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Prognostic factors of overall survival for patients with FIGO stage IIIc or IVa ovarian cancer treated with neo-adjuvant chemotherapy followed by interval debulking surgery: a multicenter cohort analysis from the FRANCOGYN study group.

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ABSTRACT

Introduction. The aim of this study was to identify prognostic factors of overall survival in patients with FIGO stage IIIc or IVa ovarian cancer (OC) treated by neo-adjuvant chemotherapy (NAC) followed by interval debulking surgery.

Materials and Methods. Data from 483 patients with ovarian cancer were retrospectively collected, from January 1, 2000 to December 31, 2016, from the FRANCOGYN database, regrouping data from 11 centers specialized in ovarian cancer treatment. Median overall survival was determined using the Kaplan-Meier method. Univariate and multivariate analysis were performed to define prognostic factors of overall survival.

Results. The median overall survival was 52 after a median follow up of 30 months. After univariate analysis, factors significantly associated with decreased overall survival were; no pelvic and/or para-aortic lymphadenectomy ($p=0.002$), residual disease (CC1/CC2/CC3) after surgery ($p<0.001$), positive cytology after NAC ($p<0.001$), omental disease after NAC ($p=0.002$), no pathologic complete response (pCR) ($p=0.002$). In multivariate analysis, factors significantly associated with decreased overall survival were; residual disease after surgery (HR=1.93; CI95% (1.16-3.21), $p=0.01$) and positive cytology after NAC (HR=1.59; CI95% (1.01-2.55), $p=0.05$). Patients with no residual disease after surgery had a median overall survival of 64 months versus 35 months for patients with residual disease. Patients with negative cytology after NAC had a median overall survival of 71 months versus 43 months for patients with positive cytology after NAC.

Conclusion. In this first and largest French based retrospective study, complete cytoreductive surgery in ovarian cancer remains the main prognostic factor of overall survival.

KEYWORDS: ovarian cancer, neoadjuvant chemotherapy, interval debulking surgery, overall survival.

ABBREVIATIONS:

BMI: Body Mass Index

CCS: Complete Cytoreductive Surgery

HE4: Human Epididymal protein 4

IDS: Interval Debulking Surgery

LVSI: Lymphovascular Space Invasion

NAC: Neo-adjuvant chemotherapy

OC: Ovarian cancer

OS: Overall survival

pCR: pathologic Complete Response

PFS: Progression Free Survival

Declarations of interest: none

1. INTRODUCTION

In France, ovarian cancer (OC) is the eighth leading cause of cancer in women. Incidence in France in 2018 was 4985 cases and mortality rate was 3927 deaths/year (1).

In approximately 70% of cases, patients with OC are diagnosed at an advanced stage, stage IIIc International Federation of Gynecology and Obstetrics (FIGO) or higher, and have peritoneal carcinomatosis (2,3). The prognosis of advanced OC (stage IIIc or IVa FIGO) remains poor, with a median overall survival (OS) estimated at 30 months according to the European Organization for the Research and Treatment of Cancer (EORTC) (4).

OC management is based on a complete resection surgery, preceded or not by neo-adjuvant platinum-based chemotherapy. Complete resection is a prognostic factor of survival, but excision of peritoneal carcinomatosis lesions might be impossible (5). Performing a neo-adjuvant chemotherapy (NAC) followed by an interval debulking surgery (IDS) decrease surgical resection and thus surgical morbidity without affecting patient survival. A randomized study conducted by the EORTC comparing primary surgery to NAC followed by IDS, demonstrated no significant difference in terms of recurrence-free survival and OS. NAC followed by complete resection surgery became the standard of care in patients with unresectable epithelial OC (4,6,7).

Residual tumors in the operative specimens are evaluated by pathological examinations, allowing histological response definitions. Studies have shown a prognostic impact of complete histological response or pathologic complete response (pCR) on progression-free survival (PFS) and OS. Petrillo *et al.*, studied the prognostic impact of pCR after NAC in unresectable OC. In this study, pCR was significantly associated with longer PFS and OS (8). However, pCR is a rare event in these advanced OC receiving NAC (approximately 6%) (9). Therefore it is interesting to identify other factors associated with OS in OC, receiving NAC to optimize patient management, in particular regarding adjuvant treatments after IDS. In fact,

identifying subgroups with worse OS could allow us to adapt adjuvant treatment. Two three-phase randomized studies (ICON 7 and GOG-218) have demonstrated a progression free survival (PFS) benefit of adding bevacizumab as adjuvant therapy in poor prognosis subgroup's patients (10,11).

The objectives of this study are to identify prognostic factors of OS in patients with stage IIIc or IVa OC treated with taxane/platinum-based NAC and IDS and to evaluate the prognostic impact of pCR.

2. MATERIALS AND METHODS

2.1. Population

Data from 483 patients with OC, stage IIIc or IVa treated by NAC followed by IDS were retrospectively collected, from January 1, 2000 to December 31, 2016, from the FRANCOGYN database regrouping data from 11 French centers specialized in OC treatment: "Georges-François Leclerc Cancer Center" Dijon, "International Hospital" Créteil, "University hospital Lyon Sud", "Jean Verdier Hospital" Bondy, "La Pitié-Salpêtrière Hospital" Paris, "Jeanne de Flandre University Hospital" Lille, "Hospital of Poissy", "University Hospital" Rennes, "University Hospital", Strasbourg, "Hôpital Tenon" Paris and "University Hospital", Tours. NAC was decided after a diagnostic laparoscopy. The research protocol was approved by the Institutional Review Board of the French College of Obstetrics and Gynecology (CEROG 2014-GYN-020). The inclusion criteria were: inoperable initial stage FIGO IIIc or IVa OC, treated by taxane/platinum-based NAC followed by IDS.

2.2. Clinical and pathological variables

The clinical and pathological variables studied were: age, body mass index (BMI), CA125 serum level during evaluation and after NAC, FIGO stage, menopause, BRCA mutation, and

histological type. Concerning chemotherapy, the variables studied were: number of NAC cycles, NAC protocol, and bevacizumab treatment.

Surgery variables studied were: Fagotti score, digestive resection, pelvic lymphadenectomy or para-aortic lymphadenectomy, macroscopic residual tumor, and intraoperative capsular rupture.

Pathology variables studied were: peritoneal cytology, lymphovascular space invasion (LVSI), omentum invasion, grade of serous tumors, differentiation, involvement of pelvic and para-aortic nodes and histological response.

2.3. *Definition of the histological response*

At the end of IDS, an anatomopathological examination of the surgical specimens was carried out to define histological response in three types: complete response, partial response and no response. Pathologic complete response (pCR) was defined by the absence of invasive residual tumor in operative specimens. Partial histological response was defined by the presence of degenerative changes of the tumor cells. Absence of a histological response was defined by the absence of anatomopathological response to NAC. An expert in gynecological pathology performed histology in all cases.

2.4. *Statistical analysis*

Univariate and multivariate analysis were performed to identify clinical, pathological, chemotherapy and surgery variables significantly associated with OS. To identify factors associated with OS, each variable was tested in univariate analysis using the log-rank test. Survival medians were defined according to the Kaplan-Meier method. Variables included in multivariate analysis had a p value equal or inferior to 0.10, a significant confidence interval (CI) in univariate analysis and less of 20% missing data.

Multivariate analysis was performed according to a Cox model. Results were considered significant when p value was equal or inferior to 0.05. Survival curves obtained using the Kaplan-Meier method and compared according to the log-rank test. Patients were censored at death or at 137 months if alive.

Data were managed with an Excel database (Microsoft Corporation, Redmond, WA, USA) and analyzed using R 3.3.1 software (R Foundation, Vienna, Austria), available online (<http://lib.stat.cmu.edu/R/CRAN/>). The research protocol was approved by the institutional review board of the French College of Obstetricians and Gynecologists (CEROG 2016-GYN-1003).

3. RESULTS

3.1. Population characteristics at initial evaluation

Data from 483 patients with NAC-treated OC followed by IDS were retrospectively collected from 11 French expert centers.

Population characteristics are summarized in Table 1. The average age was 61.5 years ($\pm$ 11 years). BMI was in average 25.1 kg/m² ($\pm$ 5.3 kg/m²). 83.2% patients were menopausal. Thirty-eight patients had a germline mutation BRCA gene (7.9%) but the BRCA gene status was unknown for 72.9% of patients. Three hundred and fifty-eight patients had FIGO stage IIIc (74.1%) and 97 FIGO stage IVa (20.1%). The majority of patients had a serous ovarian tumor (81.6%).

Of the NAC protocols used, 442 patients received taxane/platinum-based chemotherapy (91.5%). Ninety-eight patients received adjuvant therapy with bevacizumab (20.3%).

The mean CA125 serum level was 2181 U/ml ($\pm$ 4499 U / ml), 247 patients had a CA125 level $\leq$ 1000 U/ml (51.2%), 115 patients had a CA125 between 1000 and 3000 U/ml (23.8%), and 87 patients had a CA125 $\geq$ 3000 U / ml (18%).

Three hundred and sixty-one patients underwent exploratory surgery, of which 291 had exploratory laparoscopy (80.6%), 44 had exploratory laparotomy (12.2%) and 4 had a conversion to laparotomy (1.1%). In this surgical evaluation, sixty-nine patients had a Fagotti score lower than 8 (14.3%) and 199 patients had a Fagotti score ≥ 8 (41.2%). Initial peritoneal cytology was positive in 179 patients (69.8%).

3.2. *Evaluation after NAC*

Regarding the number of NAC cycles, 195 patients received 2 or 3 or 4 cycles (40.4%), 200 patients received 5 or 6 cycles (41.4%), 170 patients received 6 cycles (35.2 %) and 47 patients had more than 6 cycles (9.7%) (table 2).

Regarding radiological evaluation after NAC, 238 patients had a TAP scan (49.3%) and 35 patients underwent a PET scan (7.2%). In this radiological evaluation, 56 patients had ascites (11.6%) and omentum invasion was found in 70 patients (14.5%). With respect to lymph node assessment, 36 patients had suspicious pelvic nodes (7.5%) and 33 patients had suspicious para-aortic nodes (6.8%). Eight patients seem to have small bowel involvement (1.7%) and 22 patients seem to have colon involvement (4.6%).

3.3. *Characteristics of IDS and histological response after NAC*

The Characteristics of IDS and histological response after NAC are summarized in table 2. After NAC, the average CA125 level was 152U/ml (+/- 316U/ml). One hundred and thirty patients had a CA125 level ≤ 35 U/ml (26.9%) and 120 patients had a CA125 level >35 U / ml (24.8%).

During IDS, Fagotti score was less than 8 for 105 patients (21.7%) and ≥ 8 for 65 patients (13.5%). Bowel resection was performed in 140 patients (28.9%). Three hundred and seventeen patients underwent pelvic and para-aortic lymphadenectomy (65.6%), 14 patients had only pelvic lymphadenectomy (2.9%) and 8 patients received a para-aortic

lymphadenectomy only (1.7%). Among 36 patients with positive pelvic lymph nodes on imaging, 24 patients had a pelvic lymphadenectomy and 22 had a para-aortic lymphadenectomy. Among patients with negative nodes on imaging, 114 patients had a pelvic lymphadenectomy and 110 patients had a para-aortic lymphadenectomy. Among 33 patients with positive para-aortic lymph nodes on imaging, 23 had a para-aortic lymphadenectomy. After IDS, three hundred and fifty-five patients had no visible residual tumor CC0 (73.5%) and 106 had a CC1 or CC2 or CC3 macroscopic residual tumor (21.9%). After histopathological analysis, 31 patients had a pCR (6.4%), 403 patients had a partial histological response (83.4%) and 8 patients showed no response to NAC (1.7%). Capsular rupture was found in 100 patients (20.7%). Peritoneal cytology was positive for 230 patients (47.6%), omentum was invaded for 281 patients (58.2%). One hundred and nineteen patients had positive pelvic lymph nodes (24.7%) and para-aortic lymph nodes were metastatic in 258 patients (53.4%).

3.4. Univariate and multivariate analysis of OS

Univariate analysis of OS is summarized in table 1 and 2. Median follow-up was 30 months and median OS was 52 months.

In univariate analysis, age, BMI, menopausal status, germline BRCA mutation, FIGO stage, histological type, NAC protocol, CA 125 at evaluation, Fagotti's score before NAC, and adjuvant bevacizumab didn't significantly affected OS (table 1). At the contrary, positive peritoneal cytology at evaluation was associated with worse OS ($p=0.04$).

Regarding the characteristics of IDS, the absence of pelvic and/or para-aortic lymphadenectomy, and the absence of complete cytoreductive surgery (CCS); CC1/CC2/CC3 was associated with worsen OS (respective p value: 0.002 and <0.001). There was no significant difference of OS regarding patients with surgical resection ($p=0.23$).

Concerning pathological analysis after IDS, variables significantly associated with a decrease in OS were positive peritoneal cytology at evaluation ($p=0.04$) and after NAC ($p<0.001$), omentum invasion at evaluation ($p=0.02$) and after NAC ($p=0.002$), para-aortic lymphadenectomy after NAC ($p=0.01$), presence of LVSI ($p=0.04$), absence of pCR ($p=0.002$) and capsular rupture ($p=0.03$).

Among significant variables in univariate analysis ($p\leq 0.10$), only those with less than 20% missing data were studied in multivariate analysis. These variables were: absence of pelvic and /or para-aortic lymphadenectomy, presence of residual tumor during interval surgery, positive peritoneal cytology after NAC, omentum invasion after NAC and absence of pCR.

After multivariate analysis, the presence of residual tumor (CC1/CC2/CC3) and positive peritoneal cytology after NAC were significantly associated with a decrease in OS (respectively HR = 1.93, 95%CI (1.16-3.21), $p=0.01$ and HR = 1.59, 95%CI (1.01-2.55), $p=0.05$) (figure 1).

The median OS of patients with no visible residual tumor (CC0) was 64 months, while that of patients with a CC1, CC2 and CC3 was 35 months. The median OS of patients with a positive peritoneal cytology after NAC was 43 months, and 71 months for patients with negative peritoneal cytology after NAC. Survival curves according to residual tumor and peritoneal cytology results are shown in figure 2.

4. DISCUSSION

This is the first and largest French based retrospective study examining the outcome for patients with stage IIIc or IVa OC treated with NAC. It confirms that CCS remains the main prognostic factor. In our study, 73.5% of patients underwent macroscopically complete resection (CC0) during IDS, and 106 were CC1/CC2/CC3. This rate is relatively high compared to literature data where this level varies between 30 and 85% (2,12–15). We have also shown that the presence of residual tumor after ICS is one of the major prognostic factors of decreased OS of stage IIIc or IVa OC treated with NAC. The median OS of patients with no visible residual tumor (CC0) was 64 months, while that of patients with a CC1, CC2 and CC3 was 35 months. The importance of residual tumor has been shown in many studies (16). Indeed, in 2009, Du Bois *et al.* demonstrated in an analysis of 3 randomized studies (AGO-OVAR 3, 5 and 7) that CCS for stage IIb to IV OC was associated with significant improvement in OS: the median OS was 99 months for patients with no residual tumor, 36 months for patients with a residual tumor of 1 to 10 mm and 29 months for patients with a residual tumor strictly larger than 10 mm ($p<0.0001$) (17). Similarly, Bristow *et al.* showed that the 24.5 months median OS was significantly associated with CCS ($p=0.027$). Indeed, a 10% increase in CCS rate, increased median survival by 1.9 months (18). However, it is sometimes difficult to compare data from literature as the definition of CCS varies according to studies, that often define CCS as residual tumor of less than 1 cm (4,9,15,19–21). In our study, CCS was not defined by a residual tumor less than 1 cm but by absence of residual tumor (CC0), limiting the biases associated to this factor. Obtaining no residual tumor after surgery is increased by NAC as demonstrated by Lee *et al.* (22). Similarly, the EORTC-NCIC study demonstrated that obtaining a residual tumor of less than 1 cm concerned 41.6% of patients during primary surgery and 80.6% after IDS (23). In addition, the CHORUS study conducted by Kehoe *et al.*, showed the non-inferiority of the NAC compared to the primary

surgery, therefore it seemed interesting to perform a NAC in patients with major peritoneal dissemination to reduce peri-operative morbidity/mortality and to increase CCS rate (13). However, Hacker *et al.* demonstrated that primary CCS remained the gold standard for patients with OC immediately resectable. In fact, inflammation after NAC can make surgery complicated and ovarian tumors sensitivity to platinum salts can't be predicted (24).

In the present study, residual tumor seems to predominate over pCR, that does not appear to be significantly associated with OS in multivariate analysis ($p=0.5$). Furthermore, pCR rate is 6%, similar to what has been previously reported (9). This low rate can be explained by the peritoneal diffusion of OC. However, many studies have demonstrated the importance of histological response after NAC, since NAC is significantly associated with PFS. Rose *et al.* showed that pCR rate was 19.9%. In this study, PFS was 16.1 months in a pCR, 13.5 months in a partial response and 11.7 months when no response was observed ($p=0.018$) (25). Therefore, Petrillo *et al.*, searched for predictors of pCR. Only the FIGO stage was significantly associated with pCR ($p=0.21$) (8).

Taking in consideration the previously described data, it seemed important to identify other prognostic factors of OS and PFS of IIIc or IVa ovarian stage cancers, to adapt neoadjuvant and adjuvant therapies to subgroups at risk. Scores for predicting OS could be created and implemented using different variables such as the CA125 marker, the presence of BRCA mutation, omental disease. Indeed, Rutten *et al.*, created a nomogram based on clinical-pathological variables, to estimate the 5-year survival of patients with OC treated by primary surgery or IDS. The variables used in this nomogram were age, primary surgery or IDS, post-surgical residual tumor, histological type, FIGO stage, WHO performance status, ascites amount and BRCA status. The total number of points resulting from all variables analysis allowed defining 1-year, 3-year and 5-year survival (26).

In our study, a CA125 serum level higher than or equal to 3000 U/ml at evaluation was significantly associated with decreased OS in univariate analysis ($p=0.08$). As missing data rate was higher than 20%, this marker was not studied in multivariate analysis. Nevertheless, several authors have shown interesting results with this marker. Mahdi *et al.*, showed that a CA125 level of less than 20 U/ml was a predictor of progression-free survival (HR = 0.37, 95%CI (0.20-0.66), $p<0.001$) but not OS (HR = 0.64, 95%CI (0.34-1.21), $p=0.17$) (27). Other markers could also be used for their prognostic value. The human epididymal protein 4 (HE4) is overexpressed in serous and endometrioid-type OC and can be used for both diagnosis and follow-up of these cancers (28). Thus, Chudecka *et al.* demonstrated that post-treatment normalization or a 50% reduction in HE4 was significantly associated with increased recurrence-free survival and OS (29). Similarly, a meta-analysis performed by Yuang *et al.*, showed that a high pre-operative HE4 level had a negative impact on OS (HR=1.91, 95%CI (1.40-2.61), $p<0.001$) (30).

Pathological variables such as omental disease could also be implemented in these scores. In our study, omentum invasion after NAC was significantly associated with decreased OS in univariate analysis but was no longer in multivariate analysis. On the other hand, Le *et al.* demonstrated that omentum involvement and its response to NAC were prognostic factors of PFS (20). Given these different data, the combination of biological and pathological criteria could be helpful to identify subgroups with poor prognosis.

In our study, the presence of BRCA1/2 mutation was not significantly associated with OS, in contrast with previously reported data but there were missing data for 72.9% of patients. The prognostic value of a BRCA1/2 mutation was assessed in a large number of retrospective cohorts and a recent meta-analysis involving 34 studies concluded that patients with a BRCA1/2 mutation had a benefit in terms of PFS (HR = 0.62, 95%CI (0.53-0.73), $p=0.261$) and OS (HR = 0.67, 95%CI(0.57-0.78), $p=0.001$) and this benefit was more important in

1 patients with a BRCA2 mutation (31). In another study, the presence of a BRCA1/2 mutation
2 was associated with a better prognosis in the short term ($p=0.03$) but was not found after 10
3 years of follow-up (32). These data might be explained by a higher sensitivity of patients with
4 a BRCA mutation to platinum-based chemotherapy, as demonstrated by Gorodnova *et al.*
5 (33).

6 In recent years, the development of molecular biology and genomics has revolutionized the
7 treatment and understanding of neoplastic diseases, particularly breast cancer. This is still not
8 the case for OC. Mendiola *et al.* demonstrated that 5 overexpressed genes found in malignant
9 ovarian tumors (ANGPT1, CD34, CD44, MMP7, PDGFB) were favorable prognostic factors
10 of OS of high-grade serous OC (34). Mutation identification or new biomarkers associated
11 with survival will be necessary to define subgroups of patients with poor prognosis leading to
12 treatment intensification. In fact, the use of bevacizumab as an adjuvant is still not consensual
13 and is depended on the benefit/risk balance in patients with stage IIIc/IVa OC treated with
14 NAC. Thus, no prognostic score objectively defines patients belonging to high-risk
15 subgroups, who require this adjuvant treatment. Finally, identifying new biomarkers may lead
16 to the development of new therapies such as targeted therapies that may improve the bad
17 prognosis of this pathology.

18 19 **5. CONCLUSION**

20 This is the first and largest French based retrospective study about prognostic factors of OS in
21 stage IIIc or IVa OC treated with NAC. It confirms that CCS remains the main prognostic
22 factor (HR = 1.93, 95%CI (1.16-3.21), $p=0.01$) and residual tumor after IDS seems to
23 predominate over pCR ($p=0.5$). At the time of personalized medicine in oncology, identifying
24 clinical, pathological, surgical, molecular or genomic factors, prognosis of OS and PFS would

optimize patient management leading to treatment intensification in subgroups with poor prognosis.

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Table 1 : Univariate analysis of prognostic factors of OS in population characteristics

Variables	Values (n = 483)	Median overall survival (months)	p
Age at diagnosis (mean ± SD, years)	61.5±11		
≤ 50 (reference)	78 (16.1%)	60	
50 to 70	284 (58.9%)	54	0.75
≥ 70	120 (24.8%)	43	0.13
Unknown	1 (0.2%)		
BMI (mean ± SD, years)	25.1±5.3		
≤ 25	252 (52.2%)	46	
>25	187 (38.7%)	53	0.15
Unknown	44 (9.1%)		
Menopause			
Yes	402 (83.2%)	50	
No	47 (9.7%)	69	0.22
Unknown	34 (7.1%)		
BRCA mutation			
Yes	38 (7.9%)	73	
No	93 (17.1%)	67	0.28
Unknown	352 (72.9%)		
FIGO stage			
IIIc	358 (74.1%)	54	
IVA	97 (20.1%)	46	0.08
Unknown	28 (5.8%)		
Histological type			
Serous (reference)	394 (81.6%)	54	
Endometrioid	22 (4.6%)	48	
Clear cells	11 (2.3%)	42	
Other	22 (4.6%)	46	0.7
Unknown	34 (7%)		
NAC protocol			
Taxane/platinum-based chemotherapy	442 (91.5%)	53	
Others	41 (8.5%)	41	0.3
CA125 at evaluation (U/ml)			
≤ 1000 (reference)	247 (51.2%)	55	
1000 to 3000	115 (23.8%)	46	0.61
≥ 3000	87 (18%)	41	0.08
Unknown	34 (7%)		
Fagotti score before NAC			
< 8 (reference)	69 (14.3%)	69	
≥ 8	199 (41.2%)	46	0.1
Unknown	215 (44.5%)		
Peritoneal cytology at evaluation			
Positive (reference)	176 (69.8%)	46	
Negative	31 (12.3%)	74	0.04
Unknown	276		
Adjuvant bevacizumab			
Yes (reference)	98 (20.3%)	46	
No	255 (52.8%)	54	0.87
Unknown	130 (26.9%)		

Abbreviations : BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics,
NAC = neo-adjuvant chemotherapy

Table 2: Univariate analysis of prognostic factors of OS after IDS

Variables	Values (n = 483)	Median overall survival (months)	p
Fagotti score after NAC			
< 8	105 (21.7%)	43	0.1
≥ 8	65 (13.5%)	49	
Unknown	313 (64.8%)		
CA125 post NAC (mean±SD, U/ml)	152±317		
≤ 35	130 (26.9%)	54	0.22
> 35	120 (24.8%)	46	
Unknown	233 (48.3%)		
Surgical resections			
Digestive resections			
Yes	140 (28.9%)	54	0.23
No	342 (70.8%)	46	
Unknown	1 (0.2%)		
Pelvic and para-aortic lymphadenectomy			
Yes	317 (65.6%)	60	<0.001
No	151 (31.3%)	44	
Unknown	1 (0.2%)		
Residual tumor after IDS			
CC1/CC2/CC3	106 (21.9%)	64	<0.001
CC0	355 (73.5%)	35	
Unknown	22 (4.6%)		
Peritoneal cytology after NAC			
Positive	230 (47.6%)	43	<0.001
Negative	153 (31.7%)	51	
Unknown	100 (20.7%)		
Pathological response to NAC			
None (reference)	8 (1.7%)	24	0.2
Partial	403 (83.4%)	49	
Complete	31 (6.4%)	66	
Unknown	41 (8.5%)		
Capsular rupture			
None	113 (23.4%)	72	0.03
Yes	100 (20.7%)	42	
Unknown	270 (55.9%)		
Invaded omentum after NAC			
Yes	281 (58.2%)	44	0.002
No	101 (20.9%)	73	
Unknown	101 (20.9%)		
Invaded pelvic nodes after NAC			
Yes	113 (35.6%)	53	0.073
No	180 (56.8%)	65	
Unknown	24 (7.6%)		
Invaded para-aortic nodes after NAC			
Yes	125 (39.4%)	49	0.01
No	139 (43.8%)	74	
Unknown	53 (16.8%)		
Embolus			
Yes	47 (9.7%)	41	0.04
No	80 (16.6%)	72	
Unknown	356 (73.7%)		

Abbreviations : NAC = Neo-adjuvant chemotherapy; CC0 = no visible residual tumor; CC1/CC2/CC3 = macroscopic residual tumor

Fig 1. Prognostic factors of overall survival in multivariate analysis.

NAC = neo-adjuvant chemotherapy; CC0 = no visible residual tumor; CC1 or CC2 or CC3= macroscopic residual tumor.

Fig 2. Estimation of overall survival according to residual tumor (A) and peritoneal cytology (B) after interval debulking surgery in Stage IIIc or IVa ovarian cancer patients treated with NAC.

CONFLICTS OF INTEREST

None.

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