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Titre

Impact of the number of Neoadjuvant Chemotherapy (NAC) courses on survival and morbidity in patients with advanced epithelial ovarian cancer FIGO III-IV.

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Summary

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Abbreviations:

FIGO	International Federation of gynecology and obstetric
NAC	Neoadjuvant Chemotherapy
PDS	Primary debulking surgery
IDS	Interval debulking surgery
OS	Overall survival
PFS	Progression free survival
PS	Performans statut
PCI	Peritoneal cancer index
CM	Centimeters
MM	Millimeters
CEROG	Ethical Committee of research in gynecology and obstetric
CT	Chemotherapy
AEOC	Advanced Epithelial Ovarian Cancer
HR	Hazard Ratio
CDS	Closing Debulking Surgery

Title:

Impact of the number of Neoadjuvant Chemotherapy (NAC) courses on survival and morbidity in patients treated for advanced epithelial ovarian cancer (AEOC) stage FIGO IIIc-IV.

I. Background

Ovarian cancer is the leading cause of gynecological cancer related death for women and the second most common women cancer in developed countries. Around 75% of the patients have been diagnosed in advanced stages of the disease (stage IIIc or IV according to the International Federation of Gynecology and Obstetrics, or FIGO, mentioned Appendix 1) with 5 years survival reduced to 30% (1-4).

The median age for diagnosis was 66 years old (5). The most common ovarian histological type was represented by the epithelial type which corresponds to 85% of ovarian cancers. Among the epithelial cancer type, we noticed 4 main subtypes represented by the serous histology (70% of high-grade ovarian cancer), the endometrioid histology (10% of ovarian epithelial cancer), the mucinous (3%) and the clear cells subtypes (10% of ovarian epithelial cancer) (6).

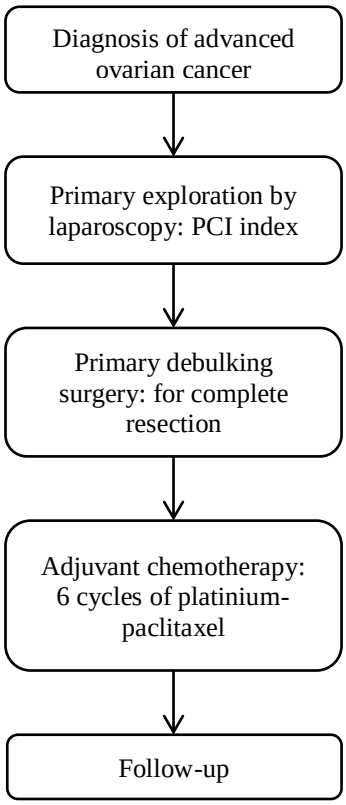
The final anatomopathological analysis of the surgical tumoral resection defined the extent of the ovarian cancer, the rate of mitosis, presence of cyto nuclear atypies, distributed between high and low grade carcinoma. We differenciate (7):

- a grade 1 ovarian cancer which is well differenciated with less than 5% of solid portion
- a grade 2 tumoral disease with 6 to 50 percent of solid lesion and moderately differenciated
- a grade 3 carcinoma less differenciated with 50% or more of solid portion.

The histological type and the FIGO's stage of diagnostic characterize the severity of the disease and determine the adapted therapeutics used.

International guidelines standards for the advanced ovarian cancer treatment were based on the association between optimal primary debulking surgery (PDS) followed by adjuvant chemotherapy based on 4 or 6 cycles of platinum and paclitaxel chemotherapy (8) (Figure 1). The primary surgical cytoreduction allowed a more efficient treatment with best overall survival (OS) observed in clinical study (5, 9-11).

Figure 1: Standard management for advanced ovarian cancer (FIGO IIIc, IV)



Surgical guidelines recommended a complete surgical cytoreduction without tumoral residue.
In fact, Griffith et al. in 1975 showed that one of the most important prognostic factor to predict survival was the size of the largest residual tumoral mass after surgery. Survival time decreased if the diameter of the largest tumoral lesion exceeded 1.5 centimeters irrespective of total tumor volume (mean OS=12.7 months) (12).
In 2009, Dubois et al. led a meta-analysis of 3 prospective studies and analyzed 3126 patients receiving PDS followed by adjuvant chemotherapy, classified in three groups: (A) complete resection, (B) residual tumor burden of 1-10 mm and (C) macroscopical residue > 1cm.
The Median survival in group (A) without any visible residual tumor was 99.1 months, whereas the median survival was 36,2 (95% CI, 34.6, 39.4) months for the group (B) with poor tumoral residue and 29,6 months (95% CI, 27.4, 32.2) in case of macroscopic tumoral resection (13). These observations (median survival of 99 months after complete surgery) required an exact patient selection with accurate evaluation of the surgical resectability (13).

To obtain as much as possible a complete cytoreductive surgery without tumor burden, it was important to propose an extensive upper abdominal and complete debulking surgery in

specialized center with hysterectomy, bilateral annexectomy, lymph node resection, omentectomy, peritonectomy, and sometimes splenectomy, bowel or liver resections (14).

This surgery had to be practiced to improve quality of the tumoral resection but remained complicated and morbid in elderly and fragile patients with poor Performance Satut (PS) (14, 15, 16). Extensive surgery could lead to an increased risk of surgical complications or to an increase of the length of hospital stay among fragile and undernourished patients (16).

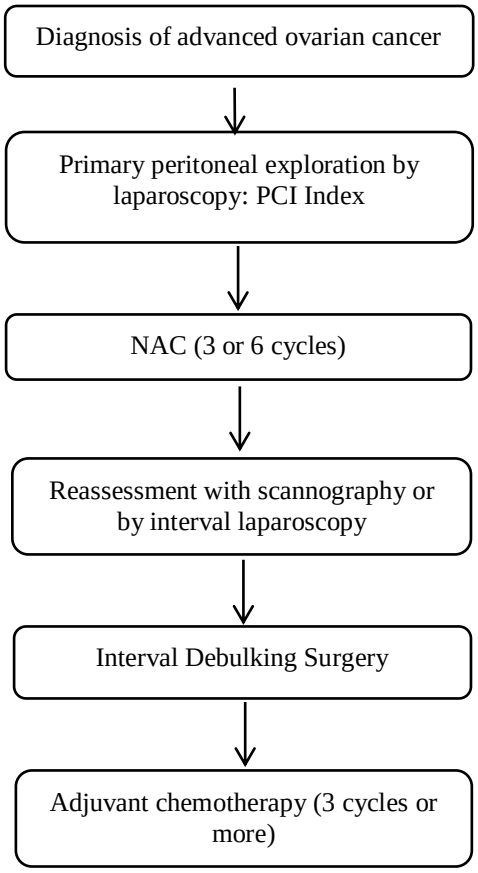
An initial good evaluation of the tumoral disease extension with laparoscopic staging using the FAGOTTI or adapted PCI score could lead to an optimal management and decrease morbidity (17) (Appendix 2). In the event of impossible complete surgical cytoreduction, NAC could have a place (9).

An alternative to the primary debulking surgery (PDS) appeared from 2011 to 2015 (18-21) and consisted in the realization of NAC based on platinum and paclitaxel following by Interval Debulking Surgery (IDS) (22-23) (Figure 1bis). The aim was to increase the possibility of complete surgical resection, and to decrease the surgical morbidity for older or poor PS patients with advanced ovarian cancer without difference on overall survival (18). In a meta-analysis involving 21 studies, Kang et al. found no difference in survival on OS and progression free survival (PFS) for patients who underwent primary or interval surgical debulking (24). This meta-analysis included patients having an AEOC treated initially by NAC.

In 2010, Vergote et al. with a European multicenter randomized trial, have shown a median OS of 29 months in the PDS group and 30 months in the NAC group without statisticly difference (20). Kehoe et al. in a second multicenter randomized trial in 2015, found a median OS of 22,6 months after PDS and 24,1 months after NAC (HR 0.87, IC95% (0.72-1.05), p=0.376) (25). Although these studies didn't show no difference on survival after NAC, OS was worst that observed after PDS as Vergote's study (20, 25). NAC was a justified option only in case of extensive tumoral disease non-accessible to a complete surgical resection (26).

It was reasonable to reserve NAC as optional for older patients with altered Performance statut, or high grade of tumoral disease (Advanced epithelial ovarian cancer: AEOC) and extent disease, in order not to delay the chemotherapy initiation and to performe surgery without complication (20).

Figure 1 bis: Management of advanced ovarian cancer unresecable straightaway with primary Neoadjuvant chemotherapy.



Duration of NAC and time of cytoreductive surgery remained unknown. Some authors recommended a number of 6 cycles of NAC based on platinium and paclitaxel before performing closing debulking in case of insufficient tumoral response after 3 cycles of NAC (9, 21). Others supposed that NAC created a negative selection pressure on the ovarian tumoral clones by increasing the chemo resistance (9, 21). Sometimes, one additional cycle of NAC was used to facilitate logistical issues around timing of interval surgery.

In addition, the clinical and radiological criteria (laparoscopy, scanography, CA 125 serum level) used to assess the feasibility and relevance of the NAC remained unclear from a study to another one (22).

Place and efficacy of 6 courses of NAC efficiency was not extensively evaluated. Three studies asked the following question (1, 4, 27). In 2014, Miranda et al. in a first retrospective multicentric study included 656 patients treated for AEOC and have compared the impact on OS of 6 or 8 cycles of NAC (1). No difference was observed between these two groups in this study.

Few studies evaluated the impact of the number of cycles of NAC before intermediate or closing surgical debulking, on morbidity and survival (28).

The objective of our study was to evaluate the impact on survival (OS and PFS), morbidity and quality of cytoreductive surgery, of the number of NAC courses, in patients treated for AEOC.

II. Methods:

Study design and Inclusion criteria

We conducted a retrospective study using the Cancer Research Center René Gauducheau database in Saint Herblain city. Patients were managed by subspeciality trained gynaecological oncologists in a Departmental Hospital or in a specific Center of cancer research. Patients treated for an AEOC, stage IIIc-IV of the FIGO International Classification, by platinum-based NAC following by IDS or closing debulking surgery were included from 2000 to 2016.

We included every patient with histological proved AEOC, stage FIGO>IIIb, treated by 3, 4 or 6 courses of NAC associated with IDS or closing surgical cytoreduction.

Patients receiving first optimal PDS, hyper thermal intraperitoneal chemotherapy, having a high-grade endometrial cancer (>IB FIGO stage) or another non gynecological carcinoma associated, with incomplete clinicopathological data, or with a non-epithelial ovarian cancer histology were excluded from this study. We excluded patients receiving a number of NAC courses < 2 or > 6. During the period of follow up, receiving 1 course or 7 to 9 courses of NAC represented exclusion criteria.

We have constituted 3 arms of treatment to compare the therapeutics sequences according to the number of courses of NAC received:

- Group 1: 3 or 4 cycles of NAC (carboplatine – paclitaxel) following by IDS following by adjuvant chemotherapy (carboplatine – paclitaxel)
- Group 2: 6 cycles of NAC (carboplatine – paclitaxel) following by Closing Debulking Surgery (CDS).
- Group 3: 6 cycles of NAC (carboplatine – paclitaxel) following by CDS following by Consolidation Chemotherapy (carboplatine – paclitaxel)

Surgery and Resecability of peritoneal carcinomatosis

Whenever possible, the extent of ovarian disease was assessed laparoscopically using the staging criteria according to the International Federation of Obstetricans and Gynecologists (FIGO, Appendix 1).
Extent of peritoneal carcinomatosis was quantified using the Peritoneal Cancer Index (PCI) from Sugarbaker (Appendix 2). This peritoneal cancer index (PCI) is used to assess the extent of ovarian cancer throughouth the abdomino-pelvic cavity. For this purpose, the peritoneal cavity is divided in 13 well-defined regions. In each of the 13 regions, the size of the largest tumor nodule is measured. If no tumor is visualized, a score of "0" is given to that region. If the largest tumor nodule was smaller than 0.5 centimeters (cm), the score was "1". For tumoral lesions measuring between 0.5 cm and 5 cm, the score was "2". For lesions larger than 5 cm, the score was "3". If there was layering or a confluence of multiple small tumor nodules, the score was "3". The PCI is calculated by adding the scores of all 13 regions together with a maximum score of 39 (Appendix 2). This score obtained by laparotomy was transposed for a laparoscopic staging.

Following criteria have been used to define unresecable disease of incomplete surgical cytoreduction: biological data as high CA 125 level > 500, abdomino-pelvic scan data as lymph nodes achievement, large mesenteric or sus mesocolic tumoral lesions, ascitis > 1000 ml, and surgical data as definition of reviewed PCI Index (total colic resection, or extensive small bowel resection, splenic or hepatic achievement). Eligible patients were referred for neoadjuvant chemotherapy because their abdominal disease was too extensive for primary cytoreductive surgery or because surgery had been performed incompletely (21).

Every patient's file and therapeutic decision were presented and discussed during a multidisciplinary oncologic meeting.

Quality of cytoreductive surgery was noticed for each of them and based on the size of the residual disease (centimeters, cm). We defined the complete tumoral cytoreduction as no residual tumoral disease after cytoreductive surgery (CC0). We defined a cytoreduction CC1 as the presence of residual tumoral disease < 0,25 cm and CC2 as the presence of residual tumoral disease from 0,25 to 2,5 cm.

At least a hysterectomy, bilateral annexectomy, appendicectomy, omentectomy and standard lymph nodes resections were realized. Some patients were part of an ongoing French multicentric prospective and randomized study, occurring in the cancer center René Gauducheau and called "CARACO" (NCT number: NCT01218490); patients were randomized in two arms: either lymph nodes dissection performed or no surgical resection performed for patients without lymph nodes involvement detected on the pre-operative CT scan (22). Today's time, guideline recommended to practice a systematic lymphadenectomy (5). The time of the cytoreductive surgery was decided for each patient after clinical examination (Performans Statut evaluation), biological (CA 125), CT scan and laparoscopic evaluation of residual tumoral disease. If the residual tumoral lesions after 3 or 4 courses of NAC allowed a complete surgical cytoreduction, an interval surgery was performed; if not, NAC was pursued up to 6 cycles. The objective of surgical cytoreduction was to obtain the best completeness cytoreductive score.

The NAC regimen was left to the discussion of each oncologic member of the participating team.

Pathological response of NAC was evaluated according to the size of the residual tumoral disease on the histological analysis (lymph nodes involvement, omentum, peritoneum, or bowel involvement).

Data analyses

For each patient, we retrospectively analyzed the following data: demographics data as WHO PS and age, the clinical, biological (CA 125 level), and CT scan criteria of optimal debulking, the number of courses of NAC, the final surgical histology after NAC and involvement of the histologic surgical resection, the size of the tumoral residual disease, the overall and progression free survival, surgical morbidity (only grade III complications provided with Clavien and Dindo classification, Appendix 3)
Data on PFS and OS were censored at the date of the last contact, for patients remining alive with no evidence of disease.

Every histological data were analyzed according to the reality of the surgical resection and the involvement's statut on the histological analysis (1p+ or 1p-).

Follow-up

Patients received every 6-months a clinical examination, tumor markers assay (CA 125 level) and CT-scans. The date of last follow-up was listed.

Endpoints of the study

The primary end point was PFS, which was defined as the time from diagnostic to the date of first progression. Disease progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) or on the basis of an increasing from baseline of the CA 125 level.
Secondary end points included OS, defined as the time from the initial diagnostic until death and surgical morbidity. Quality of the tumoral surgical cytoreduction (CC0-CC1-CC2) was defined according to the size of macroscopic tumoral residue.
Post surgical morbidity (side effects grade II and III with Clavien classification) was analyzed.

Statistical analysis

We used a descriptive statistical analysis to compare the distributions of the interested values between the three arms of treatment. A multinomal propensity score was calculated with a boosted logistic regression and led to an adaptated Inverse Probability of Treatment Weighting. This score is used to re-equilibrate and assign weight at 3 different arms, because data of the study remained observational.
The significance of the differences observed was evaluated with the KRUSKAL-WALLIS test (non parametric test) for the quantitative values, and with the CHI2 test or FISHER test to analyse the qualitative values; according to the law of the application of these tests.

Statistical analysis was performed with R v3.5.1.
The date of the end of treatments was defined as the date after the end of the adjuvant chemotherapie when received or after the end of the interval debulking surgery in case of lack of adjuvant chemotherapie.
The descriptive or modalized survival curves were performed with the KAPLAN-MEIER method.

We conducted then a global survival analysis and progression free survival analysis with the COX model with a significativity, calculated with a likelihood ratio test (LR-test).
The correlation analysis between the survival in the different arms of treatments and variables of interest, has been research.
The integrated variables in this multivariate model were selected with a rate of significativity <0,2.
The siginifcant level was fixed at 0,05 for the global analysis.
We calculated the Hazards ratios and their 95% Confidence Interval (95% CI).

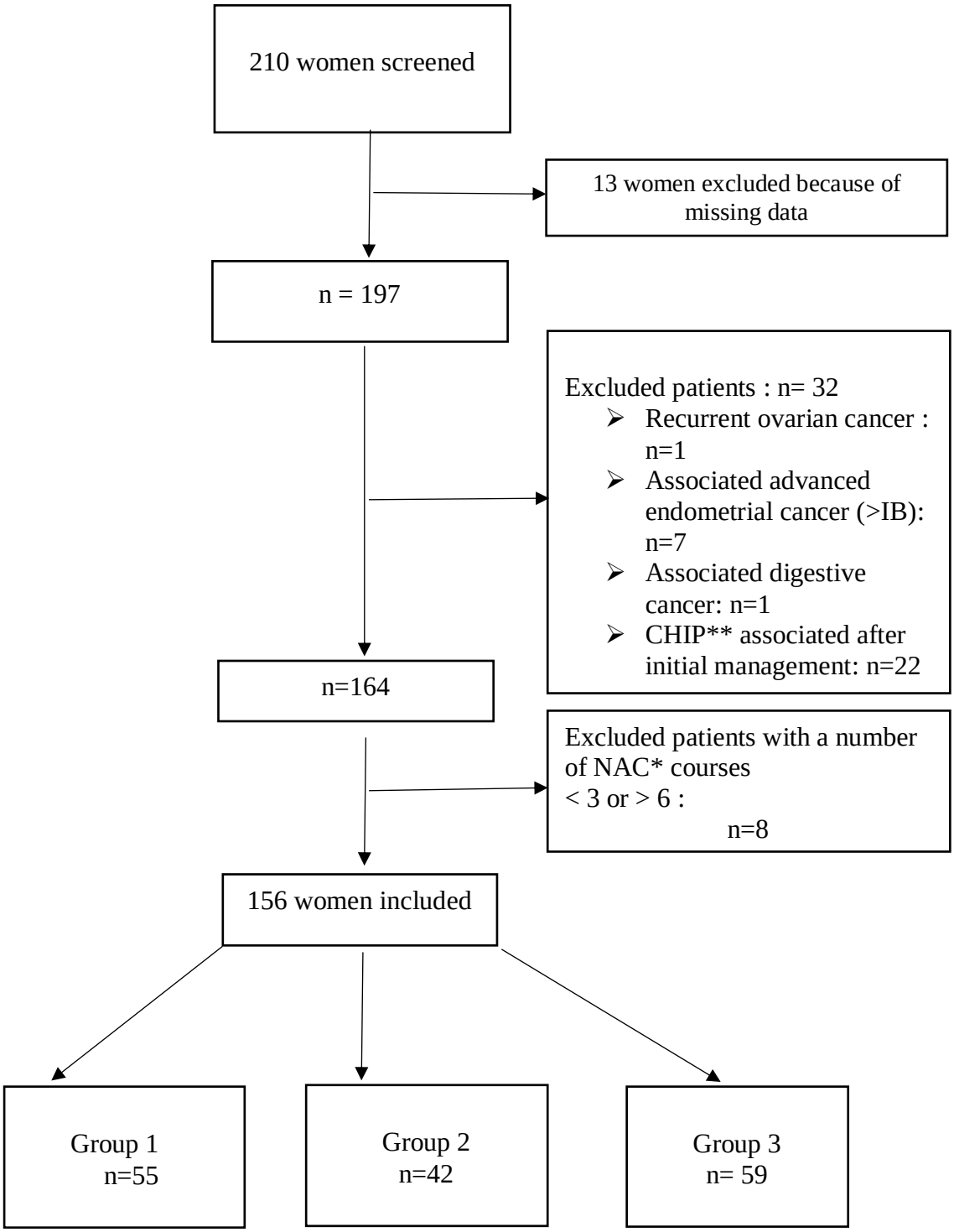
Ethic

The ethical approval for this retrospective study was obtained from the CEROG (Ethical Committee of research in gynecology and obstetric).

III. Results

Between May 2000 and July 2016, 210 patients were recruited retrospectively from the Cancer Center René Gauducheau database.
On these 210 patients, 47 were excluded of the final analysis because of no available data (n=13), receiving CHIP (n=22), having a concomitant advanced endometrial (n=7) or digestive cancer (n=1) or presence of an ovarian cancer recurrence (n=1). Eight patients who received <2 or >6 cycles of NAC were excluded from this analysis. We included 156 patients having eligibility criteria. These results were listed in the Flow Chart (Figure 2).

Figure 2: Flow Chart



Legend: n = number of patients included, NAC* = neoadjuvant chemotherapy, CHIP** = intra peritoneal chemotherapy.

Characteristics of patients and treatments received

The demographic description of the population's study was represented Table 1. Fifty-six patients were assigned in the group 1, 42 in the group 2 and 59 in the group 3. The median age was 63 years without statistical difference. There were no statistically significant differences between the three groups in FIGO tumoral stage, tumoral grade. The histological serous type was significantly predominant in the 3 groups (p=0,043).

Only epithelial cancer was reported in this study. The histologic repartition was represented Figure 3.

The Performance Statut was ranged between 0 and 3 with close distribution between the three groups.

There were no statistically significant differences about the initial care in a special Unit of cancer treatment for the 3 groups of patients: 38% in group 1, 57% in group 2, and 51% in group 3 (p=0.131) (Table 1).

Figure 3: Sous type of epithelial histology repartition.

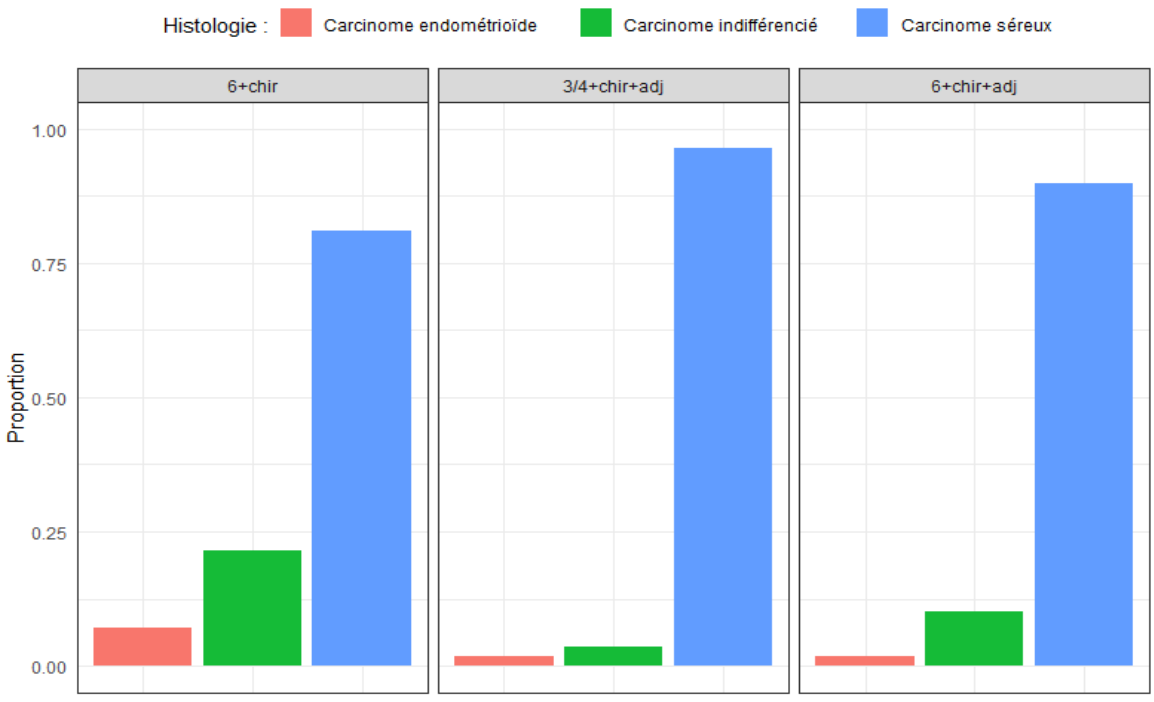


Table 1: Demographic and baseline disease characteristics, surgical and chemotherapy treatments informations.

	Group 1	**Group 2**	**Group 3**	p	Missing (%)
N	56	42	59		
Median Age [interquartile range]	63.00 [58.25, 68.00]	64.50 [57.25, 70.75]	61.00 [52.50, 68.00]	0.574	0.0
Median BMI* [interquartile range]	22.30 [20.73, 25.75]	23.80 [21.00, 27.00]	23.00 [20.55, 26.93]	0.476	6.4
FIGO IIIc, n (%) **FIGO IV**, n (%)	39 (69.3) 17 (30.4)	29 (69.0) 13 (31)	43 (72.9) 16 (27.1)	0.895	0.0
Grade high, n (%) **Grade intermediate** n (%)	50 (89.3) 6 (10.7)	38 (90.5) 4 (9.5)	54 (93.1) 4 (6.9)	0.767	0.6
Histology : serous n (%)	54 (96,4)	34 (81)	53 (89,8)	0.043	0.0
Histology : endometrioid n (%)	1 (1,8)	3 (7.1)	1 (1.7)	0.233	0.0
Histology : undifferanciated n (%)	2 (3,6)	9 (21,9)	6 (10.2)	0.019	0.0
Initial PS** n (%)				0.225	2.5
0	26 (46.4)	16 (41.0)	25 (43.1)		
1	25 (44.6)	22 (56.4)	25 (43.1)		
2	4 (7.1)	0 (0.0)	8 (13.8)		
3	1 (1.8)	1 (2.6)	0 (0.0)		
Management in Special Unit Center, n (%)	21 (37.5)	24 (57.1)	30 (50.8)	0.131	0.0
Chemotherapy thesaurus, n (%)				0.251	0.0
(Platinium + taxol)	47 (83.9)	41 (97.6)	48 (81.4)		
Median number of courses NAC*** [interquartile range]	3.00 [3.00, 4.00]	6.00 [6.00, 6.00]	6.00 [6.00, 6.00]	< 0.001	0.0
Median number of courses adjuvant chemo-therapy [interquartile range]	3.00 [3.00, 3.00]	0.00 [0.00, 0.00]	3.00 [2.00, 3.00]	< 0.001	0.6
Median total number of courses [interquartile range]	6.00 [6.00, 7.00]	6.00 [6.00, 6.00]	9.00 [8.00, 9.00]	< 0.001	0.6
Major toxicity of NAC, n (%)	5 (8.9)	11 (26.2)	10 (16.9)	0.075	0.0
NAC stop, n (%)	4 (7.1)	4 (9.5)	6 (10.2)	0.839	0.0

Legend: BMI* = Body Mass Index, PS**= performance Staut, NAC***= neoadjuvant chemotherapy.

CA 125 blood sample data and post-operative histological analysis are shown in Table 2. We found no statistical differences in initial CA 125 rate between 3 groups: 846 UI/l for group 1, 693 UI/l for group 2, and 801 UI/l for group 3 (p=0.958).

Presence of ascitis on the initial evaluation CT scan was noticed without statistical difference for 79%, 90% and 85% of the patients in group 1, 2, and 3 respectively (p=0.316). The size of the main tumoral lesion was 70 millimeters (mm), 68 and 55 mm in group 1, 2, and 3 respectively (p=0.632) (Table 2).

We have reported a bowel involvement on the initial CT scan for 15% of patients in group 1, and 32,4% in group 2 and 21% in group 3 (p=0.158).

Lymph nodes involvement on histological analysis was reported in 52,8% of group 50% of group 2 and 45,3% of group 3 (p=0,736) (Table 2).

Table 2: CA 125-Blood sample and post operative histological analysis

	Group 1	Group 2	Group 3	p	Missing (%)
n	56	42	59		
Median initial CA125 [interquartile range]	846.00 [238.75, 1918.50]	683.00 [365.25, 1907.25]	801.00 [424.25, 1436.75]	0.958	3.2
Median CA125 decrease between 0 and 3/4 courses NAC * [interquartile range]	91.23 [72.80, 95.63]	88.93 [82.55, 95.00]	88.80 [75.31, 94.41]	0.601	15.9
Median CA125 decrease between ¾ and 6 courses NAC * [interquartile range]	73.44 [59.70, 88.83]	79.18 [60.53, 85.01]	69.14 [51.62, 84.78]	0.624	54.8
Median CA125 decrease between 0 and 6 courses of NAC* [interquartile range]	98.02 [78.74, 98.77]	97.30 [95.77, 98.50]	96.08 [91.88, 97.73]	0.136	49.0
Ascitis, n (%)	44 (78.6)	36 (90.0)	50 (84.7)	0.316	1.3
Maximal residual burden (mm), n (%)	70.00 [40.00, 80.00]	68.00 [44.25, 100.00]	55.00 [35.00, 87.50]	0.632	42.7
Sus mesocolic involvement n (%)	33 (62.3)	23 (67.6)	28 (51.9)	0.299	10.2
Bowel involvement, n (%)	8 (15.1)	11 (32.4)	11 (20.8)	0.158	10.8
Lymph nodes involvement n (%)	28 (52.8)	17 (50.0)	24 (45.3)	0.736	10.8
Distant involvement n (%):				0.166	8.9
- No	21 (39.6)	19 (54.3)	30 (54.5)		
- Mediastinal	7 (13.2)	2 (5.7)	3 (5.5)		
- Liver	1 (1.9)	6 (17.1)	5 (9.1)		
- Pleural	13 (24.5)	2 (5.7)	9 (16.4)		
- Pulmonary	3 (5.7)	0 (0.0)	3 (5.5)		
- Bone	0 (0.0)	1 (2.9)	0 (0.0)		
- Axillary	1 (1.9)	0 (0.0)	0 (0.0)		
- Bladder	0 (0.0)	0 (0.0)	1 (1.8)		
- Pleural + mediastinal	4 (7.5)	2 (5.7)	2 (3.6)		
- Pleural+pulmonary	2 (3.8)	2 (5.7)	1 (1.8)		
- Pleural + liver	1 (1.9)	0 (0.0)	0 (0.0)		
- Pleural+pulonary+ mediastinal	0 (0.0)	0 (0.0)	1 (1.8)		

Legend: NAC*= neoadjuvant chemotherapy.

Table 3 showed the characteristics of surgical therapeutics.

A lombo-aortic lymph nodes dissection was performed for 73% of patients in group 1, 59,5% of patients in group 2 and in 34,2% of patients in group 3 (p=0.206). The median number of removal lymph nodes was 9, 5, and 4 for the lombo aortic localization in group 1, 2 and 3 respectively without statistical difference (p=0.077) (Table 3). The median number of removal pelvic lymph nodes was 6, 5 and 4 respectively without involvement (p=0.464).

We observed no statistical differences in the rate of bowel resection between the 3 groups: 30,9% in groups 1, 31% in group 2, and 28,8% in group 3 (p=0.962). 5,5 percents of patients in group 1 have had a liver/spleen or pancreas resection, but it increased to 11,9% in group 2 and 3 (p=0.429) (Table 3).

After anatomopathological analysis, the epiploic tumoral burden was significantly reported in 81,5 % of cases in group 1, 59 % in group 2 and 72,7 % in the group of treatment number 3 (p=0.057). Peritoneal residual carcinomatosis was reported for 65,2 % of patients in group 1 and 39,4 % in group 2 but 64,7 % in group 3 (p=0.036) (Table 3).

Table 3: Surgical treatment characteristics and post-operative events

	Group 1	**Group 2**	**Group 3**	p	Missing N/A (%)
N	56	42	59		
CCS surgery score, n (%) :				0.374	1.3
- CC0	38 (69.1)	32 (78.0)	39 (66.1)		
- CC1	14 (25.5)	8 (19.5)	13 (22.0)		
- CC2	3 (5.5)	1 (2.4)	7 (11.9)		
Lombo Aortic LND*, n (%):				0.206	0.0
- Not made	15 (26.8)	17 (40.5)	26 (44.1)		
- made	41 (73.2)	25 (59.5)	32 (54.2)		
Median Lombo Aortic LND* [interquartile range]	9.00 [0.00, 13.00]	5.00 [0.00, 12.00]	4.00 [0.00, 9.00]	0.077	1.3
Median Lombo Aortic LND* involved [interquartile range]	0.00 [0.00, 2.00]	0.00 [0.00, 1.25]	0.00 [0.00, 2.00]	0.943	38.9
Pelvic LND*, n (%)	38 (67.9)	23 (54.8)	34 (57.6)	0.359	0.0
Median Pelvic LND* [interquartile range]	6.00 [0.00, 10.25]	5.00 [0.00, 12.00]	4.00 [0.00, 8.00]	0.464	1.3
Median Pelvic LND* involved [interquartile range]	0.00 [0.00, 0.75]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.830	40.8
Bowel resection, n (%)	17 (30.9)	13 (31.0)	17 (28.8)	0.962	0.6
Median bowel résection [interquartile range]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.25]	0.780	3.8
Type of bowel resection n (%):				0.713	70.7
- Sigmoide	9 (52.9)	8 (66.7)	11 (64.7)		
- Rectum	1 (5.9)	1 (8.3)	0 (0.0)		
- Large bowel	2 (11.8)	1 (8.3)	4 (23.5)		
- Small bowel	3 (17.6)	2 (16.7)	1 (5.9)		
Spleen/liver/ pancreas, n (%)	3 (5.5)	5 (11.9)	7 (11.9)	0.429	
Number of peritoneal samples [interquartile range]	2.00 [0.75, 4.00]	2.00 [1.00, 4.00]	3.00 [1.00, 4.00]	0.627	0.6

Histological response : n (%)					
Bowel residue	12 (75.0)	11 (84.6)	12 (70.6)	0.666	7.6
Spleen/liver/pancreas residue	2 (66.7)	3 (60.0)	5 (71.4)	0.918	70.7
Hysterectomy residue	21 (43.8)	13 (34.2)	22 (44.9)	0.559	90.4
Annexectomy residue	38 (76.0)	26 (72.2)	42 (84.0)	0.394	14.0
Appendicectomy residue	6 (31.6)	7 (30.4)	7 (30.4)	0.996	13.4
Epiploon residue	44 (81.5)	23 (59.0)	40 (72.7)	0.057	58.6
Peritoneal residue	30 (65.2)	13 (39.4)	33 (64.7)	0.036	5.7
Ureteral residue	1 (100.0)	1 (25.0)	0 (0.0)	0.269	17.2
Blood transfusion, n (%)	11 (19.6)	11 (26.2)	11 (18.6)	0.625	96.2
Digestive occlusion, n (%)	5 (8.9)	4 (9.5)	3 (5.1)	0.641	0.0
Bowel derivation, n (%)	0 (0.0)	1 (2.4)	2 (3.4)	0.401	0.0
Re intervention, n (%)	2 (3.6)	0 (0.0)	2 (3.4)	0.472	0.0
Per operative complication n (%)	1 (1.8)	3 (7.1)	2 (3.4)	0.383	0.0
Intensive care unit Transfert n (%)	0 (0.0)	2 (4.8)	1 (1.7)	0.231	0.0
Eventration complication n (%)	3 (5.4)	2 (4.8)	5 (8.5)	0.699	0.0
					0.0

Legend: *LND: lymph node dissection

Progression-free Survival and Overall Survival

a) Progression free survival

We found a median follow up of 48 months (Figure 4). The median PFS was 8,4 months for the groups 1 and 2, and 8,16 months for group 3 with no statistical difference after performing a propensity statistical analysis.

Removing epiploon, involved or not, by performing a complete omentectomy, was associated with improved PFS (HR 0.134; 95% CI [0.063-0.287], p<0.001) (Table 4).
Performing an incomplete surgical cytoreduction CC1was associated with a decreaseof PFS (HR 1.623; 95% CI [1.189;2.215]. Involved peritonectomy and bowel resection were also associated with a decrease of PFS [HR respectively from 1.444; 95% CI [1.010-2.064], p=0.044 and 1.971; 95% CI [1.371-2.833]; p<0.001].
PFS increased after performing a lombo aortic lymph nodes dissection, if not involved. In case of lymph nodes dissection involvement, PFS was unchanged (HR 0.938; 95% CI [0.670-1.313]; p=0.710).

Presence of thromboembolic complications, small or large bowel resection, toxicity of the chemotherapy and transfert in an Intensive Care Unit, decreased PFS (Table 4).

Table 4: Progression free survival according to propensity score matching analysis.

Variable	HR (95% IC)	p
CCS score		
- CC1 vs CC0	1.623 (1.189;2.215)	0.003***
- CC2 vs CC0	0.477 (0.265;0.858)	0.014**
Hysterectomy performed vs absence of residual disease	1.038 (0.682;1.580)	0.862
Hysterectomy performed vs presence of residual disease	0.803 (0.509;1.266)	0.345
Epiploon surgery performed vs absence of residual disease	0.083 (0.038;0.183)	<0.001***
Epiploon performed vs presence of residual disease	0.134 (0.063;0.287)	<0.001***
Peritonectomy performed vs absence of residual disease	0.925 (0.632;1.355)	0.690
Peritonectomy performed vs presence of residual disease	1.444 (1.010;2.064)	0.044**
Bowel resection performed vs absence of residual disease	0.947 (0.597;1.503)	0.818
Bowel resection performed vs presence of residual disease	1.971 (1.371;2.833)	<0.001***
Lombo Aortic lymphadenectomy performed vs absence of residual disease	0.628 (0.447;0.882)	0.008***
Lombo Aortic lymphadenectomy performed vs presence of residual disease	0.938 (0.670;1.313)	0.710
Thromboembolic event	3.107 (1.740;5.547)	<0.001***
Blood transfusion	0.653 (0.462;0.924)	0.017**
Fistula	1.674 (0.798;3.513)	0.173
Bowel derivation	3.901 (1.230;12.379)	0.021**
Intensive Care Unit Transfert	3.194 (1.397;7.302)	0.006***
NAC * toxicity (3/4)	1.340 (0.972;1.847)	0.074*
Observations	145	
R^2	0.623	
LR Test	141.338 (df = 20)	<0.001***

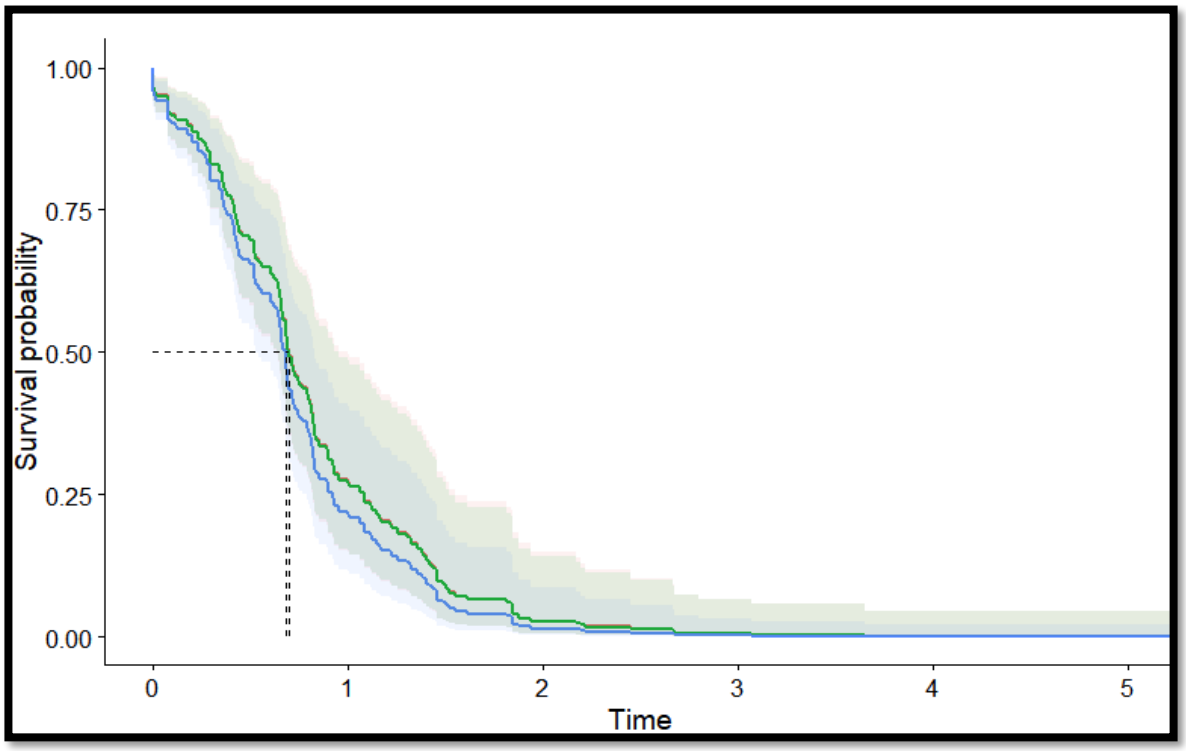
Legend:

NAC*= neoadjuvant chemotherapy.

The indicated coeficients were hazard ratios (HR) with their 95% confidence interval (IC 95%).

The rate of significativity was indicated with: *p<0.1; **p<0.05; ***p<0.01.

Figure 4: Kaplan–Meier Estimates of Recurrence-free Survival



- Red curve: Group 1
- Green curve: Group 2
- Blue curve: Group 3

b) Overall survival

With a median follow up of 48 months, no stastical difference was found for OS between the 3 groups (Figure 5). We observed a median OS of 57,4 months in the group 1, 49,2 months in group 2 and 55,4 months in group 3.

All data about OS were reported Table 5.
Involvement of the sus mesocolic surgical debulking (liver/spleen/pancreas) was associated with an OS increasing of 80% (HR 0.216; 95%CI [0.078-0.594], p=0.004).
Performing a pelvic lymph nodes dissection, involved or not, was associated with increased of OS (0.283 [0.124;0.650]).

Involvement of the bowel resection was associated with a decrease of OS with a HR=1.653; 95% CI [1.120-2.441], p=0.012.

Appendicectomy resection data were associated with a decrease of OS (HR 2.039; 95% CI [1.316-3.157]; p= 0.002).

The transfert in an Intensive Care Unit was associated with a decrease of the OS (HR 2.694; 95% CI [1.176-6.171]; p=0.020).

Table 5: Overall survival according to propensity score matching analysis

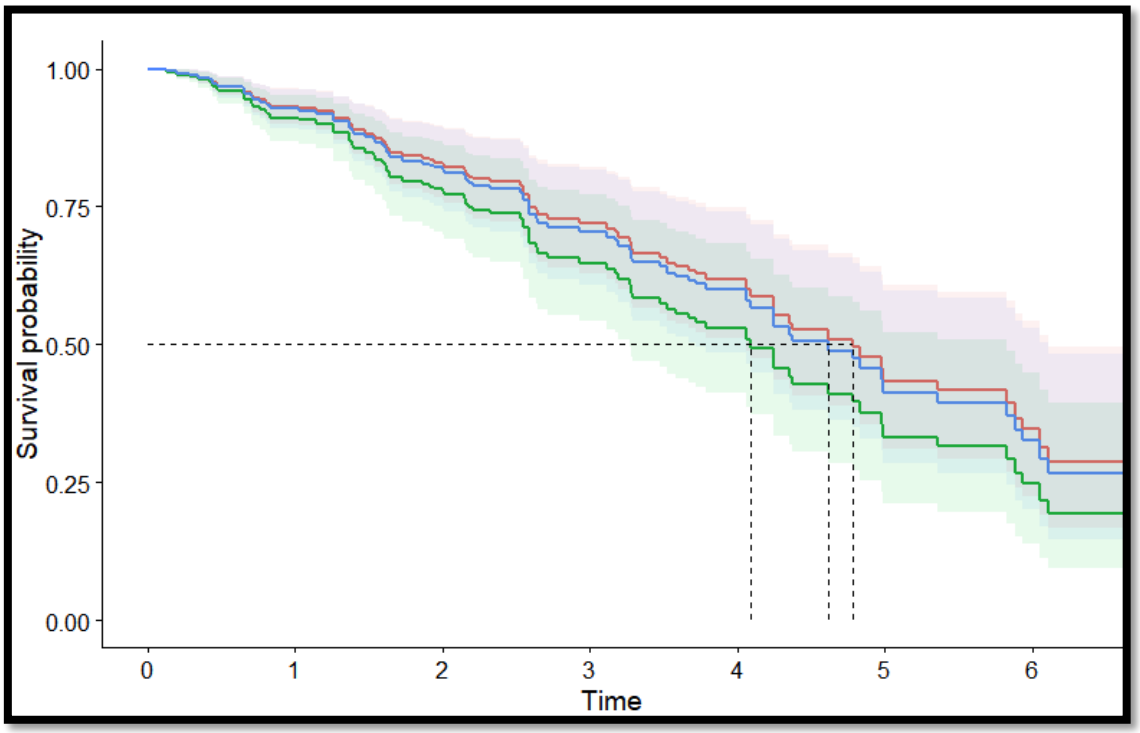
Variables	HR	p
Type of treatment Group 1 vs 2	0.757 (0.509 ;1.125)	0.169
Group 3 vs 2	0.804 (0.563 ;1.149)	0.232
Spleen, pancreas, liver performed vs presence of residual disease	0.216 (0.078;0.594)	0.004***
Bowel resection performed vs absence of residual disease	0.786 (0.466;1.324)	0.365
Bowel resection performed vs presence of residual disease	1.653 (1.120;2.441)	0.012**
Pelvic lymph nodes dissection performed vs absence of residual disease	0.332 (0.156;0.704)	0.005***
Pelvic lymph nodes performed vs presence of residual disease	0.283 (0.124;0.650)	0.003***
Lombo Aortic lymph nodes dissection performed vs absence of residual disease	1.797 (0.836;3.861)	0.134
Lombo Aortic lymph nodes dissection performed vs presence of residual disease	0.000 (0.000;Inf.)	0.995
Per operative complication	0.308 (0.086;1.112)	0.073*
Intensive Care Unit transfert	2.694 (1.176;6.171)	0.020**
Chemo toxicity (grade 3/4)	1.355 (0.933;1.967)	0.111
Observations	155	
R^2	0.474	
LR Test	99.603 (df = 17)	<0.001***

Legend :

The indicated coeficients were hazard ratios (HR) with their 95% confidence interval (IC 95%).

The rate of significativity was indicated with: *p<0.1; **p<0.05; ***p<0.01.

Figure 5: Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival



- Red curve: group 1
- Green curve: group 2
- Blue curve: group 3

Quality of cytoreductive surgery.

Concerning the rate of complete macroscopic resection (CC0), there was no difference between the three groups: 69% for group 1, 78% and 66% for groups 2 and 3 respectively (p=0.315) (Table 3). An incomplete surgery CC1 was observed for 25,5% of patients in group 1, 19,5 % in group 2 and 22% in group 3 (p=0.374) (Table 3).

Perioperative and Postoperative Morbidity, Clavien III-IV.

No significant difference about surgery's complications between the 3 groups of treatments was showed (Table 3). The rate of transfusion was 19,6% in the group 1, 26,2% in the group 2, and 18,6% in the group 3 without significant difference (p=0.625). The rate of reintervention was 3,6% for the group 1, 3,4% for the group 3 and decrease to 0% for group 2 (p=0.472). Nobody in group 1, 4,8 % percent of women in group 2 and 1,7 % in group 3 were transfered to an Intensive Care Unit after surgery (p=0.231).

We reported a rate of eventration of 5,4% for group 1, 4,8% for the group and 8,5% for group 3 (p=0.699) (Table 3). We recorded a rate of post operative morbidity, Clavien III-IV, of 8,9 % in the group 1, 26,2% for the group 2 and 16,9 % for the group 3 (Appendix 3).

IV. Discussion

The aim of this study was to define the impact on survival, of the timing of surgery for patients treated by NAC for AEOC. With a median time follow up of 48 months, the therapeutic sequence had not shown any impact on OS and PFS between the three groups after using a propensity score. The purpose of this score was to induce 3 comparable groups as a randomized study with more statistical power. Stoeckle et al., found the same results (29). In this retrospective study about 647 patients treated for AEOC, OS and PFS were evaluated before 4 courses of NAC and after 5 courses of NAC. They observed that OS was not inferior in the late IDS group compared to the early IDS group with 37 vs. 22 months, respectively (p=0.09). Furthermore, late IDS yield higher complete resection rates than early IDS (29). Phillips et al. achieved in 2018, a retrospective study, about 367 patients distributed in 2 therapeutics groups: < 4 courses and > 5 courses of NAC and had to assess the outcome on OS and PFS (30). No difference in OS was found between these 2 groups, but complete surgical cytoreduction rate increased after 5 courses of NAC + CDS (30).
These results were different to those observed in our study: we have raported a similar rate of complete macroscopic cytoreduction CC0, between the 3 groups of treatments, with a mean rate of 71%. The timing of cytoreductive surgery appeared to have no impact on the quality of the surgical cytoreductive, but a complete surgical resection improve PFS in our study independantely of the time of cytoreductive surgery

Bristow et al. in 2002 have shown in a large study from 81 cohorts that median survival time for patients with ovarian cancer stage FIGO III-IV was 22.7 months in case of cytoreduction < 25% and increase at 33.9 months in case of maximal surgical cytoreduction > 75% (32). Furthermore, Colombo et al in a prospective study in 2014, found that complete cytoreduction CC0, was associated with a prolongated survival for patients treated independantely by PDS or IDS with a median survival of 44.4 months (4). In our study, improvement of PFS after surgical incomplete cytoreduction CC2 was observed abnormally; it could be explained by the low number of incomplete tumoral resection and a small sample size of included patients

For AEOC stage FIGO IIIc-IV, decision of the best treatment between cytoreductive surgery and NAC could be difficult. Objective is to perform the best quality of cytoreductive surgery.

To ansewer the question about the timing before surgery, Lecuru et al. in a retrospective study in 2017, have developed a reproductible 100-point score to classify patients into one of the three risk groups of incomplete cytoreduction (31). Patients would be classified into one of the three risk's groups of incomplete cytoreduction following clinical, biological, and radiological evaluation. Patients classified as high risk would immediately be referred for neoadjuvant chemotherapy. This score could help to decide of NAC performing. It would be interesting to evaluate the impact on survival of the use of this score.

NAC had to avoid some surgical and post operative complications as: longer hospital stays, blood lost, blood transfusion, fistula, denutrition, and infections (14). Stoeckle et al. observed in a study about 397 patients an increase of complete surgical cytoreduction (94%) after 6 courses of NAC, associated with a decrease of the bowel resections rate and so the morbidity as diarrhea, ostomy, fistula, and irritable bowel syndrome (27). Schwartz et al., in a retrospective and non-randomized study, identified significantly, lower blood loss and lower hospitalization stay (11 days in case of PDS and 7 days in case of NAC) in the group NAC vs PDS ($p<0,001$) (18). A transfert in an Intensive Care Unit was significantly associated in our study with a decreased OS rate [HR=2.694 (95% CI [1.176-6.171], p=0.02)] and PFS rate [(HR=3.194; 95% CI [1.397-7.302], p=0.006)]. In fact, the transfert in an intensive care unit was associated with an extensive surgical cytoreduction (sus mesocolic surgical resection: diaphragmatic resection and splenectomy, or extensive digestive resection) and a higher risk of post surgical complications for patients with comorbidities: it represented a strong selection bias. Performing cytoreductive surgery after 6 courses of NAC in patients with better PS and without therapeutic interruption, appeared to be a reasonable option in the absence of survival impact.

In our study, appendice involvement and small bowel or large bowel resections were associated with worst survival (HR=2.039; 95% CI [1.316-3.157], p=0.002, and HR=1.653; 95% CI [1.120-2.441], p=0.012 respectively). These observations could be associated with the extension of the tumoral disease up to digestive serosa or in the intestinal lumen, increasing the risk of tumor invasion on the neighbouring organs and spreading tumoral lesions in the sus mesocolic stage (18). In case of visceral disease, surgical cytoreduction not seemed to be effective for patients undergoing surgery alone. Salani et al., in a case-control study, led on 102 patients treated for AEOC between 1997 and 2006, observed a median survival at 37,8 months if one digestive resection was performed but decreased at 28,3

months if 2 or more digestive resections were achieved (33). In fact, extensive bowel resections were associated with the increase of stay in hospital, the morbidity and the blood transfusion rate. Performing an extensive bowel surgery was not recommended (33).

Inversely, a sus mesocolic parietal extensive surgical cytoreduction in case of spleen, liver or pancreas involvement was associated in our study with an increase of overall survival (HR=0.216; 95% CI [0.078-0.594], p=0.004). Peiritti et al. in 2010, reported that a supra mesocolic tumoral resection increased OS (median OS 57,6 months) and lead to an increased rate of optimal cytoreduction (tumoral burden < 1 centimeter) of 76% vs 48% in 1996-2000 (15). These surgical practices needed a special surgical formation and a multidisciplinary management. Chi et al. in a retrospective study in 2009 included a cohort of 378 patients with advanced ovarian cancer stages IIIc or IV, have shown an improvement of 80% of the optimal cytoreduction between 2001 and 2004 (vs 40% between 1996 and 1999) with better OS, but associated with an increasing of the rate of surgical complications (14). For these authors, NAC seemed also to be useful to decrease peritoneal and parietal carcinomatosis and surgical morbidity.

In our study, pelvic lymph nodes dissection with or without lymph nodes involvement was associated with increased OS. A free pelvic lymph nodes involvement was associated with a better OS thanks to smaller HR 0.282 (p=0.003). Also, PFS was better in case of free lombo aortic lymph nodes dissection without impact of the lombo aortic lymph node's involvement (HR 0.938; 95%IC [0.670;1.313]; p=0.710). This result suggested that lymph nodes with free involvement, were associated with a better prognosis, with a direct impact of the lymph node dissection. In the last update of guidelines for AEOC treatments, pelvic and aortic lymphadenectomies are recommended only in case of suspicious clinical or radiological tumoral lymph nodes, before primary debulking surgery (34).

In absence of clinical or radiological argument for tumoral nodes associated with a complete peritoneal resection during initial debulking surgery, lymphadenectomy could be omitted. In fact, this extensive and morbid surgery didn't change neither the processing nor overall survival. New recommandations about primary debulking surgery agreed to say that pelvic and lombo aortic lymphadenectomy won't increase global survival (34). Harter et al. in a prospective randomized study in 2019, showed no significant difference in PFS or OS between the groups of treatment with or without lymph nodes dissection in case of AEOC treated by PDS (35). They observed an increased rate of complications in the

lymphadenectomy group (lymph cysts, repeat laparotomy for complications, death, p<0,05) (35). In case of primary neoadjuvant chemotherapy, the question about lymph nodes dissection was unresolved. The therapeutic multicentric trial called CARACO (NCT number: NCT01218490) was initiated to answer this question. The final results were awaiting (36). In fact, lymph nodes dissection was used to performe a staging of the tumoral extension and predict adjuvant therapies. Permormed alone, they didn't improve survival.

In our study, we found a low rate of complete histological response. We observed a rate of tumoral residue on the excised tissue extending from 0 to 100% (Table 3). These observations showed the apparition of chemoresistant tumoral clones and platinium-refractory tumours associated with poor short-term survival. This data was observed first after primary surgical cytoreduction which aim was to obtain complete surgical resection. Some authors like Colombo et al. in 2014, described a reducing of the chemotherapy efficiency due to the emmergence of resistant tumoral clones (9). Neoadjuvant therapy had to be reserved for patients in a fragile state or in case of extent tumoral carcinomatosis with impossible complete surgical cytoreduction. Emergence of tumoral resistances and progress in research led us to develop new targeted therapy. In fact, some germinal or somatic mutations on genes implicated in the tumoral development of serous ovarian adenocarcinoma, called BRCA 1-2, were described. BRCA1-2 were tumor suppressor genes. They were associated with an increased risk of associated breast and ovarian cancer development. In addition, these genes were implicated in the DNA homologous recombination after DNA damage and could lead to an increased risk of cancer. The BRCA mutation had to be detected consistently in every diagnosis of high-risk ovarian cancer by an oncogenetic consultation. The detection of a BRCA mutation could lead to a use of a targeted therapy: Anti-PARP immunotherapy. Some prospective study like PAOLA I (NCT number: NCT02477644) were established to compare patients with AEOC, high grade fallopian tube, or peritoneal cancer treated with standard first-line treatment, combining platinum-taxane chemotherapy or bevacizumab concurrent with chemotherapy. Definitive results are to be expected in 2022 (37). Other ongoing study like « FIRST » (NCT number: NCT03602859) had to evaluate the interest of new therapeutic strategy in case of NAC.

Strenghts of this study were the high number of included patients (n=156), the long time of follow up about 16 years, the homogeneity in patient's management and study population, and the use of a statistical propension analysis.

Limitations of the study were its retrospective and not randomized character with poor statistical power, and the lack of resectability criteria initially defined making a lost of informations. It represented a low level of proof. Therefore, prospective and randomized studies are required to answer the question asked about the useful number of NAC cycles.

To improve our knowledge in the ovarian cancer with a better statistical power, new multicentric, prospective and randomized study have begun like the « CHRONO study » (NCT number NCT03579394) to show the therapeutic impact of NAC. The remaining limitations are the difference between the applicated adjuvant treatment and the delay in the follow up including all the different patients. A german study called « TRUST » (NCT number NCT02828618) has also started up to compare in a prospective study PDS vs NAC associated with IDS from scannographic and biologic data, and to determine the impact on PFS and OS. The results are being analyzed to change the AEOC management.

In conclusion, no difference in the PFS or OS was observed between ¾ or 6 courses of NAC. It seemed possible to performe closing cytoreductive surgery after 6 courses of NAC to facilitate the chronology of NAC delivery.
Nevertheless, complete surgical cytoreduction was associated with an improvement of PFS and extensive parietal and sus mesocolic surgery were associated with an improvement of OS.

Multicentric, prospective and randomized studies remain necessary to confirm our impression.

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Appendix 1 : FIGO (International Federation of Gynecology and Obstetrics) Classification

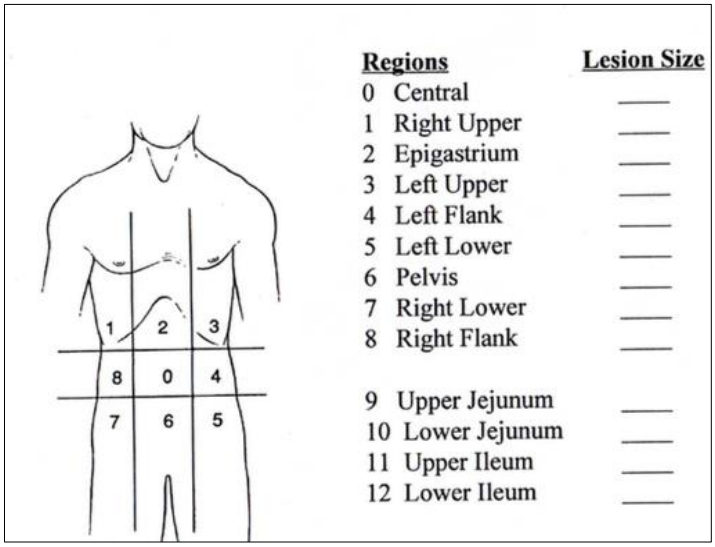
Stade I	IA	IB	IC
2014	Tumor con ned to one ovary or fallopian tube, intact capsule, no tumor on surface, no tumor cells in ascites or washings	Tumor involves both ovaries or fallopian tubes, otherwise like stage IA	IC1: Intraoperative spill IC2: Capsule rupture before surgery or tumor on ovarian or fallopian tube surface IC3: Positive peritoneal washings or ascites

Stade II	IIA	IIB
2014	Extension to or implant on uterus or fallopian tubes or some combination	Extension to other pelvis intraperitoneal tissues

Stade III	IIIA	IIIB	IIIC
2014	IIIA1 : Positive retroperitoneal lymph nodes only (i) Metastasis ≤ 10 mm (ii) Metastasis > 10 mm IIIA2 : Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

Stade IV	IV A	IV B
2014	Pleural effusion with positive cytology	Hepatic and/or splenic parenchymal metastasis, metastasis to extra- abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Appendix 2 : PCI score 0 to 39 after laparotomic surgical exploration, transposed for laparoscopy.



Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence

Regions	Anatomic structures
0 Central	Midline abdominal incision - entire greater omentum - transverse colon
1 Right upper	Superior surface of the right lobe of the liver - undersurface of the right hemidiaphragm - right retro hepatic space
2 Epigastrium	Epigastric fat pad - left lobe of the liver - lesser omentum - falciform ligament
3 Left upper	Undersurface of the left hemidiaphragm - spleen - tail of pancreas - anterior and posterior surfaces of the stomach
4 Left flank	Descending colon - left abdominal gutter
5 Left lower	Pelvic sidewall lateral to the sigmoid colon - sigmoid colon
6 pelvis	Female internal genitalia with ovaries, tubes and uterus - bladder, Doublas pouch - rectosigmoid colon
7 right lower	Right pelvic sidewall - cecum - appendix
8 left flank	Right abdominal gutter - ascending colon
9 upper jejunum	
10 lower jejunum	
11 upper ileum	
12 lower ileum	

Appendix 3 : Clavien and Dindo classification

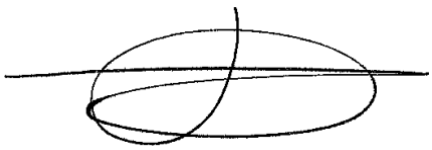
Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
Grade III - IIIa - IIIb	Requiring surgical, endoscopic or radiological intervention Intervention not under general anesthesia Intervention under general anesthesia
Grade IV - IV a - IV b	Life-threatening complication (including CNS complications)* requiring IC/ICU-management single organ dysfunction (including dialysis multiorgandysfunction
Grade V	Death of a patient

Vu, le Président du Jury,

Pr Jean Marc Classe

Vu, le Directeur de Thèse,

Dr Cécile LOAEC



Vu, le Doyen de la Faculté,

Professeur Pascale JOLLIET

NOM : GODFROY PRENOM : Marine

Titre : Impact of the number of Neoadjuvant Chemotherapy (NAC) cycles on survival and morbidity in patients with advanced epithelial ovarian cancer FIGO III-IV.

V. ABSTRACT (10 LINES)

Objectives:

To assess the impact of 3-4 vs 6 cycles of neoadjuvant chemotherapy (NAC) and cytoreductive outcomes on overall survival (OS) and progression free survival (PFS) in patients undergoing interval debulking surgery (IDS) or closing debulking surgery for advanced ovarian cancer.

Methods:

A retrospective study conducted in patients treated for AEOC and receiving NAC followed by IDS or closing surgery between 2000 and 2017. Patients were analysed according to the number of NAC cycles received: group 1 received 3-4 cycles of NAC followed by IDS and adjuvant chemotherapy and group 2 and 3 received 6 cycles of NAC followed by closing debulking surgery (CDS) (2) or CDS with consolidation chemotherapy (3). Outcomes were stratified by cytoreductive complications, surgical complexity, quality of the surgical resection, stage of the tumoral disease and chemotherapy exposure and tolerance.

Results
No effects on OS and PFS of the three different therapeutic sequences. Decreasing of the OS rate was observed in case of bowel resection involved (HR=1.653; IC95(1.120-2.441), p=0.012), transfert in an Intensive Care Unit (HR=2.694; IC95(1.176-6.171), p=0.020). Decreasing of PFS was associated with involved bowel resection, incomplete cytoreduction CC1, and per-post operative complications.

Discussion
No difference on PFS or OS was observed between the 3 groups of therapeutics. Furthermore, obtention of a complete surgical cytoreduction and a decrease of the transfert rate in an intensive care unit were associated with a prolongated OS. Necessity of a propective and multicentric study to confirme our impression.
-

KEY WORDS

Epithelial ovarian cancer, neoadjuvant chemotherapy, number of cycles, interval surgery, complications, overall survival, progression free survival.

NOM : GODFROY PRENOM : Marine

Titre de Thèse :

Impact du nombre de cures de Chimiothérapie Néoadjuvante sur la survie et morbidité dans le cancer de l'ovaire épithélial avancé FIGO III-IV.

V. RESUME (10 LINES)

Objetifs:

Evaluation de l'impact de 3-4 cycles vs 6 cycles de chimiothérapie néoadjuvante (CNA), et du devenir de la cytoreduction tumorale chirurgicale sur la survie globale et sans récidive, chez les patientes bénéficiant d'une chirurgie d'intervalle ou cloture pour cancer avancé épithélial (CAEO).

Methode:

Une étude retrospective a été menée chez les patientes traités pour CAEO et recevant une CNA suivie d'une chirurgie d'intervalle ou de cloture entre 2000 et 2017. Les patientes inclues sont réparties en fonction du nombre de cures de CNA reçue : le premier groupe a reçu 3-4 cures de CNA suivie d'une chirurgie d'intervalle puis chimiothérapie adjuvante, le groupe 2 a reçu 6 cures de CNA suivie d'une chirurgie de cloture, et le groupe 3 a reçu 6 cures de CNA suivie par une chirurgie de cloture puis d'une chimiothérapie de consolidation. Les devenirs étaient définis par les complications de la chirurgie cytoréductive, la complexité chirurgicale, la qualité de la cytoréduction chirurgicale, le stade et grade de la maladie tumorale ainsi que l'exposition et la tolérance à la chimiothérapie.

Resultas
Pas de difference sur la survie globale et sans récidive n'a été observée entre les 3 groupes de traitement. Une diminution de la survie globale a été montrée après résection digestive envahie (OR=1.653; IC95(1.120-2.441), p=0.012), et en cas de transfert en Unité de Soins Continus (USC) (OR=2.694 ; IC95(1.176-6.171), p=0.020).
L'envahissement des résections intestinales, la cytoréduction incomplète CC1 et les complications per et post opératoires étaient associés à une dominution de la survie sans récidive.

Discussion
Pas de difference n'a été identifiée sur la survie sans récidive et globale entre les 3 groupes de traitement. Cependant, l'obtention d'une cytoréduction tumorale complete et la baisse du taux de transfert en USC étaient associés avec une prolongation de la survie globale. Nécessité d'une étude prospective, multicentrique pour confirmer nos impressions.

MOTS CLES

Cancer de l'ovaire épithélial, Chimiothérapie néoadjuvante, nombres de cycles de chimiothérapie, chirurgie d'interval, chirurgie de cloture, complications, survie globale, survie sans récidive.