-free survival *(median, 95%IC, months)*	26.5 (20.6-43.1)	29.9 (17.0-48.3)	**0.890**
Overall survival *(median, months)*	NR	NR	**0.790**

NR: not reached

Supplementary Figure 1. Flow chart of the eligible and the included patients.