Interval debulking surgery after neoadjuvant chemotherapy in advanced ovarian cancer - retrospective study comparing surgery after 3 cycles or more of chemotherapy

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Title: INTERVAL DEBULKING SURGERY AFTER NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CANCER - RETROSPECTIVE STUDY COMPARING SURGERY AFTER 3 CYCLES OR MORE OF CHEMOTHERAPY

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Abstract

Objective – To evaluate and compare overall survival and progression-free survival in two groups of patients with advanced ovarian cancer, managed by neoadjuvant chemotherapy (3 cycles or more) followed by interval debulking surgery. Secondary objectives regarded surgical morbidity and extent of cytoreduction.

Material and Methods – We conducted a retrospective study, in a referral center, evaluating the management of patients diagnosed with advanced ovarian cancer (FIGO IIIC-IV) beneficiating of interval surgery after neoadjuvant chemotherapy. We compared two groups, one in which patients underwent 3 cycles of chemotherapy before surgery, and a second group in which patients underwent more than 3 cycles.

Results – 140 patients underwent interval surgery after neoadjuvant chemotherapy. Among these patients, 45 patients underwent 3 or less cycles (group 1) and 95 patients more than 3 cycles (group 2). There was no statistical difference for overall and progression free survival. The mean overall survival was 58,4 months for group 1 and 58,3 for group 2 (p.value = 0.56). The mean progression free survival was 30,5 months for group 1 and 23,8 months for group 2 (p.value = 0.17). More posterior pelvectomies were realized in group 1 compared to group 2 with a statistically significant difference (p=0,01). There was no difference regarding complete macroscopic difference during the surgery between the 2 groups (p=0,09).

Conclusion – Debulking surgery is an invasive and heavy procedure and is not always possible in first line. Neoadjuvant chemotherapy followed by interval debulking surgery is an accepted alternative. The number of administered cycles is questionable, and does not seem to have a significant impact on overall survival and progression free survival. However, surgical morbidity is significantly reduced by increased cycles of chemotherapy.

Introduction

Ovarian cancer is the most lethal gynecologic cancer in developed countries[1]. Worldwide, it is responsible for 150 000 women deaths per year for an annual incidence of about 200 000[2]. Epithelial ovarian cancer represents 95% of all ovarian cancer. Genomic predisposition is now well recognized in up to 15% of affected women. Survival rates for ovarian cancer have changed modestly for decades,

and remain at 45 % 5 years after diagnosis[2]. One of the main factors contributing to the high death to incidence rate is the advanced stage of the disease at time of diagnosis, due to the absence of specific early symptoms. About 75% of the diagnosis are made at FIGO Stage III or IV.
The standard of care for ovarian cancer has been primary debulking surgery followed by platinum-based chemotherapy. Complete resection of all macroscopic disease at primary debulking surgery has been shown to be the single most important independent prognostic factor for survival in advanced ovarian carcinoma.[3][4] [5][6][7]
Interval debulking surgery was initially developed in the 1980's as a salvage strategy for patients who had received suboptimal primary surgery[8][9]. Later on, in the management of ovarian cancer, IDS became defined as debulking surgery after the administration of neoadjuvant chemotherapy in order to reduce tumor size thus reducing surgical morbidities.
The approach of neoadjuvant chemotherapy before attempting debulking surgery has been accepted and is now recommended since 2016 by the American Society of Oncology in advanced ovarian cancer not suitable for complete primary debulking surgery (stage IV ovarian cancer, very high metastatic tumor load, or in patients with a poor general condition)[10][11].
For patients receiving neoadjuvant chemotherapy, the number of cycles that should be administered before the interval debulking surgery and that is associated with the best results on overall survival has not yet been determined. Studies have showed heterogenous and opposite results concerning complete cytoreduction and overall survival when comparing early (≤4 cycles) and late (> 4cycles) interval debulking surgery[12][13][14].
Thus, the association between the number of cycles of neoadjuvant chemotherapy before interval debulking surgery and the time of optimal surgery is still questionable.
The aim of this retrospective study was to compare two groups of patients presenting advanced ovarian carcinoma benefiting from neoadjuvant chemotherapy followed by interval debulking surgery after 3cycles or more than 3 cycles. The main objective of this study was to compare overall survival and progression free survival. Secondary objectives concerned surgery morbidity and extent of cytoreduction.

Material and Methods

We conducted an observational retrospective descriptive study in a referral cancer center in Clermont Ferrand, France.
This study was reported to the CNIL (French data protection agency). The study protocol was approved by the intuition's board and was conforming to the French ethical standards and the 2008 Helsinki declaration. Included patients were part of the ESME OVAIRE program for which they had given their consent for the use of their clinical data.

Population, treatment and surgery description
Analysis of the medical records of all patients with advanced ovarian carcinoma between 1997 and 2017 was performed. Eligible patients were those with a confirmed diagnosis of advanced ovarian carcinoma managed by neo-adjuvant chemotherapy followed by debulking surgery. All patients received first line platinum-based neo-adjuvant chemotherapy (Paclitaxel 175mg/m^2 and Carboplatin AUC5). All patients underwent surgery with the intent to achieve complete cytoreduction. Surgical procedures included hysterectomy with bilateral salpingo-oophorectomy, omentectomy, appendicectomy, para-aortic, and pelvic lymph-node dissection, complete resection of peritoneal carcinomatosis including bowel or diaphragmatic resection. Systematic lymphadenectomy stopped being the standard of treatment over the years, and was left to the discretion of each surgeon. Residual tumor was written at the end of each operating report. Surgical complications in the first 30 days were reported using the Clavien Dindo scale.
Excluded patients were those undergoing laparoscopic procedures instead of usual laparotomy; patients unsuitable for surgery after neo-adjuvant chemotherapy; and patients lost from follow-up. All patients were followed up until their death or until April 30th 2021.

Clinical and Pathological features

Clinical and pathological data were retrospectively collected in the cancer center, from January 1st 1997 to April 30th 2021. The following characteristics were collected for each patient: age at diagnosis, characteristics at diagnosis (WHO performance status score, initial CA125 level, histological type and grade, FIGO stage), characteristics of surgery (date of surgery, procedures performed), surgical strategy (interval surgery after 3 cycles of more than 3 cycles). Patients usually underwent a radiologic (CT-scan) reevaluation or laparoscopic reevaluation in order to decide if they should undergo more cycles of neoadjuvant chemotherapy or undergo surgery. Characteristics of the systemic treatment were also collected such as adjuvant Bevacizumab therapy. During this time period, three surgeons of the center were performing the surgeries. After the debulking surgery, patients were followed-up was organized with a medical visit one month after the surgery, then at 3 months, 6 months, 18 months and 24 months then once a year; CA125 dosage was realized once a year; radiologic reevaluation by CT-scan was realized when suspecting a disease recurrence.
Overall survival was defined as the duration in months from surgery to death from any cause. Progression free survival was defined as the duration in months from the surgical date to any relapse of the cancer.

Statistical analysis
A descriptive analysis of all included patients was performed. Patient characteristics by number of chemotherapy cycles were compared using Student's test for quantitative variables and X^2 test for qualitative variables. Survival curves were constructed using the Kaplan-Meier method. Multivariate analysis for overall survival and progression free survival were performed using Cox regression models. Proportional hazards assumption was graphically verified. Bilateral tests were computed and the significance p.value was set at 0.05.

Results

One hundred and fifty-five patients benefited from neo-adjuvant chemotherapy for advanced ovarian cancer, stage IIIC and IV. Fifteen patients were excluded: two patients could not benefit from interval debulking surgery; eight patients underwent laparoscopic surgery, and five were lost from fellow up. In the end, one hundred and forty patients benefited from interval debulking surgery. Among these patients, 45 benefited from ≤ 3 cycles (group 1) and 95 from > 3 cycles (group 2), (Flow chart). For patients in group 2, the mean number of administrated cycles of neoadjuvant chemotherapy was of 4.7 cycles; 61 patients underwent 4 cycles, 31 underwent 6 cycles, and 3 patients underwent 5, 7 and 9 cycles respectively.

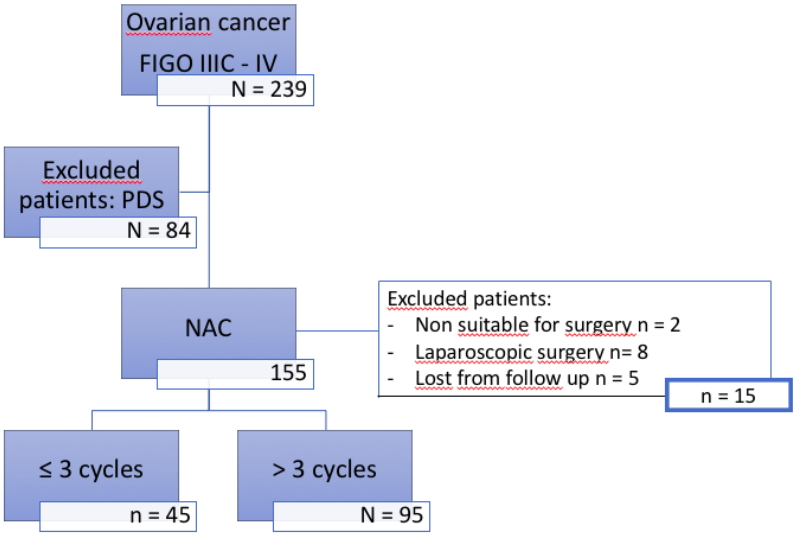

Figure A - Flow-chart

The mean age was 62,6 years (SD 10,4), with no statistical difference between the two groups. Considering the patient's characteristics, we found statistically differences regarding the FIGO stage between the two groups: indeed, there were more patients FIGO stage III in the group 1 and more patients FIGO stage IV in the group 2 (p.value = 0.02 and 0.02 respectively). All other patients and tumor characteristics were balanced without statistically significant differences. (Table 1)

	NAC ≤ 3 **Group 1**	**NAC > 3** **Group 2**	*p-value*
Number of patients	*45*	*95*	
Age (mean ±SD)	60.1 (± 14)	64.0 (± 0,7)	0.41
WHO performance status			
0	26 (57.7%)	45 (47.3%)	0.24
1	15 (33.3%)	40 (42.1%)	0.98
2	4 (8.8%)	6 (6.3%)	0.58
3	0 (0%)	1 (1.05%)	0.48
CA 125 level (mean ± SD)	1076 (±136.4)	1523.7 (± 700)	**0.04**
Missing data (%)	11 (24%)	28 (29%)	
FIGO STAGE			
III	40 (88.8%)	61 (64.2%)	**0.02**
IV	5 (11.1%)	34 (35.7%)	**0.02**
IV Nodes	2 (40%)	4(11.7%)	
IV Pleural	3 (60%)	20 (58.8%)	
IV Metastatic	0 (0%)	2(1.2%)	
Missing data	0 (0%)	8 (23%)	
HISTOLOGY			
Serous	44 (97.8%)	82 (86.3%)	**0.03**
Endometrioid	1 (1,2%)	3 (3.1%)	0.75
Clear cells	0	1 (1.0%)	
Mucinous	0	1 (1.0%)	
Other	0	5 (5.2%)	
GRADE			
Low grade	3 (6.6%)	10 (10.5%)	
High grade	32 (71.1%)	56 (58.9%)	
Missing data	10 (22.2%)	29 (30.5%)	
Bevacizumab	10 (22.2 %)	16 (16.8 %)	0.21
Number of adjuvant chemotherapy cycles (mean)	3	2,5	0.82

Table 1 – Patients characteristics
PDS:primary debulking surgery – NAC :neoadjuvant chemotherapy - WHO : world health organization performance status

Results are shown in Table 2.
Mean overall survival was 58,4 months for group 1, and 58,3 months for group 2. (p.value 0.56). The mean progression free survival was 30,5 months for group 1, and 23,8 months for group 2 (p.value 0.17). Kaplan Meier curves are shown in Figure 2 and 3.
Complete surgery (R0) was defined as no macroscopic residual tumor left. In the two groups, the rate of R0 was similar: 88.8% in the group 1 and 76.8% in the group 2 (p=0.09). Concerning the surgical procedures, there were no differences as for the presence of supramesocolic disease 55.5% and 46.3% (17/34) respectively (p=0.30). There were more diaphragm resection/stripping in group 1 (33,3%) than in group 2 (25.2%) without statistical difference (p=0.30). There were more posterior pelvic exenteration in the group 1 (33%) than in the group 2 (14.7%) with a statistical difference (p=0.06). There were no differences concerning the realization of lymphadenectomy between the two groups. At 30 days of the surgery, one patient in the group 1 underwent a surgical complication grade III of the Clavien Dindo scale and four in the group 2.

	NAC ≤ 3		***NAC > 3***		p.value
	N	%	N	%	
Death	29	64.4	68	71.5	0.39
Overall survival (months)	58.4	-	58.3	-	0.56
Remission	*6*	13.3	*6*	6.3	0.16
Progression free survival (months)	30.5	-	23.8	-	0.56
Early relapse <6 months	8	17.7	20	21	-
Resection grade					
R0	40	88.8	73	76.8	0.09
R1	1	2.2	9	9.4	0.11
R2	1	2.2	4	4.2	0.55
Surgical data					
Sus mesocolic disease	25	55.5	44	46.3	0.30
Digestive resection	20	44.4	28	29.4	0.08
Posterior pelvectomy	15	33.3	14	14.7	**0.01**
Diaphragmatic resection/stripping	15	33.3	24	25.2	0.32

Lymphadenectomy	28	62.2	46	48.4	0.12
Mean Peritoneal Cancer Index Sugarbaker (PCI) at surgery PCI Interval *Missing data*	7,8 [1;25] *15*	- *33*	7,4 [0;27] *44*	- *46*	0.7
Complication grade III (Clavien Dindo) at 30 days *Missing data*	1 *3*	2.2 *6.6*	4 *9*	4.2% *9.4*	- -

Table 2 – Results

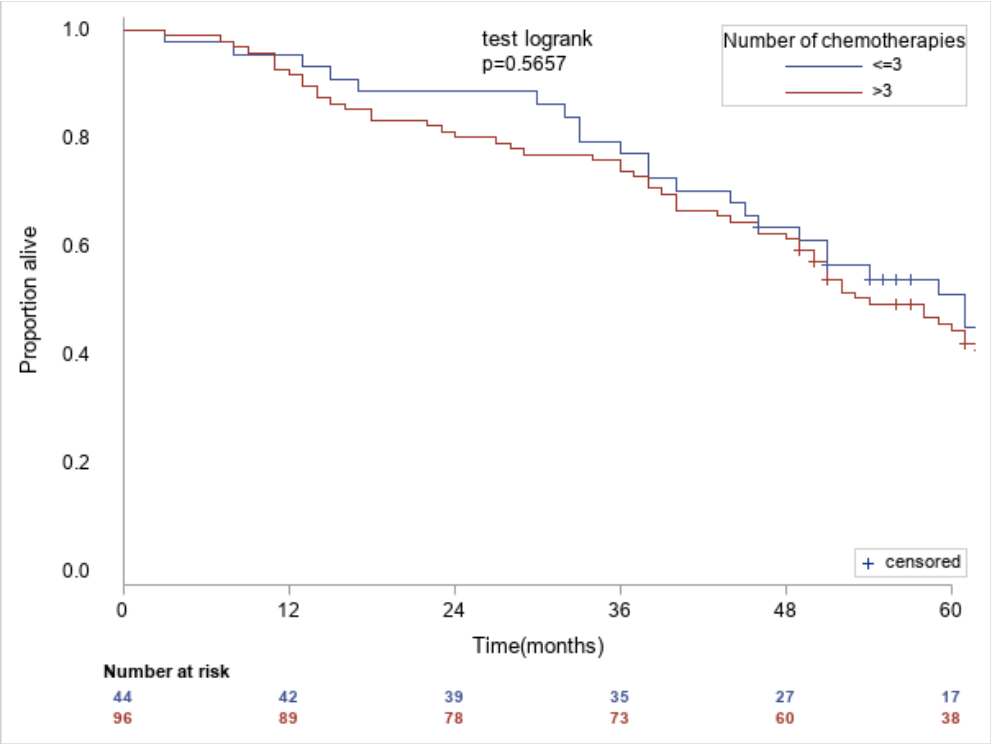

Figure 2 – Overall survival in patients with an advanced ovarian cancer according to the number of cycles of NAC

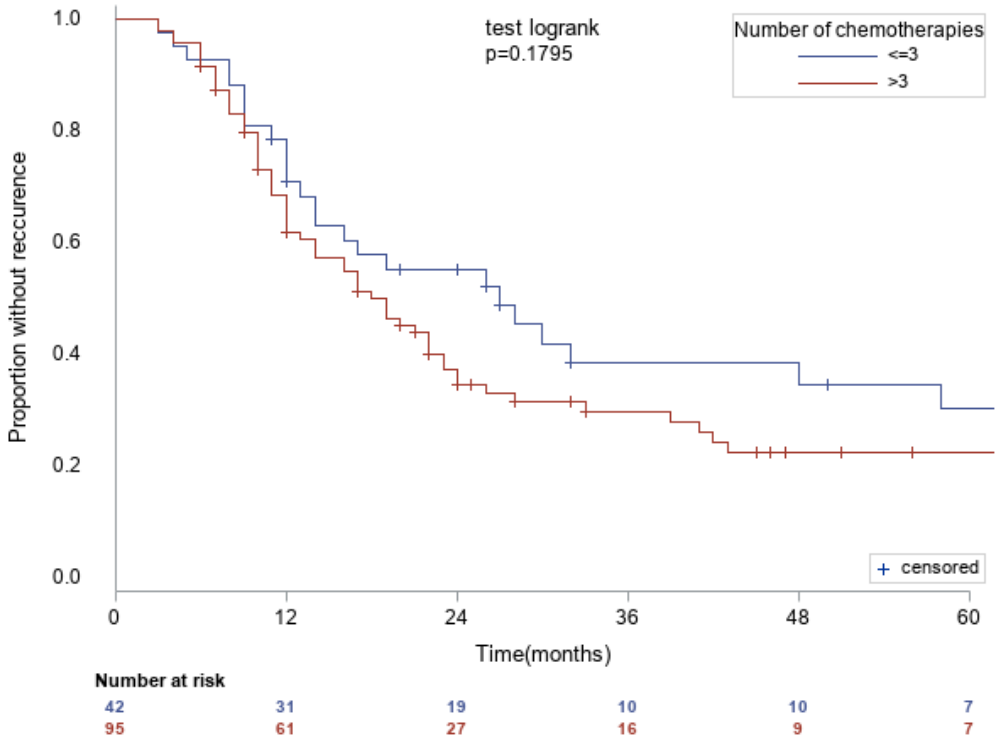

Figure 3 – Progression free survival with an advanced ovarian cancer according to the number of cycles of NAC

Discussion

The aim of ovarian cancer cytoreduction surgery is the complete removal of all macroscopic disease, which has proved to be the most important prognostic factor on overall survival. It is now accepted that neo-adjuvant chemotherapy is the preferred treatment for patients with poor performance status or with unresectable disease in the upfront setting. Two randomized trials have furthermore demonstrated that perioperative morbidity as well as quality of life score are more favorable in neo-adjuvant chemotherapy with interval debulking surgery than in primary debulking surgery in advanced ovarian cancer patients with high tumor load[15], [16]. However, neo-adjuvant chemotherapy seemed to have failed to improve overall survival and progression free survival[11], [17][18][19].

The optimal number of neo-adjuvant chemotherapy cycles before interval debulking surgery is not to date defined. Studies have showed discordant results on whether increasing the number of cycles prior to interval debulking surgery allowed better complete cytoreduction surgery without altering overall survival[13], or on the contrary observed inverse relationship between prognosis and the number of neo-adjuvant chemotherapy cycles[12]. In a recent multicenter study, it was suggested that surgery after five or more cycles of chemotherapy should only be offered on an individualized basis to patients with a high chance of complete resection, and should otherwise be considered as salvage surgery[20].

In our study, we did not find any significant difference in terms of overall survival and progression free survival between patients benefitting from interval debulking surgery after ≤ 3 cycles or > 3 cycles of neo-adjuvant chemotherapy.

From a molecular point of view, the lack of initial surgery and the repeated cycles of neo-adjuvant chemotherapy could lead to the selection of resistant tumor cells[21][22]. Retrospective data has suggested that neo-adjuvant chemotherapy and interval debulking surgery compared to in primary debulking surgery might increase the risk of developing platinum resistance[23]. Bogani et al even described a correlation between the number of neo-adjuvant chemotherapy cycles and platinum – resistant relapse[24]. On the other hand, in favor of late interval debulking surgery would be the presence of proapoptotic factors in tumor specimen that have shown to be more effective after 6 cycles than after 3 cycles[25]. Petrillo et al. showed in a study of 322 patients treated with neo-adjuvant chemotherapy that complete pathological response was in an uncommon event in advanced ovarian cancer patients (6.5%), and that it was associated with longer progression free survival and overall survival compared with women with residual disease, even microscopic, after interval debulking surgery with no gross residual disease. [26]

Interpretation of these data and these divergent results is complex. In general, and as underlined in our study, patients receiving neo-adjuvant chemotherapy and a fortiori more cycles before surgery have worse prognostic factors with more advanced disease at the time of presentation, or more chemo-resistant tumors. In our study, the groupe undergoing more cycles of neoadjuvant chemotherapy had significantly more patients with a FIGO stage IV disease. If this could be a selection bias, it is actually an accurate representation of the population of patients with advanced ovarian cancer, with patients with worse prognosis at diagnosis receiving more cycles before surgery. What is interesting though is that with a group with a fortiori worse prognosis, there is no difference in overall survival.

If the timing of surgery does not make consensus, complete cytoreductive surgery is the most crucial factor impacting on overall and disease free survival in advanced ovarian cancer[27][28][29][30][31].

It is interesting to note the absence of difference in survival despite unequally realized pelvic and paraaortic lymphadenectomy in both groups, concordant with studies suggesting that lymphadenectomy does not play a role in overall survival in advanced ovarian cancer[32].

The limitations of this study include the inherent biases associated with its retrospective nature. Its single-institution source may limit the external validity of our results. Additionally, although postoperative chemotherapy regimens were all platinum/taxane based, exact regimens were variable.

Another point to underline, is the use of hyperthermic intraperitoneal chemotherapy which has demonstrated a 12 months increase in overall survival [33], which was not part of the management proposed in our center.

The complexity of the management of patients with advanced ovarian cancer needs to consider the performance status and comorbidities of the patients. The tradeoff between short term morbidity and

overall survival is complex. A less aggressive surgical effort results in poorer overall survival, but the risk of complications are substantial for complex surgeries in the highest-risk patients[34].
This should underline the importance of the management of ovarian cancer with the support of a multidisciplinary team from an expert center. Through these and other efforts, it may be possible to evolve from empirical patient selection to a more individualized treatment approach. The CHRONO[35] study currently recruiting should bring answers to these questions.

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