Post-operative residual disease and number of cycles of neoadjuvant chemotherapy in advanced epithelial ovarian carcinoma

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ABSTRACT

Background The optimal number of neoadjuvant chemotherapy cycles in patients with advanced ovarian cancer is still disputed.

Objective To evaluate the impact of the number of neoadjuvant chemotherapy cycles and role of optimal cytoreduction on the prognosis of patients with advanced ovarian cancer.

Methods Clinical and pathological details were examined. Patients were evaluated combining the number of cycles of neoadjuvant chemotherapy—namely, 'interval debulking surgery' after up to four neoadjuvant chemotherapy cycles, and 'delayed debulking surgery' after more than four cycles of therapy.

Results A total of 286 patients were included in the study. Complete cytoreduction with no residual peritoneal disease (CC0) was achieved in 74 (74%) patients with interval debulking surgery and 124 (66.7%) patients with delayed interval debulking. Of those with residual disease, there were 26/88 (29.5%) patients in the interval debulking surgery group and 62/88 (70.5%) patients in the delayed debulking surgery group. Comparison of patients with delayed debulking-CC0 and interval debulking-CC0 showed no difference in progression-free survival (p=0.3) or overall survival (p=0.4), while significantly worse outcomes were observed in patients with interval debulking-CC1 (p=0.02 and p=0.04, respectively). Specifically, patients with interval debulking-CC1 had an approximately 67% increased risk of disease progression (p=0.04; HR=2.01 (95% CI 1.04 to 4.18)) and a 69% higher risk of death than patients with delayed debulking-CC0 (p=0.03; HR=2.34 (95% CI 1.11 to 4.67)).

Conclusion Increasing the number of neoadjuvant chemotherapy cycles does not worsen patient outcomes if complete resection is achieved. Nevertheless, additional prospective trials are necessary to establish the optimum number of neoadjuvant chemotherapy cycles.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The current recommendation for patients responding to neoadjuvant chemotherapy is to perform surgery after ≤4 neoadjuvant chemotherapy cycles. However, data about the optimal number of neoadjuvant chemotherapy cycles are discordant, with no general consensus reached.

WHAT THIS STUDY ADDS

⇒ Residual disease after surgery is the most important parameter for progression-free survival and overall survival and delaying surgery does not worsen patient outcomes if complete surgical resection is achieved. Residual disease, even if minimal, significantly worsens patient survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings might aid clinicians' choice when deciding on surgical timing in patients with ovarian cancer.

INTRODUCTION

Ovarian, fallopian, and primary peritoneal cancer ovarian cancer is an uncommon but lethal disease, being the eighth leading cause of death from neoplasia in women worldwide according to data from the American Cancer Society.[1] In Italy it is detected at advanced stages (International Federation of Gynecology and Obstetrics (FIGO) stage III/IV) in 75–80% of cases, leading to a 5- year overall survival rate of 43%.[2]

In recent years, the extension to the upper abdomen of primary debulking surgery combined with adjuvant chemotherapy has improved the prognosis of patients with carcinomatosis and is now considered the most effective treatment in patients deemed operable based on their baseline clinical conditions and disease extension at initial diagnosis.[3 4] Another option to reduce the tumor burden is neoadjuvant chemotherapy with subsequent interval debulking surgery, usually offered in cases of poor surgical candidates or with a low likelihood of complete cytoreduction. Neoadjuvant chemotherapy, in addition to the higher rate of complete cytoreduction, allows for less extensive surgical procedures, fewer post-operative complications, and is an *in vivo* test for assessing sensitivity to chemotherapy.[5 6] However, it may also be an option worth considering in patients with high tumor load in whom primary debulking surgery would

be too aggressive as evidenced by the SCORPION study. In these cases, neoadjuvant chemotherapy and interval debulking surgery are not inferior for progression-free survival and overall survival, as they have the advantage of fewer complications.[4]

Guidelines[7] suggest three to four cycles of neoadjuvant chemotherapy, followed by both clinical and radiological reassessment prior to interval debulking surgery, which is followed by an additional three cycles of chemotherapy. This number of cycles has been arbitrarily established, believing that fewer cycles result in better survival, as shown in the Bristow meta-analysis and according to the EORTC 55971 and CHORUS trials.[8 9] Moreover, patients not yet eligible for surgery either because of performance status or poor response to chemotherapy continue neoadjuvant chemotherapy for a total of at least six cycles until surgery (delayed interval debulking).[10] Data that evaluated the overall survival of interval debulking surgery and delayed debulking surgery are controversial, with some studies showing similar survival and others worse in delayed debulking surgery.[11–13]

Residual disease after primary debulking surgery and interval debulking surgery is recognized as the major prognostic factor, as it strongly impacts both progression-free survival and overall survival.[14 15] Thus, optimal debulking surgery is unequivocally advocated whenever possible to ensure the best possible outcome.[16] Today most authors consider optimal cytoreduction as macroscopically absent residual tumor.[17] Achieving this result is highly dependent on the biology of the disease, especially its sensitivity to chemotherapy. However, finding a balance between the optimal number of neoadjuvant chemotherapy cycles and the optimal cytoreduction is still debated, and current data are heterogeneous and discordant.[18–20] The purpose of this study was to analyze the impact of different cycles of neoadjuvant chemotherapy associated with residual disease on progression-free survival and overall survival of patients with advanced ovarian cancer.

METHODS

Study Design and Population

This retrospective, observational study was approved by the ethics committee of Area Vasta Emilia Centro under EC CODE 524/2022/Oss/AOUBo and was conducted in accordance with all the requirements of the Good Clinical Practice Guidelines and the ethical principles of the 1964 Declaration of Helsinki (World Medical Association).[21] The study population comprised patients diagnosed with ovarian cancer with FIGO stages IIIB–IVA and treated with neoadjuvant chemotherapy with platinum and paclitaxel following the standard of care scheme.[22]

Inclusion criteria were as follows: pathological diagnosis of ovarian cancer with high-grade serous or endometrioid histology; platinum-based treatment according to standard guidelines; exploratory laparoscopy or laparotomy for surgical assessment to establish patients' operability[23]; minimum follow-up of 12 months. The exclusion criteria were: patients under 18 years of age; low-grade, mucinous, clear-cell, and carcinosarcoma histotype; synchronous or previous cancer history in the past 5 years; patients deemed 'frail' and unfit for surgery owing to a health condition based on geriatric or anesthesiologic assessment at the date of the first diagnosis; intraperitoneal hyperthermic chemotherapy following neoadjuvant chemotherapy; HIV-positive subjects on anti-retroviral treatment, cirrhosis; and involvement in interventional research protocols.

Data Collection

Clinical, pathological, and surgical data were retrieved for all patients. Patients were divided into four groups based on the number of cycles of neoadjuvant chemotherapy ('interval debulking', after up to four cycles; 'delayed debulking', after at least six cycles) and residual disease (CC0: no macroscopical residual disease; CC1: minimal residual disease less than 2.5 mm, CC2: residual disease between 2.5 mm and 2.5 cm, CC3: extended residual disease more than 2.5 cm. CC≥1 includes all patients with residual disease). Typically, patients in the interval debulking surgery group received additional adjuvant chemotherapy for a total of at least six cycles, while the delayed debulking surgery group had at least six cycles of systemic treatment before surgery and another three cycles after. Further details about the data collection can be found in the online supplemental methods.

Statistical Analysis

Descriptive statistics were reported for all variables. Depending on the type of variable, X^2, Fisher exact tests, analysis of variance, and Kruskal-Wallis tests were used to analyze the differences between patient groups. Progression-free and overall survival were analyzed using the log-rank test while the impact of variables on patient's prognosis was evaluated using the Cox proportional hazard model. Results with a p value ≤0.05 were considered statistically significant.

RESULTS

Population Characteristics

From a total of 1317 identified patients who were diagnosed with ovarian cancer, 1031 patients did not meet the selected requirements and were excluded (Figure 1). A total of 286 patients diagnosed between July 1999 and December 2019 were included in the study, among which 100 patients underwent interval debulking surgery, and 186 patients underwent delayed debulking surgery (Online supplemental table s1). Complete cytoreduction with no residual peritoneal disease (CC0) was achieved in 198 (69.2%) of all patients, 74 patients (37.4%) in the interval debulking surgery group, 124 patients (62.6%) in the delayed debulking surgery group. Eighty-eight patients (30.8%) had post-operative residual disease, of whom 26 patients (29.5%) were in the interval debulking surgery group and, 62 patients (70.5%) in the delayed debulking surgery group (Figure 1). The baseline characteristics of the four groups showed no differences in the demographic and clinical parameters. In particular, ovarian cancer stage at diagnosis was uniformly distributed (p=0.29), and the majority of patients presented with serous histotype (p=0.08) (Online supplemental table s1). A total of 95 (37.5%) patients received bevacizumab and 22 (8.7%) patients received poly-(ADP-ribose)-polymerase (PARP) inhibitors as part of the adjuvant chemotherapy scheme (Online supplemental table s1).

Surgical Analysis

For surgical parameters, 115 (62.1%) patients were judged unresectable by laparoscopy after 3–4 cycles of neoadjuvant

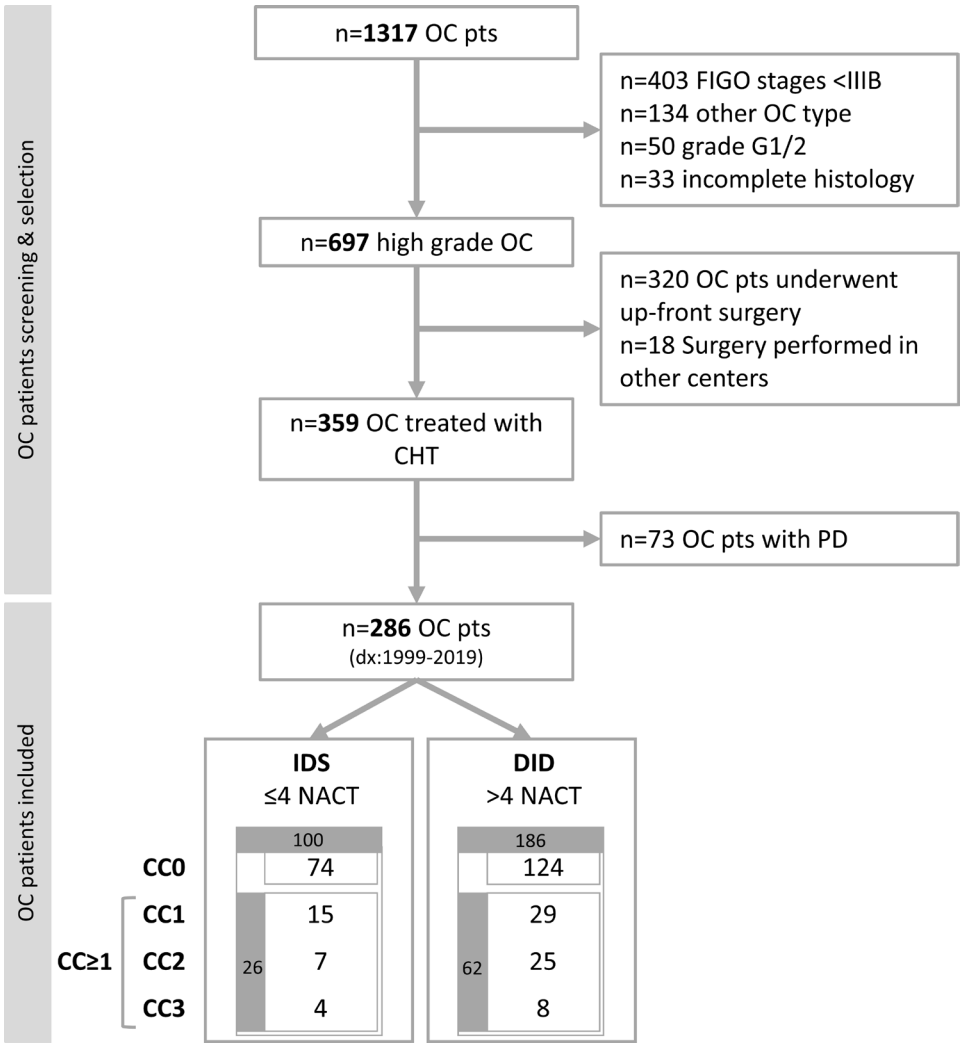

Figure 1 Screening of patients included in the study. CC0, no residual disease after cytoreduction surgery; CC≥1, residual disease after cytoreduction surgery (comprising CC1, CC2, and CC3); CHT, chemotherapy; DID, delayed debulking surgery (>4 NACT cycles); FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery (≤4 NACT cycles); NACT: neoadjuvant chemotherapy; OC, ovarian carcinoma; PD, progressive disease.

chemotherapy. The peritoneal cancer index after neoadjuvant chemotherapy was correlated with the degree of residual disease after surgery (p<0.001), with the lowest score recorded in patients with delayed interval debulking-CC0, while there was no difference between patients with interval debulking-CC≥1 and delayed interval debulking-CC≥1. The Aletti score was similar between patients with interval debulking-CC0 and those with delayed interval debulking-CC0, while a lower score was observed in the interval debulking-CC≥1 and delayed interval debulking-CC≥1 groups (p<0.001) (Online supplemental table s1). No association was found between the number of neoadjuvant chemotherapy cycles and the resulting completeness of cytoreduction score (Online supplemental table s2).

Progression-free and Overall Survival

Median follow-up was 5.2 years (IQR 3.18–8.58). During this time frame both progression-free survival and overall survival were significantly different among groups (Figure 2A, Online supplemental figure s1A). The 5- year progression-free survival rate was 27% in the interval debulking-CC0 group, and 18% in the delayed interval debulking-CC0 group, while in patients with interval debulking-CC≥1 and delayed interval debulking-CC≥1, these rates were significantly lower, 8% and 3% respectively (p<0.001) (Online supplemental table s1, Figure 2A). Cumulative overall survival at 5 years demonstrated that patients with interval debulking-CC0 and delayed interval debulking-CC0 had significantly higher survival rates than patients with interval debulking-CC≥1 and delayed interval debulking-CC≥1 (median 7.74 and 4.87 vs 2.76 and 2.29 years; respectively p<0.001). In detail, 50% of patients with interval debulking-CC0 and 43% of those with delayed interval debulking-CC0 were alive (p=0.4). As expected, the worst 5- year survival rates were observed in patients with interval debulking-CC≥1 and delayed interval debulking-CC≥1, 20% and 19% respectively (Online supplemental table s1, Figure 2A). These unfavorable results of both progression-free survival and overall survival were also observed in patients with CC1; specifically, interval debulking-CC1 had significantly lower progression-free survival and overall survival with respect to delayed interval debulking-CC0 (median 1.94 vs 2.29 years, p=0.02 and 2.73 vs 4.87 years, p=0.04, respectively) (Figure 2B).

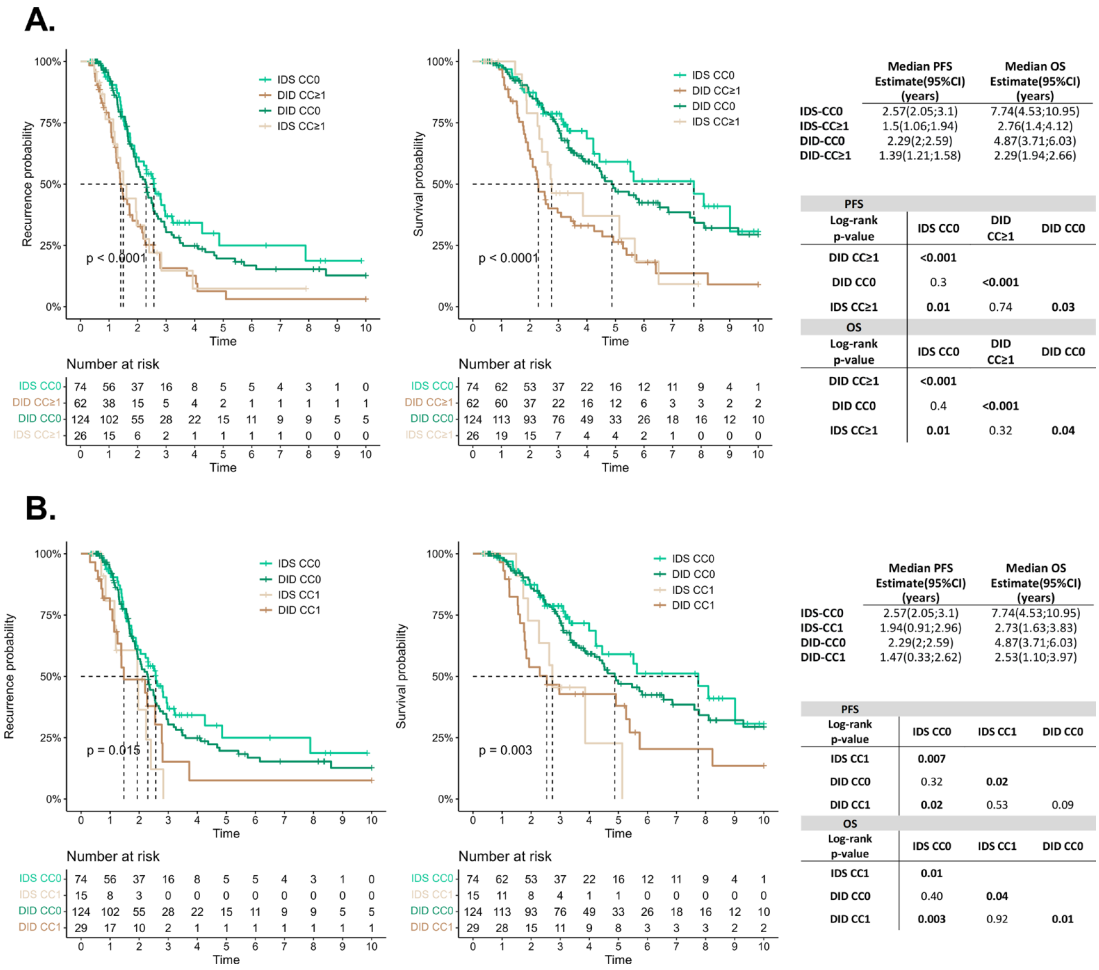

Figure 2 Progression-free survival and overall survival of patients with advanced ovarian cancer included in this study. Time is measured in years. IDS, interval debulking surgery after ≤4 NACT cycles; DID, delayed debulking surgery after >4 NACT cycles; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival.

To eliminate the possible bias introduced by the presence of chemosensitive patients, we performed the same analyses on the chemoresistant patients only (chemotherapy response score 1/2), further confirming our results (Figure 3A,B). Again, the best outcomes were seen in patients with CC0: median progression-free survival of 2.56 years in the case of interval debulking-CC0 and 2.36 years in the case of delayed interval debulking-CC0, while for overall survival, 4.22 years for interval debulking-CC0 and 5.71 years for delayed interval debulking-CC0. Patients with interval debulking-CC1 had decreased progression-free survival and overall survival of 1.94 and 2.62 years, respectively (Figure 3, Online supplemental figure s1B).

Univariable analysis identified residual disease as a strong predictor of both worse progression-free survival and overall survival (p<0.001 for both) (Table 1), whereas receiving more than four neoadjuvant chemotherapy cycles was not significantly associated with a patient's outcome. In patients with CC0, delaying surgery did not impact either progression-free survival or overall survival (p=0.34; HR=0.83 (95% CI 0.57 to 1.22)) and p=0.37; HR=0.81 (95% CI 0.51 to 1.29), respectively). Patients with interval debulking-CC1, on the other hand, had worse outcomes than those with delayed interval debulking-CC0 (p=0.04; HR=2.01 (95% CI (1.04 to 4.18)) (Table 1).

Multivariable analysis revealed that patients with CC≥1 had a worse outcome for both progression-free survival and overall survival. This was also seen when considering the amount of residual disease. Specifically, interval debulking-CC1 patients had approximately 67% increased chances of disease progression (p=0.04; HR=2.01 (95% CI 1.04 to 4.18)) and a 69% higher risk of death than patients with delayed surgery but in which CC0 was achieved (p=0.03; HR=2.34 (95% CI 1.11 to 4.67)) (Table 2).

DISCUSSION

Summary of Main Results

Our study showed that delayed interval debulking-CC0 was not associated with worse progression-free survival and overall survival compared with interval debulking-CC0, whereas patients with interval debulking-CC1, had a significantly worse outcome than those with delayed interval debulking-CC0. This finding suggests that achieving complete cytoreduction is more important than the numbers of administered neoadjuvant chemotherapy cycles.

Results in the Context of Published Literature

The current recommendation is to perform surgery after three or maximum four cycles of neoadjuvant chemotherapy for patients

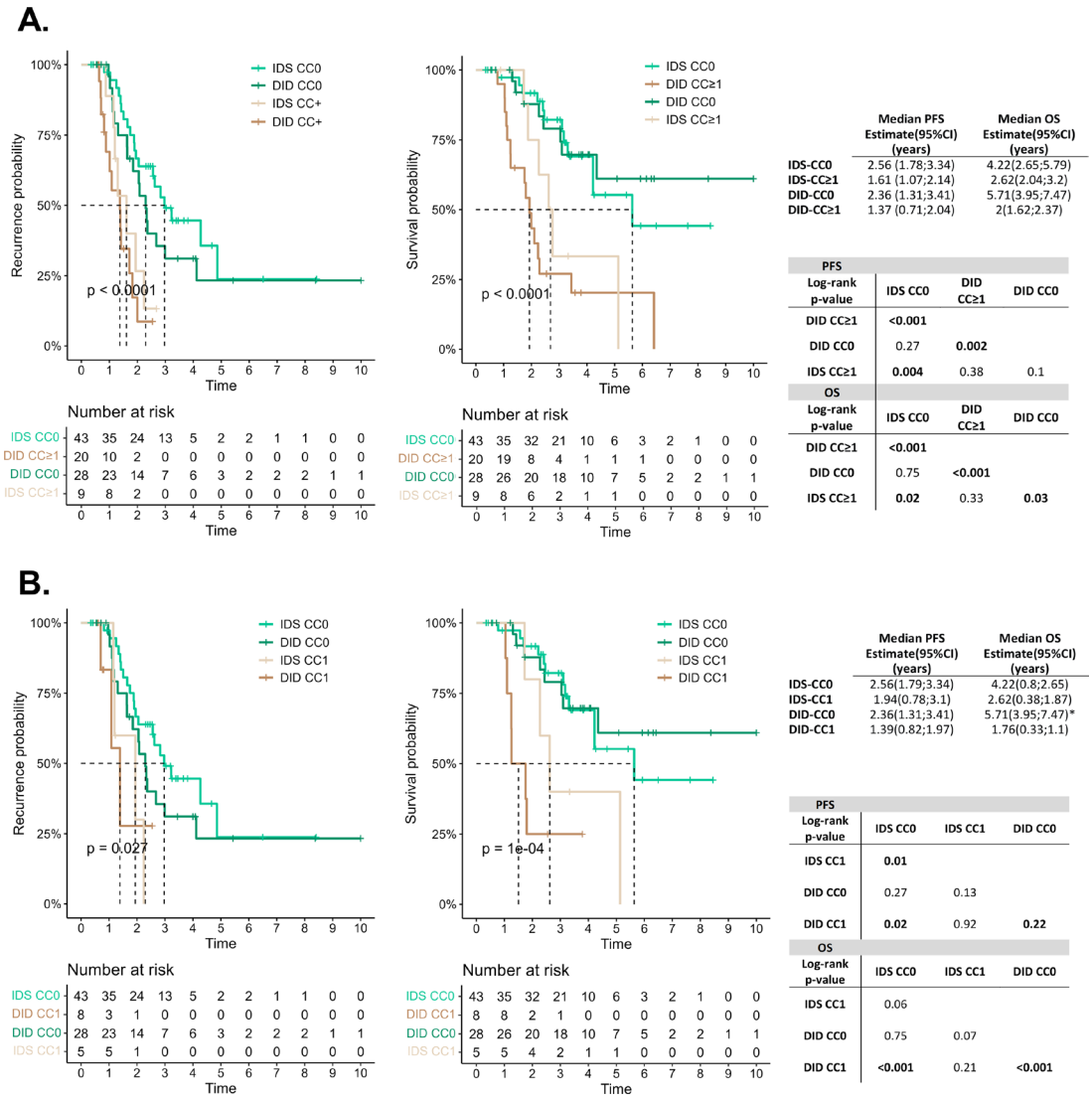

Figure 3 Progression-free survival and overall survival of patients with advanced ovarian cancer exhibiting a chemotherapy response score of 1 or 2. Time is measured in years. DID, delayed debulking surgery after >4 NACT cycles; IDS, interval debulking surgery after ≤4 NACT cycles; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival. *Estimation was limited to the largest survival censored time.

who are responding to treatment,[7] as the maximum outcome is achievable when interval debulking surgery is performed at this time.[24] Moreover, data about the number of neoadjuvant chemotherapy cycles are discordant. Some studies[25 26] reported that patients who had received >4 cycles of neoadjuvant chemotherapy had worse survival than those who received ≤4 cycles, so much so that they were discouraged from having surgery and especially aggressive surgery although potentially with maximal outcomes.

This poor outcome requires further discussion since in most cases, data regarding the survival of patients undergoing over four cycles are difficult to evaluate due to the presence of biases.[7] For instance, six or more cycles of neoadjuvant chemotherapy are frequently used in frail and old patients with many co-morbidities and such parameters are always a justification for not performing surgery after three cycles.[27] On the contrary, some authors have postulated that interval debulking surgery could be delayed for six or more cycles without detrimental consequences for long-term survival[28 29] and that residual disease is the main driver for successful outcome even in late neoadjuvant chemotherapy.[30]

Yao et al showed on 337 cases of interval debulking-CC0 and 46 of delayed interval debulking-CC0, that achieving cytoreduction without macroscopic residual disease remains imperative regardless of the number of neoadjuvant chemotherapy cycles, with similar progression-free survival (median months 26 vs 37) and overall survival (median months 49 vs 51).[31] Our study confirmed these results with similar progression-free survival (median months 30.8 vs 27.5) and overall survival (median months 92.8 vs 58.4) in interval debulking-CC0 versus delayed interval debulking-CC0, respectively. This was achieved in a much larger number of patients with delayed debulking surgery (186 in our study), with more homogeneous tumor type and grade and most importantly, with a uniform strategy for selection of surgical timing.

Certainly, the best outcomes in this setting are always observed in the interval debulking-CC0 group, but this is not necessarily due

Table 1 Univariable analysis of parameters impacting the prognosis of patients with advanced ovarian cancer

Variables			Univariable analysis			
			PFS		OS	
			P value	Hazard ratio (95.0% CI)	P value	Hazard ratio (95.0% CI)
Age (years)			0.7	1 (0.99 to 1.02)	0.04	1.02 (1 to 1.04)
Age	<50	n=44		ref		ref
	51–60	n=67	0.21	1.35 (0.77 to 2.35)	0.28	1.35 (0.84 to 2.16)
	61–70	n=115	0.88	0.97 (0.69 to 1.96)	0.56	1.16 (0.62 to 1.5)
	>70	n=60	0.1	1.36 (1.09 to 3.35)	0.02	1.92 (0.84 to 2.24)
BMI	Normal weight	n=146		ref		
	Overweight	n=77	0.76	1.1 (0.75 to 1.48)	0.27	0.79 (0.47 to 1.07)
	Obese	n=42	0.99	1 (0.64 to 1.59)	0.55	1.16 (0.71 to 1.84)
	Underweight	n=11	0.73	0.86 (0.38 to 1.98)	0.27	1.51 (0.73 to 3.11)
Stage (FIGO 2014)	IIIB	n=11		ref		ref
	IIIC	n=216	0.12	0.61 (0.33 to 1.14)	0.74	1.15 (0.51 to 2.62)
	IV	n=59	0.56	0.82 (0.42 to 1.61)	0.33	1.54 (0.64 to 3.7)
Number of NACT cycles	>4	n=186	0.19	1.23 (0.9 to 1.68)	0.12	1.34 (0.92 to 1.94)
Residual disease	CC≥1	n=88	<0.001	2.06 (1.51 to 2.81)	<0.001	2.25 (1.62 to 3.14)
Residual disease (CC score)	0	n=198		ref		ref
	1	n=44	0.005	1.83 (1.2 to 2.79)	0.001	2.09 (1.35 to 3.2)
	2/3	n=44	<0.001	2.29 (1.56 to 3.36)	<0.001	2.56 (1.7 to 3.84)
Patient group	DID-CC0 NACT>4	n=124		ref		ref
	IDS-CC0 NACT≤4	n=74	0.34	0.83 (0.57 to 1.22)	0.37	0.81 (0.51 to 1.29)
	IDS-CC≥1 NACT≤4	n=26	<0.001	2.01 (1.39 to 2.91)	<0.001	2.29 (1.57 to 3.36)
	DID-CC≥1 NACT>4	n=62	0.04	1.75 (1.04 to 2.96)	0.03	1.9 (1.06 to 3.41)
Patient group	DID-CC0 NACT>4	n=124		ref		ref
	IDS-CC0 NACT≤4	n=74	0.34	0.83 (0.57 to 1.22)	0.37	0.81 (0.51 to 1.29)
	IDS-CC1 NACT≤4	n=15	0.04	2.01 (1.04 to 4.18)	0.03	2.34 (1.11 to 4.67)
	DID-CC1 NACT>4	n=29	0.08	1.58 (0.95 to 2.64)	0.01	1.91 (1.16 to 3.14)
	IDS-CC2/3 NACT≤4	n=11	0.29	1.49 (0.72 to 3.07)	0.32	1.54 (0.66 to 3.56)
	DID-CC2/3 NACT>4	n=33	<0.001	2.49 (1.6 to 3.9)	<0.001	2.74 (1.73 to 4.35)

BMI, body mass index; CC, completeness of cytoreduction score; DID, delayed debulking surgery; FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; N, number of patients; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression free survival.

to the fewer neoadjuvant chemotherapy cycles, but probably rather to a more chemosensitive tumor. Thus, these patients are intrinsically biologically different from those who need more cycles in order to obtain the same favorable outcome.[32] Moreover, interval debulking-CC1 might include both patients slowly responding to neoadjuvant chemotherapy in which CC0 would be eventually achieved after an increased number of neoadjuvant chemotherapy cycles, and patients who would never reach CC0 despite multiple cycles because they are non-responders. This aspect also highlights another unmet clinical need, that of discovering effective markers that can predict overall neoadjuvant chemotherapy response.

Some cancers require a longer time of exposure to chemotherapy to manifest their platinum sensitivity as proposed by the Goldie-Coldman hypothesis,[33] although in a recent work, Bétrian et al showed that six cycles of chemotherapy were associated with a modest increase of only 9% in pathologic response, which did not

Table 2 Multivariable analysis of parameters impacting progression-free survival and overall survival of patients with advanced ovarian cancer

Multivariable 1		**PFS**		**OS**	
Overall significance		p<0.001		p<0.001	
Variable		**P value**	**HR (95.0% CI)**	**P value**	**HR (95.0% CI)**
Age (years)		0.67	1 (0.99 to 1.02)	0.1	1.01 (0.99 to 1.03)
Patient group	DID-CC0 NACT>4		ref		ref
	IDS-CC0 NACT≤4	0.36	0.84 (0.57 to 1.23)	0.4	0.82 (0.51 to 1.3)
	DID-CC≥1 NACT>4	<0.001	2.02 (1.4 to 2.93)	<0.001	2.26 (1.55 to 3.31)
	IDS-CC≥1 NACT≤4	0.03	1.76 (1.04 to 2.98)	0.04	1.87 (1.04 to 3.36)
Multivariable 2					
Overall significance		<0.001		<0.001	
Variable					
Age (years)		0.73	1 (0.99 to 1.02)	0.11	1.01 (0.99 to 1.03)
Patient group	DID-CC0 NACT>4		ref		ref
	IDS-CC0 NACT≤4	0.36	0.84 (1.04 to 4.19)	0.4	0.82 (0.51 to 1.3)
	IDS-CC1 NACT≤4	0.04	2.09 (1.04 to 4.19)	0.03	2.27 (1.08 to 4.79)
	DID-CC1 NACT>4	0.08	1.59 (0.95 to 2.66)	0.01	1.89 (1.15 to 3.12)
	IDS-CC2/3 NACT≤4	0.27	1.5 (0.72 to 3.11)	0.31	1.54 (0.66 to 3.56)
	DID-CC2/3 NACT>4	<0.001	2.5 (1.6 to 3.91)	<0.001	2.69 (1.69 to 4.26)

CC, completeness of cytoreduction score; DID, delayed debulking surgery; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival.

translate to a survival benefit of these patients.[34] Our study cannot respond to this issue because the pursuit of chemotherapy treatment to complete the six courses was never offered to operable patients. Indeed, to answer this question two prospective randomized trials, GOGER (NCT02125513) and CHRONO (NCT03579394) are ongoing.

The importance of achieving no residual disease was emphasized by a recent Cochrane analysis,[17] as a major prognostic factor of patients' survival. This was especially the case for interval debulking surgery, in which minimal or greater residual disease were equally detrimental. Moreover, they highlighted the need for multiple studies stratifying patients into relevant and better-defined classes of residual disease as well as neoadjuvant chemotherapy, as grouping renders analyses and interpretations challenging. Indeed, the results of our analysis showed that even minimum postoperative residual disease resulted in a significant drop in survival (median months: 32.7 in interval debulking-CC1 versus 58.4 in delayed interval debulking-CC0). As a result, surgery in patients with with any residual disease should be avoided, possibly by continuing neoadjuvant chemotherapy until completion of scheduled cycles, increasing the chances of obtaining an improvement in survival.

Strengths and Weaknesses

The strengths of the current study include: (1) our unit is an ESGO-certified[35] center for ovarian cancer treatment and it is the third-largest ovarian cancer center in Italy, being classified as a level III hub of maximum expertise, according to the Italian Ministry of Health 2022 data and further recognized as a center of excellence for women's care by the ONDA Foundation; (2) it is a single-center study, and thus patients' clinical management was homogeneous as the surgical timing was always decided by the same team who perform more than 100 ovarian cancer surgeries/year; (3) patients who underwent six cycles of neoadjuvant chemotherapy were certainly inoperable after 3–4 cycles because they were evaluated by computer tomography, CA-125, and laparoscopy; and (4) patient groups had similar baseline characteristics.

Our analysis had several limitations including its retrospective nature. This possibly affects survival rate comparisons, as data such as detailed information regarding the toxicity of adjuvant treatments are unavailable, which might have led to treatment interruptions, with consequent impacts on disease recurrence. Moreover, the presence of BRCA mutations, a factor known to be associated with patients' response to chemotherapy, was unavailable for a considerable number of patients since it was only recently introduced in clinical practice.

Implications for Practice and Future Research

Currently, surgery is recommended after three or maximum four cycles of neoadjuvant chemotherapy in responding patients.[7] Moreover, studies on the appropriate number of cycles before surgery are lacking. In our study we found that surgery with absent residual disease after more than four cycles is not detrimental for patient survival. Therefore, performing surgery just to ensure fewer neoadjuvant chemotherapy cycles, might not be an optimal choice as previously reported in literature.[25 26] This implies that studies with more neoadjuvant chemotherapy cycles associated with no residual disease are advocated not only in frail patients as performed in the past. Nevertheless, additional prospective trials are necessary to

establish the exact number of neoadjuvant chemotherapy cycles and to confirm our findings.

CONCLUSION

Our study highlights the importance of residual disease after surgery in patients with advanced ovarian cancer undergoing neoadjuvant chemotherapy. Moreover, increasing the number of neoadjuvant chemotherapy cycles does not worsen patient outcomes as long as complete surgical resection is achieved.

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Contributors All authors provided substantial contributions to the final manuscript and had the opportunity to review and approve the planned submission. AMP, CAC, GR, PDI: methodology, investigation, data curation, writing – original draft, writing – review and editing, visualization, project administration. CAC, GR, ADL, EDC, MT, SDC: methodology, investigation, data curation, writing – review and editing. AMP, PDI: conceptualization, methodology, investigation, writing – review and editing, supervision, project administration, funding acquisition. CAC: validation, formal analysis, visualization. AMP, CAC, GR, ADL, GD, EDC, MT, SDC, LG, DR, CZ, PDI: writing – review and editing.

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